Vincenzo Mirone
Editor

Clinical Uro-Andrology

Springer

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Springer

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ISBN 978-3-662-45017-8 ISBN 978-3-662-45018-5 (eBook)
DOI 10.1007/978-3-662-45018-5
Springer Berlin Heidelberg New York Dordrecht London

Library of Congress Control Number: 2014957754

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

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Part I

Male Reproductive System?

Anatomy and Physiology of Male Erectile Function

1

E. Wespes

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The knowledge of penile anatomy is clearly very important for the physiology of erection. This latter is still much more important because it allows to discover new therapeutic modalities.

During these last years, many researches have been performed to improve knowledge on this fundamental function for the quality of life and the reproductive human system.

According to the guidelines, physical examination in patients with erectile dysfunction is limited but must cover different vascular or endocrine area.

Several radiological investigations have been created to study erectile function in practice.

This chapter develops the different aspects of these problems.

1.1 Penile Anatomy

The human penis is a unique structure composed of multiple fascial layers that surround three cylinders of erectile sinusoids, including a pair of corpora cavernosa and a single corpus spongiosum. The erectile tissue is housed within the paired corpora cavernosa which are enveloped by a membrane: the tunica albuginea. This envelope also covers the corpus spongiosum, but there it is thinner (Shetty and Farah 1999; Lue 2000; Gratzke et al. 2010).

The tunica albuginea of the corpora cavernosa is the essential fibro-skeleton necessary for rigidity during sexual intercourse. The tunica is

V. Mirone (ed.), *Clinical Uro-Andrology*,
DOI 10.1007/978-3-662-45018-5_1, © Springer-Verlag Berlin Heidelberg 2015

composed of elastic fibers that form an irregular, latticed network on which the collagen fibers rest. The microstructure provides strength and allows the tissue to return to its baseline configuration after moderate stretch. In erectile dysfunction, decrease of the elastic fibers or modification of the ratio between the different types of collagen has been observed (Hsu et al. 1992).

It is a bilayered structure in which the inner layer is arranged circumferentially and in which fibers of the outer layer are arrayed longitudinally. The inner layer completely contains and, together with the intracavernosal pillars, supports the sinusoids (Hsu et al. 1992).

At the pendulous portion of the penis, the median septum is incomplete. This septum and the tunica albuginea together facilitate penile rigidity when erect. The corpora have the ability to engorge with blood to generate the penile rigidity necessary for vaginal penetration.

Within the tunica albuginea is a conglomeration of sinusoids, which are larger in the center and smaller at the periphery. The interconnected surrounded sinusoids are separated by smooth muscle trabeculae and by elastic fibers, collagen, and loose areolar tissue covered by endothelial cells (Shetty and Farah 1999; Lue 2000; Gratzke et al. 2010). These cells protect the sinusoid spaces but also secrete a great number of neurotransmitters that will provoke contraction or relaxation of intracavernous smooth musculature (Saenz de Tejada et al. 1989b). In erectile dysfunction, the number of these cells is not decreased, but their function could be seriously affected (Sattar et al. 1995b). Alterations of the neurotransmitters are at the origin of absence of smooth muscle cells relaxation or overcontraction (Saenz de Tejada et al. 1989b; Maher et al. 1996; Gu et al. 1984).

It has been suggested that there are gap junctions in the membrane of the adjacent muscle cells to explain the synchronous activity in the cavernous tissue of patients with normal erection, while there is a relatively sparse neuronal innervation of the cavernous smooth muscles (Campos de Calvalho et al. 1993).

More proximally, towards the perineum, the corporal bodies diverge bilaterally to form the crura of the penis. Each crus is anchored to the pubic arch at the level of the ischial tuberosity, where it is surrounded by the fibers of the ischiocavernosus muscles.

The corpus spongiosum is a single cylindrical tube that lies just ventral to the paired cavernosal bodies. It surrounds the urethra in its pendulous and bulbar portions. The distal portion of the spongiosum expands and covers the distal portion of the corporal bodies; this is the glans of the penis (Shetty and Farah 1999; Lue 2000; Gratzke et al. 2010).

Superficial to the tunica albuginea is Buck's fascia, a layer of tissue that encircles both the cavernosa and the spongiosum. It is immediately superficial to the deep dorsal vein of the penis, the paired dorsal arteries of the penis, and branches of the dorsal nerves of the penis, all of which directly overlie the tunica. Buck's fascia covers the spongiosum and the crura at the penile base, helping to fix these structures to the pelvic bones and the inferior fascia of the perineal membrane (Hsu et al. 1992).

The bulbospongiosus and ischiocavernosus musculature are superficial to Buck's fascia. More superficial is the areolar dartos fascia, or Colles' fascia, which additionally invests the perineum and the scrotal contents, extending to form the scrotal septum and the median raphe of the ventral penis, the scrotum, and the perineum.

Two ligaments suspend the pendulous penis from the anterior abdominal tissues and the pubis. The suspensory ligament is the more inferiorly located of the two structures and is a thickening of Colles' fascia.

1.2 Penile Arterial Inflow

The internal pudendal arteries, the final branches of the anterior trunk of the internal iliac artery, give the penile arteries after the vessels pass the urogenital diaphragm. The penile arteries travel along the medial aspects of the inferior pubic rami and supply the corpora and the glans via branching vessels (Breza et al. 1989; Droupy et al. 1997; Huguet et al. 1981). An accessory internal pudendal artery may arise from the

obturator, inferior vesical or superior vesical (Droupy et al. 1999). The bulbourethral artery supplies the bulb of the urethra, the corpus spongiosum, and the glans penis. It may arise from cavernous dorsal or accessory pudendal arteries, and this may be at risk during radical pelvic surgery (Polascik and Walsh 1995). The urethral artery commonly arises as a separate branch from the penile artery, but many arise from the artery to the bulb, the cavernous, or the dorsal artery (Breza et al. 1989; Droupy et al. 1997; Huguet et al. 1981). It runs on the ventral surface of the corpus spongiosum beneath the tunica albuginea. The cavernous arteries run centrally within the erectile bodies, closer the septum, while sending out various helicine branches that empty into the lacunar spaces. Most of these open directly into the sinusoids bounded by trabeculae, but a few helicine arteries terminate in capillaries that supply the trabeculae. There are very important to maintain a good function of the muscular component. These arteries have a tortuous configuration to accommodate for elongation during erection.

Occasionally the cavernosal arteries divide into two or three branches inside the corpus cavernosum. There are communications between both cavernosal arteries in some instances; connections with dorsal arteries are also present (Droupy et al. 1997).

The glans is supplied by the last branches of the penile arteries, the dorsal arteries. These give off circumflex vessels that communicate with the urethral arteries and send numerous perforating vessels to the skin (Breza et al. 1989; Droupy et al. 1997; Huguet et al. 1981).

The supply of freshly perfused, highly oxygenated blood is required to support the enhanced cellular metabolism associated with erection (with oxygen reduction the smooth muscles are reduced and the intracavernous structures are more fibrotic), and there is a local homoeostatic role as oxygen alters the synthesis of local erectogenic vasodilator substances (Moreland 1998; Sattar et al. 1995b; Kim et al. 1993).

Three main vascular systems supply the anterior perineal region and scrotum via smaller tributaries: the femoral system, which provides the anterior scrotal arteries, via the external pudendal arteries; the internal iliac system, which provides the posterior scrotal arteries via the superficial perineal vessels; and the external iliac system, which provides the cremasteric arteries via the inferior deep epigastric arteries. The external pudendal arteries of the femoral system give off arterial branches at the spermatic cord (Tauber et al. 2003).

From the internal iliac system, the internal pudendal arteries send superficial perineal vessels lateral to the bulbospongiosus and superficial to the superficial perineal membrane. The internal posterior scrotal arteries branch off between the external spermatic fascia and the dartos and travel lateral to the scrotal raphe to supply the dorsal scrotal septum, the posteromedial spermatic-scrotal fascia, and the perineal fat (Tauber et al. 2003; Jordan 2002).

The testicular arteries branch off of the aorta and travel downwards through the spermatic cords to supply the blood to the testes and the upper portions of the epididymis. The testes themselves are invested in a series of distinct tissue layers. From superficial to deep, these are the scrotal skin, dartos, external spermatic fascia, cremasteric muscles, internal spermatic fascia, and the tunica vaginalis, the last of which only provides a testicular covering anterolaterally. Each testis also has an outer tunica albuginea that invaginates into the posterior aspect of the testicle to form the mediastinum testis, which sends out fibrous septa that divide the testicle into numerous lobules (Tauber et al. 2003).

The arteries to the vasa originate from the inferior vesicle or the internal iliac arteries and run posteriorly within the internal spermatic fascia along with the vasa or the ducts of the testes. The cremasteric vessels originate from the inferior epigastric arteries at the internal ring of the inguinal canal and travel with the genital branches of the genitofemoral nerves between the spermatic fascial layers (Tauber et al. 2003; Jordan 2002).

1.3 Penile Venous Outflow

Penile venous return from the pendulous penis occurs through the deep and superficial dorsal veins of the penis, whereas the proximal crura

drain through the cavernous and crural veins (Aboseif et al. 1989; Wespes et al. 1987). The endothelial-lined lacunar spaces of the corpora cavernosa are drained by small venules that form a subalbugineal plexus. These subalbugineal venules coalesce to form emissary veins that penetrate the tunica albuginea and open directly within the deep dorsal vein or through the circumflex system (Hsieh et al. 2012). More often than not one deep dorsal vein exists. Valves and polsters have been identified in the lumen of the deep dorsal vein. The deep dorsal and cavernous veins terminate in Santorini's vesicoprostatic plexus and into the internal pudendal veins. The skin, the prepuce, and the glans are drained by the superficial dorsal veins that communicate with the external pudendal vein and/or the saphenous vein. The bulb is drained by the bulbar veins which drain into the prostatic plexus. The superficial and deep venous systems are interrelated by multiple anastomoses. Thus, the venous system of the penis communicates with the internal iliac vein, spermatic venous plexus, and saphenous vein.

The relationship of the vasculature to the fibro-skeleton is interesting, and the difference of the penile venous and arterial paths is substantial. The veins traverse an oblique path between the outer layers of the tunica albuginea, whereas the arteries take more direct route. This design is facilitating penile erection in that the venous vasculature is susceptible to being compressed (Aboseif et al. 1989; Wespes et al. 1987; Hsieh et al. 2012).

The pampiniform plexuses are collections of veins deep to the internal spermatic layers that drain the testes, eventually consolidating into testicular veins. These plexuses comprise the bulk of the cord (Hsieh et al. 2012).

1.4 Neuroanatomy of the Penis

1.4.1 Peripheral Pathways

The innervation of the penis is both autonomic (sympathetic and parasympathetic) and somatic (sensory and motor) (Steers 1994; Lepor et al. 1985; Halata and Munger 1986; Lue et al. 1984). From the neurons in the spinal cord and peripheral ganglia, the sympathetic and parasympathetic nerves merge to form the cavernous nerves, which enter the corpora cavernosa and corpus spongiosum to effect the neurovascular events during erection and detumescence.

The somatic nerves are responsible for sensation and contraction of the bulbocavernosus and ischiocavernosus muscles (Steers 1994).

1.4.2 Autonomic Pathways

The sympathetic pathway originates from the eleventh thoracic to the second lumbar spinal segments and passes via the white rami to the sympathetic chain ganglia. Some fibers then travel via the lumbar splanchnic nerves to the inferior mesenteric and superior hypogastric plexuses, from which fibers travel in the hypogastric nerves to the pelvic plexus (Steers 1994; Lepor et al. 1985).

Adrenergic nerve fibers and receptors have been demonstrated in the cavernous trabeculae and surrounding the cavernous arteries, and norepinephrine has generally been accepted as the principal neurotransmitter to control penile flaccidity and detumescence. Receptor-binding studies have shown the number of α-adrenoceptors to be ten times higher than the number of β-adrenoreceptors (Levin and Wein 1980).

The parasympathetic pathway arises from neurons in the intermediolateral cell columns of the second, third, and fourth sacral spinal cord segments. The preganglionic fibers pass in the pelvic nerves to the pelvic plexus, where they are joined by the sympathetic nerves from the superior hypogastric plexus (Chuang and Steers 1999).

The cavernous nerves and branches of the pelvic plexus innervate the penis.

Acetylcholine is required for ganglionic transmission (by nicotinic receptors) and vascular smooth muscle relaxation (by muscarinic receptors). Cholinergic nerves have been demonstrated within the human cavernous smooth muscle and surrounding penile arteries, and ultrastructural examination has also identified terminals containing cholinergic vesicles in the same area. It has been suggested that acetylcholine inhibits the sympathetic

nerves and stimulates the release of NO from endothelial cells (Chuang and Steers 1999).

Nitric oxide is synthesized from endogenous L-arginine by NO synthase (NOS) located in the vascular endothelium. Nitric oxide may be synthesized and released as a neurotransmitter by the nonadrenergic/noncholinergic (NANC) neurons after their excitation by either electrical or chemical stimulation (Azadzoi et al. 1992; Saenz de Tejada et al. 1988).

NO released from NANC neurons increases the production of cyclic guanosine monophosphate (cGMP), which in turn relaxes the cavernous smooth muscle (Burnett et al. 1992).

NO diffuses locally into adjacent smooth muscle cells of the corpus cavernosum and binds with its physiologic receptor, soluble guanylyl cyclase. The enzyme catalyzes the conversion of guanosine triphosphate (GTP) to 3′,5′-cyclic guanosine monophosphate (cGMP). This cyclic nucleotide then serves as a second-messenger function by activating protein kinase G, alternatively known as cGMP-dependent protein kinase I (cGKI), which in turn exerts actions involving ion channels and contractile regulatory proteins that regulate the contractile state of corporal smooth muscle (Bush et al. 1992; Hurt et al. 2002).

Other neurotransmitters like vasoactive intestinal peptide or prostaglandin E (PGE-1) interact with different muscular receptors (Shetty and Farah 1999; Lue 2000; Gratzke et al. 2010). They increase the level of adenosine cyclic phosphate (cAMP) and also decrease the intracellular Ca^{2+} and produce relaxation of smooth muscle.

The decay in cytosolic calcium concentration provokes relaxation of the smooth muscle, resulting in dilation of arterial vessels and increased blood flow into the sinusoids of the corpora cavernosa.

Neuronal NO induced by neuronal depolarization and endothelial NO largely generated in response to shear forces brought on by increased blood flow in the penis serve, respectively, as a neurotransmitter initiating the erectile process and as a paracrine factor sustaining the full physiologic response. NO produced by the endothelial cells seems necessary to maintain the erection (Hoffman 1985).

The NO-mediated responses are progressively inhibited as a function of decreasing oxygen tension; reverting to normal oxygen tension restores endothelium-dependent and neurogenic relaxation. Currently, NO is the most likely principal neurotransmitter causing penile erection.

Stimulation of the pelvic plexus and the cavernous nerves induces erection, whereas stimulation of the hypogastric nerve causes detumescence. This clearly implies that the sacral parasympathetic input provokes tumescence, and the thoracolumbar sympathetic pathway induces detumescence. The facilitating action of androgens on penile erectile involves the upregulation of both nNOS and eNOS isoenzymes in the corpora cavernosa. This demonstration correlates with the symptoms presented by aging men: the difficulty of creating an erection but also and mainly maintaining it due to their decreased testosterone level (McConnell et al. 1979).

The sympathetic nervous system maintains the penis in a flaccid state by tonic release of norepinephrine from the nerve terminals that stimulates the α-adrenergic receptors on the cavernosal smooth muscle cells (Saenz de Tejada et al. 1989b).

Norepinephrine and also endothelin-1 and prostaglandin F2α activate receptors on smooth muscle cells to increase the intracellular levels of inositol triphosphate and diacylglycerol via a phospholipase C-mediated pathway. The accumulation of these intracellular messengers facilitates the release of CA^{2+} from stores and the opening of calcium channels on the cell membrane. The increase of intracellular Ca^{2+} concentration results in calcium binding to calmodulin and the activation of myosin light chain kinase, provoking contraction of the smooth muscle cells (Saenz de Tejada et al. 1989b). Supporting pathways in the maintenance of cavernosal flaccidity is the activation of rho-kinase by ras homolog family member A (RhoA), which affects the smooth muscle tone by altering calcium sensitivity (Chitaley et al. 2001).

1.5 Physiology of Erection

At flaccidity, the contracted trabecular smooth muscles allow for venous drainage under conditions of low outflow resistance (Shetty and Farah

1999; Lue 2000; Gratzke et al. 2010). During tumescence, the smooth muscles are relaxed, producing arterial dilatation and a filling of the lacunar spaces. The intracavernous pressure increases slightly, while the penis elongates. Compression of the subalbugineal venous plexus by the lacunar spaces against the tunica albuginea increases the resistance to flow through these vessels (Fournier et al. 1987). The intrapenile blood pressure increases to the infrasystolic pressure making the penis rigid.

The veno-occlusive mechanism depends on the relaxation of the intracavernous smooth muscles after activation of the efferent autonomic nerves, which compress the subalbugineal venous plexus. Therefore, an active process dependent upon neurogenic and endothelial-mediated corporeal lacunar smooth muscle relaxation is responsible for a passive mechanism. As it stretches during tumescence, the tunica albuginea also cuts the emissary veins and completes the veno-restrictive mechanism (Wespes and Schulman 1990). At rigidity, the entire deep venous system outside the corpora is compressed between the albuginea and Buck's fascia.

Blockage of the penile venous outflow during erection cannot be completed because priapism can develop. Elongation of the tunica albuginea, significantly less important at the base of the penis than at its anterior portion, could explain why it should be less effective in compressing the cavernous veins during rigidity and permits venous outflow through this pathway (Wespes and Schulman 1990). Contractions of the bulbocavernosus and ischiocavernosus muscles produced by dorsal nerve stimulation or voluntarily increase the intracavernous pressure and decrease the venous return (Wespes et al. 1990). This voluntary contraction-relaxation of the perineal muscles during intercourse can allow blood suction into the penis facilitating rigid erection. Therefore, the penis represents a closed system, but the brief duration of these contractions prevents the development of ischemia with tissue damage and/or priapism (Wespes and Schulman 1990).

The pressure in the lacunar spaces during rigid erection is the result of the equilibrium between the perfusion pressure of the cavernous artery and the resistance to blood outflow through the cavernous veins. Detumescence results from the vasoconstrictive process of the smooth muscle cells, which reduces the intracavernous pressure and opens the subalbugineal plexus and emissary veins (Shetty and Farah 1999; Lue 2000; Gratzke et al. 2010).

1.6 Clinical Examination in Erectile Dysfunction

Every patient erectile dysfunction must be given a physical examination focused on the genitourinary, endocrine, vascular, and neurological systems. Physical examination may reveal unsuspected diagnoses, such as Peyronie's disease, prostatic enlargement or cancer, or signs and symptoms suggesting hypogonadism (small testes) (Hatzimouratidis et al. 2010). A rectal examination should be performed in patient older than 50 years and mainly in those who might be possible candidates for testosterone therapy.

A general examination ideally should include evaluation of male secondary sex characteristics, gynecomastia, pulses, and peripheral sensations. Blood pressure and heart rate should be measured especially if they have not been assessed thoroughly in the previous 3–6 months (Montorsi et al. 2003; Ghanem et al. 2013). Waist circumference measurement is helpful in counseling the patient about the risks related to obesity and the possibility of metabolic syndrome (Corona et al. 2011). Particular attention must be paid to patients with either known or suspected cardiovascular disease (Ghanem et al. 2013).

1.7 Imaging in Erectile Dysfunction

1.7.1 Assessment of Nocturnal Penile Erection

Each man has nocturnal erections, three or four episodes per night.

The RigiScan device assesses these nocturnal erections and therefore normal erectile function.

At least two consecutive nights of recording are necessary to evaluate penile rigidity (Elhanbly and Elkholy 2012).

1.7.2 Doppler Penile Examination and Dynamic Duplex Ultrasound Penile Blood Flow Evaluation

The ultrasound procedure initially involves scanning the entire penis to observe cavernosal homogeneity, presence of plaques, fibrosis, echogenicity, or calcification.

The dynamic duplex ultrasound penile blood flow evaluation will appreciate the hemodynamic penile status (Sikka et al. 2013). It is a dynamic test requiring intracavernosal injection of a vasoactive agent to stimulate a physiologic erection. Usual when a rigid erection is obtained, most of the time there is no significant vascular alterations. However, when the test does not provoke an erection, the information about vascular status remains limited (Sikka et al. 2013).

The peak systolic velocities in both arteries are then measured using the Doppler blood flow mode. They are considered effective parameters to evaluate arterial competence; ≥30 cm/s indicates definite arterial flow after, whereas <25 cm/s is diagnostic of arterial insufficiency (Lehmann et al. 1999; Aversa and Sarteschi 2007). Conversely, the end diastolic velocity and the corresponding semiquantitative measurement of the resistive index may be informative about penile veno-occlusion normalcy. In association with a normal arterial response, >6 cm/s and <0.6 indicate a corporal veno-occlusive dysfunction is present (Aversa and Sarteschi 2007).

The standard method of diagnosing veno-occlusive dysfunction (VOD) is an organic cause of ED that occurs when an abnormal venous drainage prevents a rigid erection in the presence of a normal penile arterial flow. It should be performed only in patients failing the respond to oral/local therapy and in possible candidates for vascular reconstructive surgery.

1.7.3 Internal Pudendal Arteriography

Arteriography is the most invasive diagnostic test for vasculogenic erectile dysfunction (Delcour et al. 1984). It should be considered only in highly selected cases of young men with a history of pelvic or perineal trauma. This diagnostic procedure is not indicated when operative revascularization is not an option. Conversely, pudendal angiography, in conjunction with embolization of the arterial sinusoid fistula, is first-line therapy for high-flow priapism (Burnett and Sharlip 2013).

1.7.4 Magnetic Resonance Imaging

Magnetic resonance (MR) imaging can clearly delineate the tunica albuginea and can be used to diagnose penile fracture and Peyronie's disease (Uder et al. 2002). It is also useful in cases of priapism; in these cases, intravenously administered contrast material can help assess the viability of the corpora cavernosa and the presence of penile fibrosis (Kirkham 2012). In the assessment of a penile prosthesis, MR imaging provides excellent anatomic information (Moncada et al. 1998).

The key finding in penile fracture is disruption of the low-signal-intensity tunica albuginea, which is well seen on both T1- and T2-weighted images (Burnett and Sharlip 2013).

Rupture of the dorsal vein of the penis is a rare mimic of acute fracture and should be distinguished from a fracture at MR imaging (Nehru-Babu et al. 1999).

Contrast enhancement may be useful for several reasons. First, acute hematoma may be isointense relative to the corpora cavernosa with T1-weighted sequences, so that intracavernosal hematoma is well seen only as an enhancement defect after contrast material administration. Second, in acute fracture, dynamic contrast enhancement may show early focal enhancement at the site of rupture (Uder et al. 2002). In some equivocal cases MR imaging is better than ultrasound, and the diagnosis of rupture may confidently be excluded, thereby obviating surgical exploration.

Penile thrombosis and fibrosis are a cause of low-flow priapism. It is well seen with T1- and T2-weighted sequences and can be confirmed with the use of intravenous contrast material and could so replace biopsy (Hricak et al. 1988).

In Peyronie's disease, US is far superior in the detection of plaque calcification, but the anatomic deformity, including more subtle abnormalities that affect the surgical approach, is better seen with MR imaging (Hauck et al. 2003).

The main indication for MR imaging is the accurate depiction of deformity, tunical thickness, plaque position, and cavernosal diameter in cases in which surgery may be complex.

MR imaging is also clearly superior to physical examination for prostheses with associated pain and deformity and should be considered in difficult cases (Moncada et al. 1998).

References

Aboseif SR, Breza J, Lue TF, Tanagho EA (1989) Penile venous drainage in erectile dysfunction. Anatomical, radiological and functional considerations. Br J Urol 64:183–190

Aversa A, Sarteschi LM (2007) The role of penile color-duplex ultrasound for the evaluation of erectile dysfunction. J Sex Med 4:1437–1447

Azadzoi KM, Kim N, Brown ML, Goldstein I, Cohen RA, Saenz de Tejada I (1992) Endothelium-derived nitric oxide and cyclooxygenase products modulate corpus cavernosum smooth muscle tone. J Urol 147:220–225

Breza J, Aboseif SR, Orvis BR, Lue TF, Tanagho EA (1989) Detailed anatomy of penile neurovascular structures: surgical significance. J Urol 141:437–443

Burnett AL, Sharlip ID (2013) Standard operating procedures for priapism. J Sex Med 10:180–194

Burnett AL, Lowenstein CJ, Bredt DS, Chang TS, Snyder SH (1992) Nitric oxide: a physiologic mediator of penile erection. Science 257:401–403

Bush PA, Gonzalez NE, Ignarro LJ (1992) Biosynthesis of nitric oxide and citrulline from L-arginine by constitutive nitric oxide synthase present in rabbit corpus cavernosum. Biochem Biophys Res Commun 186: 308–314

Campos de Calvalho AC, Roy C, Moreno AP, Melman A, Hertzberg EL, Christ GJ, Spray DC (1993) Gap junctions formed of Connexin 43 are found between smooth muscle cells of human corpus cavernosum. J Urol 149:1568–1575

Chitaley K, Webb RC, Mills TM (2001) RhoA/Rho-kinase: a novel player in the regulation of penile erection. Int J Impot Res 13:67–72

Chuang AT, Steers WD (1999) Neurophysiology of penile erection. In: Carson C, Kirby R, Goldstein I (eds) Textbook of erectile dysfunction. ISIS Medical Media, Oxford

Corona G, Monami M, Rastrelli G, Aversa A, Tishova Y, Saad F, Lenzi A, Forti G, Mannucci E, Maggi M (2011) Testosterone and metabolic syndrome: a meta-analysis study. J Sex Med 8:272–283

Delcour C, Schils J, Wespes E, Schulman CC, Struyven J (1984) Radiologic and hemodynamic studies of sexual impotence of vascular origin. J Radiol 65:761–765

Droupy S, Benoit G, Giuliano F, Jardin A (1997) Penile arteries in humans. Origin – distribution – variations. Surg Radiol Anat 19:161–167

Droupy S, Hessel A, Benoit G, Blanchet P, Jardin A, Giuliano F (1999) Assessment of the functional role of accessory pudendal arteries in erection by transrectal color Doppler ultrasound. J Urol 162:1987–1991

Elhanbly S, Elkholy A (2012) Nocturnal penile erections: the role of RigiScan in the diagnosis of vascular erectile dysfunction. J Sex Med 9:3219–3226

Fournier GR Jr, Juenemann KP, Lue TF, Tanagho EA (1987) Mechanisms of venous occlusion during canine penile erection: an anatomic demonstration. J Urol 137:163–167

Ghanem HM, Salonia A, Martin-Morales A (2013) SOP: physical examination and laboratory testing for men with erectile dysfunction. J Sex Med 10:108–110

Gratzke C, Angulo J, Chitaley K, Dai YT, Kim NN, Paick JS, Simonsen U, Uckert S, Wespes E, Andersson KE, Lue TF, Stief CG (2010) Anatomy, physiology and pathophysiology of erectile dysfunction. J Sex Med 7:445–475

Gu J, Polak JM, Lazarides M, Morgan R, Pryor JP, Marangos PJ, Blank MA, Bloom SR (1984) Decrease of vasoactive intestinal polypeptide (VIP) in the penises from impotent men. Lancet 2:315–318

Halata Z, Munger B (1986) The neuroanatomical basis for the protopathic sensibility of the human penis. Brain Res 371:205–230

Hatzimouratidis K, Amar E, Eardley I, Giuliano F, Hatzichristou D, Montorsi F, Vardi Y, Wespes E, European Association of Urology (2010) Guidelines on male sexual dysfunction: erectile dysfunction and premature ejaculation. Eur Urol 57:804–814

Hauck EW, Hackstein N, Vosshenrich R, Diemer T, Schmelz HU, Bschleipfer T, Schroeder-Printzen I, Weidner W (2003) Diagnostic value of magnetic resonance imaging in Peyronie's disease: a comparison both with palpation and ultrasound in the evaluation of plaque formation. Eur Urol 43:293–300

Hoffman F (1985) The molecular basis of second messenger systems for regulation of smooth muscle contractility: state of the art lecture. J Hypertens 3:53–58

Hricak H, Marotti M, Gilbert TJ, Lue TF, Wetzel LH, McAninch JW, Tanagho EA (1988) Normal penile anatomy and abnormal penile conditions: evaluation with MR imaging. Radiology 169:683–690

Hsieh CH, Liu SP, Hsu GL, Chen HS, Moldysky E, Chen YH, Yu HJ (2012) Advances in understanding of

mammalian penile evolution, human penile anatomy and human erection physiology: clinical implications for physicians and surgeons. Med Sci Monit 18: RA118–RA125

Hsu GL, Brock G, Martinez-Pineiro L et al (1992) The three dimensional structure of the human tunica albuginea: anatomical and ultrastructural levels. Int J Impot Res 4:117–129

Huguet JF, Clerissi J, Juhan C (1981) Radiologic anatomy of pudendal artery. Eur J Radiol 1:278–284

Hurt KJ, Musicki B, Palese MA, Palese MA, Crone JK, Becker RE, Moriarity JL, Snyder SH, Burnett AL (2002) Akt-dependent phosphorylation of endothelial nitric-oxide synthase mediates penile erection. Proc Natl Acad Sci U S A 99:4061–4066

Jordan GH (2002) Scrotal and perineal flaps for anterior urethral reconstruction. Urol Clin North Am 29: 411–416

Kim N, Vardi Y, Padma-Nathan H, Daley J, Goldstein I, Saenz de Tejada I (1993) Oxygen tension regulates the nitric oxide pathway: physiological role in penile erection. J Clin Invest 91:437–443

Kirkham A (2012) MRI of the penis. Br J Radiol 85: S86–S93

Lehmann K, John H, Kacl G, Hauri D, Gasser TC (1999) Variable response to intracavernous prostaglandin E1 testing for erectile dysfunction. Urology 54:539–543

Lepor H, Gregerman M, Crosby R, Mostofi FK, Walsh PC (1985) Precise localization of the autonomic nerves from the pelvic plexus to the corpora cavernosa: a detailed anatomical study of the adult male pelvis. J Urol 133:207–212

Levin RM, Wein AJ (1980) Adrenergic alpha-receptors outnumber beta receptors in the human penile corpus cavernosum. Invest Urol 18:225–226

Lue TF (2000) Erectile dysfunction. N Engl J Med 342:1802–1813

Lue TF, Zeineh SJ, Schmidt RA, Tanagho EA (1984) Neuroanatomy of penile erection: its relevance to iatrogenic impotence. J Urol 131:273–280

Maher E, Bachoo M, Elabbady AA, Polosa C, Bégin LR, Collier B, Elhilali MM, Hassouna MM (1996) Vasoactive intestinal peptide and impotence in experimental diabetes mellitus. Br J Urol 77:271–278

McConnell J, Benson GS, Wood J (1979) Autonomic innervation of the mammalian penis: a histochemical and physiological study. J Neural Transm 45:227–238

Moncada I, Hernández C, Jara J, Hernández L, Lafuente J, Lledó E, Rodriguez E, de Tejada IS (1998) Buckling of cylinders may cause prolonged penile pain after prosthesis implantation: a case control study using magnetic resonance imaging of the penis. J Urol 160: 67–71

Montorsi F, Briganti A, Salonia A, Rigatti P, Margonato A, Macchi A, Galli S, Ravagnani PM, Montorsi P (2003) Erectile dysfunction prevalence, time of onset and association with risk factors in 300 consecutive patients with acute chest pain and angiographically documented coronary artery disease. Eur Urol 44:360–365

Moreland RB (1998) Is there a role of hypoxemia in penile fibrosis: a viewpoint presented to the Society for the Study of Impotence. Int J Impot Res 10:113–120

Nehru-Babu M, Hendry D, Ai-Saffar N (1999) Rupture of the dorsal vein mimicking fracture of the penis. BJU Int 84:179–180

Polascik TJ, Walsh PC (1995) Radical retropubic prostatectomy: the influence of accessory pudendal arteries on the recovery of sexual function. J Urol 154:150–152

Saenz de Tejada I, Blanco R, Goldstein I, Azadzoi K, de las Morenas A, Krane RJ, Cohen RA (1988) Cholinergic neurotransmission in human corpus cavernosum. I. Responses of isolated tissue. Am J Physiol 254(Heart Circ Physiol 23):H468–H472

Saenz de Tejada I, Goldstein I, Azadzoi K, Krane RJ, Cohen RA (1989a) Impaired neurogenic and endothelium-mediated relaxation of penile smooth muscle from diabetic men with impotence. N Engl J Med 320:1025–1030

Saenz de Tejada I, Kim N, Lagan I, Krane RJ, Goldstein I (1989b) Regulation of adrenergic activity in penile corpus cavernosum. J Urol 142:1117–1121

Sattar AA, Schulman CC, Wespes E (1995a) Objective quantification of cavernous endothelium in potent and impotent men. J Urol 153:1136–1138

Sattar AA, Salpigides G, Vanderhaeghen JJ, Schulman CC, Wespes E (1995b) Cavernous oxygen tension and smooth muscle fibers: relation and function. J Urol 154:1736–1739

Shetty SD, Farah RN (1999) Anatomy of erectile function. In: Carson C, Kirby R, Goldstein I (eds) Textbook of erectile dysfunction. ISIS Medical Media, Oxford

Sikka SC, Hellstrom WJ, Brock G, Morales AM (2013) Standardization of vascular assessment of erectile dysfunction: standard operating procedures for duplex ultrasound. J Sex Med 10:120–129

Steers WD (1994) Neuroanatomy and neurophysiology of erection. Sex Disabil 12:17–26

Tauber R, Pfeiffer D, Bruns T (2003) Phlebography: why it is important to study radiological imaging of spermatic veins. Arch Ital Urol Androl 75:62–67

Uder M, Gohl D, Takahashi M, Derouet H, Defreyne L, Kramann B, Schneider G (2002) MRI of penile fracture: diagnosis and therapeutic follow-up. Eur Radiol 12:113–120

Wespes E, Schulman CC (1990) Study of human penile venous system and hypothesis on its behaviour during erection. Urology 36:68–72

Wespes E, Depierreux M, Schulman CC (1987) Penile deep dorsal vein cushions and erection. Br J Urol 60: 174–177

Wespes E, Nogueira MC, Herbaut AG, Caufriez M, Schulman CC (1990) Role of the bulbocavernosus muscles on the mechanism of human erection. Eur Urol 18:45–48

Part II

Gender?

Male-to-Female Transsexualism

2

Ciro Imbimbo and Davide Arcaniolo

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2.1 Introduction

The *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, text revision [DSM-IV-TR], defines gender identity disorder (GID) as a "strong and persistent cross-gender identification and a patient's persistent discomfort with his or her sex and sense of inappropriateness in the gender role of that sex." The current edition of the *Diagnostic and Statistical Manual of Mental Disorders* has five criteria that must be met before a diagnosis of gender identity disorder can be given:

1. There must be evidence of a strong and persistent cross-gender identification.
2. This cross-gender identification must not merely be a desire for any perceived cultural advantages of being the other sex.
3. There must also be evidence of persistent discomfort about one's assigned sex or a sense of inappropriateness in the gender role of that sex.
4. The individual must not have a concurrent physical intersex condition (e.g., androgen insensitivity syndrome or congenital adrenal hyperplasia).
5. There must be evidence of clinically significant distress or impairment in social, occupational, or other important areas of functioning.

This biological sexual orientation does not correspond to the patient's inner perception of him or herself, which, in turn, causes a strong desire to alter his or her natural-born anatomical appearance. The trained mental health professional is obligated to determine if a patient meets the above-stated criteria

V. Mirone (ed.), *Clinical Uro-Andrology*,
DOI 10.1007/978-3-662-45018-5_2, © Springer-Verlag Berlin Heidelberg 2015

for an irreversible gender transposition and if he or she will benefit from sex-reassignment treatment (Cohen-Kettenis and Gooren 1999).

2.2 Epidemiology

When gender identity disorder first came to the attention of professionals, clinical perspectives were largely focused on how to identify candidates for sex reassignment surgery. As the field matured, professionals recognized that some people with bona fide gender identity disorder neither desired nor were to be considered candidates for sex-reassignment surgery. This became problematic in epidemiologic studies. The *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, regrouped different results from different investigations and reported an average prevalence of 1 in 12,000 biological men and 1 in 100,000 biological women. The difference between men and women varied depending on the time period, the country, and the study. In the majority of the studies, there were more men than women among the sex-change applicants, with an average ratio being 1:3 (women to men) (Ravenna 1998).

2.3 Diagnosis

Transsexualism is not a homogeneous phenomenon. Diagnosing transsexualism is quite difficult because the results of psychological testing are not conclusive. Standards of care of the International Harry Benjamin Gender Dysphoria Association have established a diagnostic process divided into two phases for patients seeking SRS treatment. In the first phase a formal diagnosis is made using DSM or International Classification of Diseases (ICD) criteria. Risk factors are estimated to ensure that the individual can tolerate the life changes that SRS will bring. In the second diagnostic phase, the patient has to live permanently in the role of the desired sex. The clinicians have to inform the family members, and the patient must choose a new first name. In this phase the patient can start hormonal therapy with different times and modalities depending upon the treatment center. A certain number of psychotherapy sessions are also required by some clinicians; however, psychotherapy is not mandatory.

The differential diagnosis should include nonconformity to stereotypical sex role behavior, transvestic fetishism, gender identity disorder not otherwise specified (with a concurrent congenital intersex condition), and schizophrenia (Belgrano et al. 1999).

2.4 Treatment

2.4.1 Psychotherapy

Psychotherapy is a series of highly refined interactive communications between a professional who is knowledgeable about how people suffer emotionally and how the suffering may be alleviated and one who is experiencing gender distress. The psychotherapeutic sessions initiate a developmental process by enabling a person's history to be appreciated, current dilemmas understood, and unrealistic expectations and self-destructive behavior identified. The usual objectives of psychotherapy are the enabling of a long-term, stable lifestyle with realistic chances for success in relationships, education, work, and healthy gender and role identification. Gender distress often impedes relationships, work, and educational goals. Typically psychotherapy consists of regularly held 50 min sessions. The therapist should make it clear that it is the patient's right to choose psychotherapy among many therapeutic options. Ideally, psychotherapy is a collaborative effort. The therapist must be certain that the patient understands the concepts of eligibility and readiness because they must cooperate in defining the patient's problems and in monitoring progress in dealing with them. Benefits from psychotherapy may be attained at every stage of gender evolution. This includes the postsurgical period when the anatomic obstacles to gender comfort have been removed and the transsexual continues to feel a lack of genuine comfort and skill in living in the new gender role. Psychotherapy can be beneficial to people who are merely gender confused as well as for those desiring sex reassignment

Table 2.1 Absolute and relative contraindications for hormone therapy in M-to-F transsexuals

Absolute contraindications	Severe diastolic hypertension
	Thrombophlebitis or thromboembolic disease
	Severe hepatic dysfunction
	Cerebrovascular disease
Relative contraindications	Heavy cigarette consumption
	Family history of breast cancer
	Hyperprolactinaemia
	Marked obesity (WHR 0.95)

surgery. In these cases psychotherapeutic intervention may help people to better understand and cope with gender issues and to arrive at alternative options to solving their problems. Treatment in psychiatric hospitals may be needed for those suffering from severe psychiatric conditions (American Psychiatric Association 2000; Michel et al. 2001).

2.4.2 Hormonal Therapy

Before administering hormonal therapy, the endocrinologist should perform a careful anamnesis, a complete clinical examination, and a basal hormonal checkup in order to detect possible contraindications. Relative and absolute contraindications for hormone therapy are summarized in Table 2.1. The desired effects of hormonal treatment are decrease in blood testosterone, increase in blood estradiol, mammary gland hyperplasia, a decrease in erections, reduction of facial hair, modification of speech, and gynoid fat deposit. Patients must be carefully advised about possible undesirable side effects of hormonal treatment such as thromboembolic disorders, depression, decreased libido, hyperprolactinemia, and an increase in the bilirubin blood levels which are the most prevalent. Guidelines on hormonal treatment are summarized in Table 2.2.

Table 2.2 Guidelines on hormone therapy

Phase	
Presurgical A.1.: Suppression of the original sex characteristics (optional)	LHRH superagonists (i.m. monthly?) and/or spironolactone (100 ± 200 mg/day) or cyproterone acetate (50 ± 100 mg/day)
Presurgical A.2.: Induction of designated sex characteristics	Ethinyl estradiol (50 ± 100 mg/day) or conjugated estrogen (1.25 ± 2.50 mg/day) or estradiol benzoate, estradiol phenylpropionate (25 mg/2 weeks) *Optional* Spironolactone (100 ± 200 mg/day) or cyproterone acetate (50 ± 100 mg/day)
Postsurgical B.: Post-castration	Estrogens (see A.2.) or transdermal form (50 ± 100 mg/day) *Optional* Progesterone (100 mg/day for 2 weeks/month) or classic postmenopausal hormone therapy

2.4.3 Real-Life Experience

The act of fully adopting a new or evolving gender role for the events and processes of everyday life is known as the real-life experience. The real-life experience is essential in the transition process to the gender role that conforms with personal gender identity. Since changing one's gender role has immediate profound personal and social consequences, the decision to do so should be preceded by a full awareness of what the familial, vocational, interpersonal, educational, economic, and legal consequences are likely to be. Professionals have a responsibility to discuss these predictable consequences which represent external reality issues that must be confronted in order to successfully assume the new gender role. These factors can be quite different from the personal happiness stemming from the new gender role that is envisioned prior to the real-life experience. When clinicians assess the quality of a person's real-life experience in the new gender role, the following abilities are estimated:

1. The ability to maintain full- or part-time employment
2. The ability to thrive as a student
3. The ability to function in community-based volunteer activities
4. The ability to undertake any combination of items 1–3
5. The ability to acquire a new (legal) first or last name
6. The ability to provide documentation that people other than the therapist can predict that the patient will function in the new gender role.

Surgical treatment for a person with a gender identity disorder is not merely another elective procedure. Typical elective procedures traditionally involve only a private mutually consenting contract between a suffering person and a technically competent surgeon. Surgeries for GID can be undertaken only after a comprehensive evaluation by a qualified mental health professional has been conducted. Surgery may then be performed once written documentation testifies that a comprehensive evaluation has been made and that the person has met the eligibility and readiness criteria. By following this procedure the mental health professional, the physician prescribing hormones, the surgeon, and the patient all share in the responsibility of taking the decision to make irreversible changes to the body. The patient who has decided to undergo genital or breast surgery, however, tends to view the surgery as the most important and effective treatment for correcting the underlying problem. Surgical procedures may include orchiectomy, penectomy, vaginoplasty, and augmenting mammaplasty. Vaginoplasty requires both skilled surgical procedure and competent postoperative treatment. Additive mastoplasty may be performed prior to vaginoplasty if the physician prescribing hormones and the surgeon have both attested that breast enlargement after undergoing hormonal treatment for 2 years is not sufficient for comfort in the social gender role. Other surgeries that may be performed to assist in feminization include: reduction thyroid chondroplasty, suction-assisted lipoplasty of the waist, rhinoplasty, facial bone reduction, facelift, and blepharoplasty. Unlike genital reconstruction therapy, these surgeries do not require letters of recommendation from mental health professionals. Patients who elect this procedure should wait until all other surgeries requiring general anesthesia with intubation are completed in order to protect their vocal cords.

2.5 Vaginoplasty

A male-to-female gender surgical reconversion can be performed using several different techniques; however, all of them share a few basic common surgical steps:

1. Bilateral orchidectomy
2. Penile disassembling leading to separation of urethral corpus spongiosum, corpora cavernosa, glands, and dorsal neurovascular bundle
3. Excision of corpora cavernosa and distal urethra
4. Preparation of a urethral stump and urethrocutaneous anastomosis
5. Creation of a prostatorectal space which allows to allocate the neovagina
6. Vulvoplasty

At present, the most widely used surgical techniques are:

1. Simple penile skin inversion
2. Penoscrotal flap
3. Onlay urethral flap (Perovic's technique)
4. Enterovaginoplasty

2.6 Simple Penile Skin Inversion

After anesthesia is induced, the patient is placed in the lithotomy position. A vertical perineal incision is made from the base of the penis to the midline of the scrotum to a point situated 1 cm above the anal verge. The incision is extended through the subcutaneous tissue in order to expose the urethral corpus spongiosum and corpora cavernosa bilaterally. A bilateral orchidectomy is performed by dissecting and suturing both spermatic cords at the level of external inguinal rings. Once this is done, the proximal ends of these structures will then retract into the inguinal canal. Once this happens, the external inguinal ring is closed bilaterally so as to avoid future weakness that can lead to inguinal hernia. The next step is the penile degloving where the

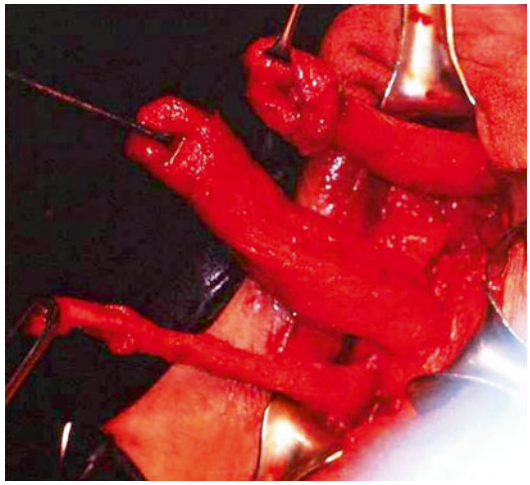


Fig. 2.1 Penile disassembling. The penile skin is severed from the corpus spongiosum and the corpora cavernosa. The glans remains with the penile skin tube

penis is stretched and two circumferential incisions through the penile skin are made; one at the base of the penis and the other distally immediately under the glans. The penile skin with the glans penis is severed from the corpus spongiosum and the corpora cavernosa. The glans remains with the penile skin tube (Fig. 2.1). Through sharp dissection the penile skin is then isolated from the shaft and then reverted and placed around a silicone vaginal mold. At the tip of the mold, the penile skin is closed with a running absorbable suture. This sutured end will become the apex of the neovagina. Following this step the corpus spongiosum is separated from the corpora cavernosa. The corpora cavernosa are cut in the midline, and hemostatic sutures are placed through the proximal base under the pubic ramus.

The section of each corpus cavernosum should be made as proximal as possible, and a limited amount of tissue should remain. A running absorbable suture is routinely performed on the residual erectile tissue in order to avoid painful erection during sexual arousal. The bulbospongiosus muscle is then severed, and the corpus spongiosum is mobilized. The central tendon of the perineum is incised, and a careful, blunt dissection is performed in order to create a wide space between the rectum and prostate where the neovagina will be placed (Fig. 2.2). The Denonvilliers fascia is then identified, and the blunt dissection continues through this avascular plane, transecting the medial fibers of the levator ani muscles in order to obtain an optimal depth. The inverted penile skin tube distended with the vaginal mold is placed in the perineal neocavity. When the patient wishes to have external sensitivity with the creation of a neoclitoris, only a quarter of the glans is left uncovered in order to form the clitoris, while three-quarters are de-epithelialized and placed subcutaneously to ensure a deep internal sensitivity. The base of the penile cylinder is fixed to the periosteum of the pubis by heavy nonabsorbable traction sutures. An elliptical 1.5 cm incision is then performed on the anterior wall of the neovagina by passing the adequately shortened urethra through this incision and suturing it with 4-0 absorbable sutures to the skin. The most posterior aspect of the skin tube is sutured to the posterior aspect of the initial incision. The sutures are continued laterally and frontally in order to form the labia majora. Finally, if necessary, cosmetic refinements can be made such as the reduction of excessive skin of the labia majora and the creation of a labia minora. At the conclusion of the procedure, a Foley catheter is inserted and a compressive dressing applied. The Foley catheter is removed after 5–7 days (Glenn 1980).

2.7 Penoscrotal Flap

The penoscrotal flap is the most widely used vaginoplasty technique in male-to-female transsexualism. This technique is particularly advisable when a penis of a small dimension does not permit the penile skin inversion technique. With the patient under general anesthesia placed in a lithotomic position, an inverted U-shape incision on the posterior aspect of the scrotum is performed (Fig. 2.3). A pedicle scrotal flap is then created taking care to carefully preserve the subcutaneous vascularization (Figs. 2.4 and 2.5). An ensuing penile degloving is conducted by both distal and proximal dissections. The penile and scrotal flap will constitute the anterior and posterior wall of the neovagina, respectively. The corpus spongiosum is then isolated starting from the crura up to

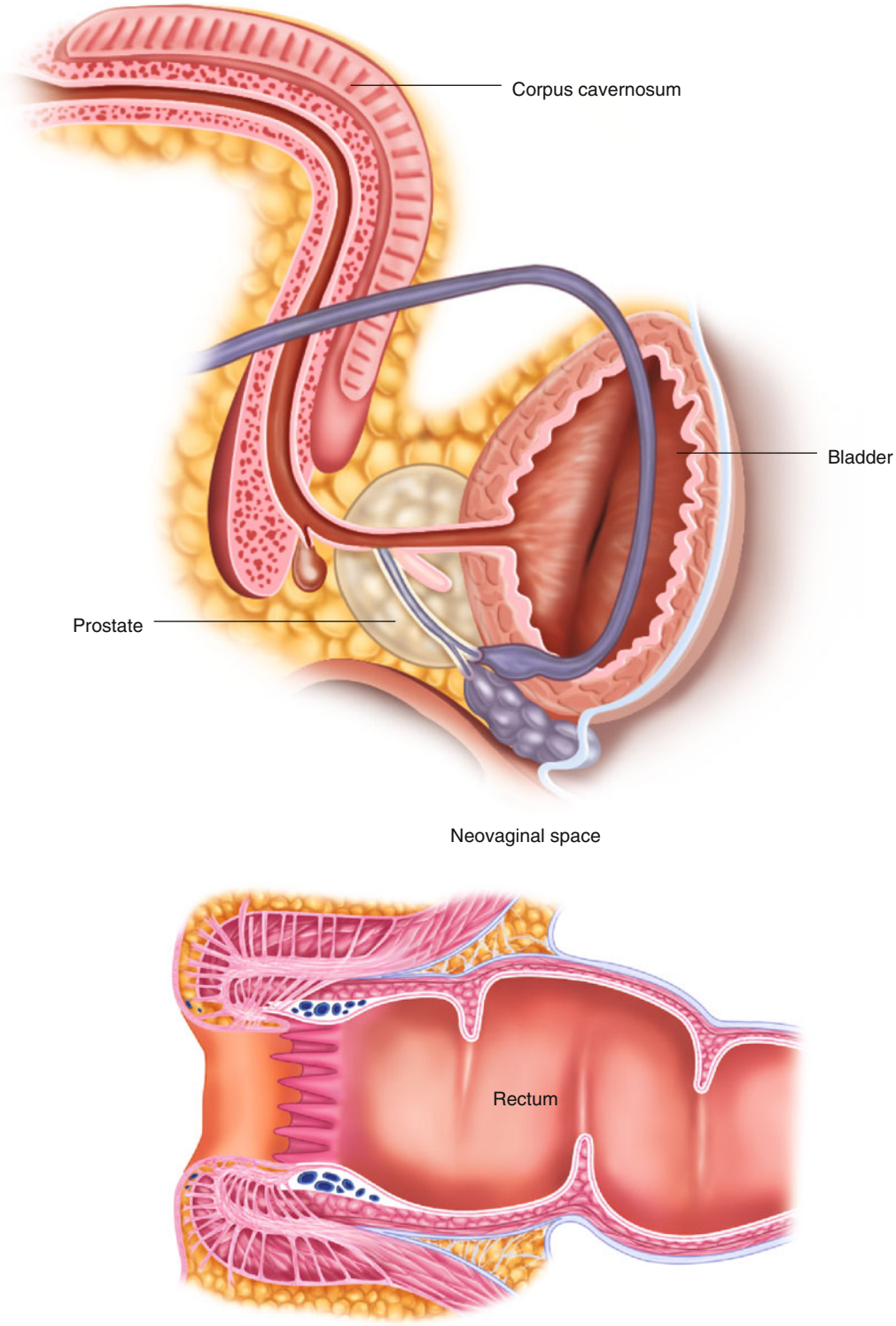


Fig. 2.2 Creation of the neovaginal space. *B* bladder, *R* rectum, *P* prostate, *CC* corpus cavernosum

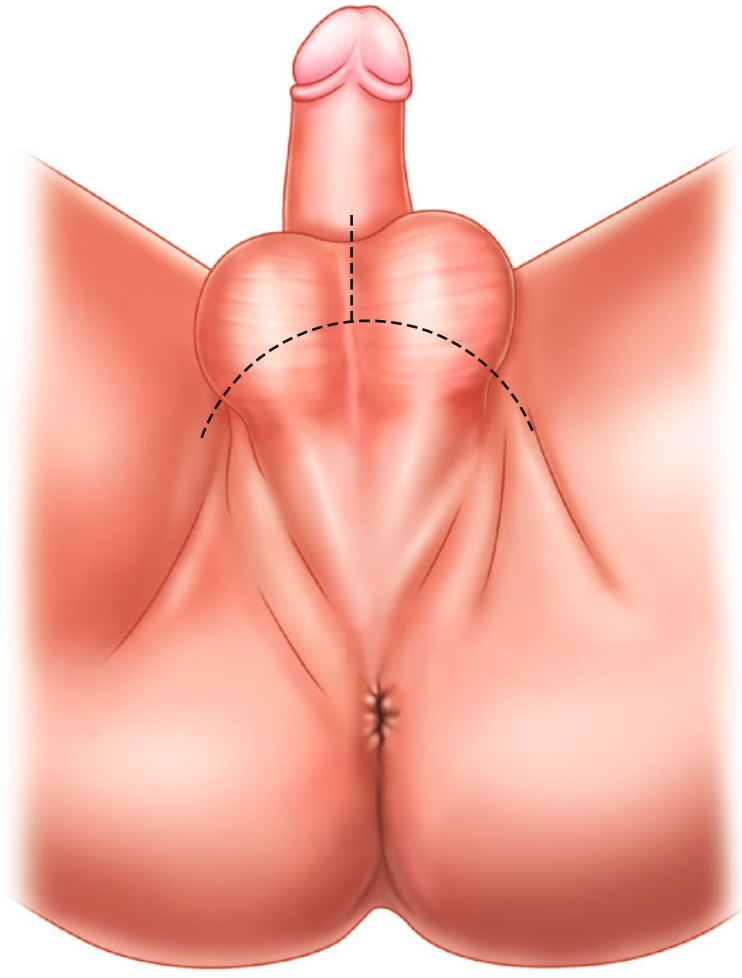
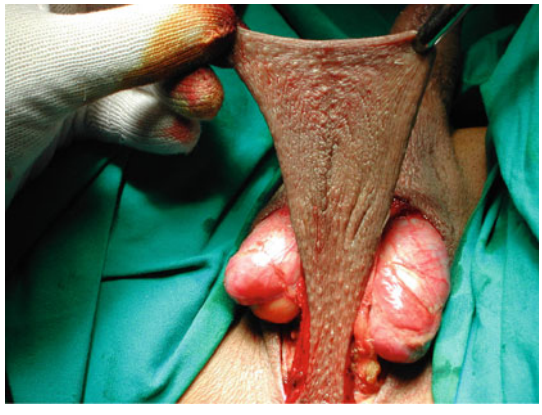
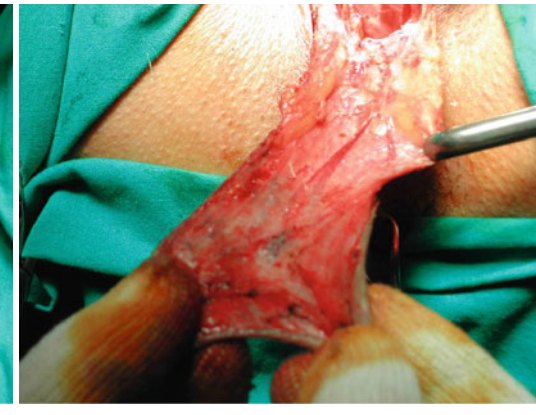


Fig. 2.3 Inverted U-shape incision of the scrotum





Figs. 2.4 and 2.5 Pedicle scrotal flap with subcutaneous vascularization carefully preserved

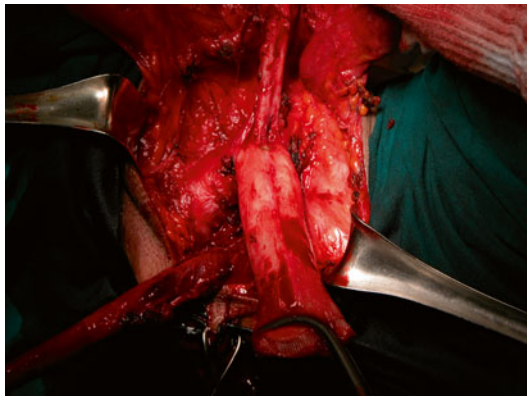


Fig. 2.6 Penile disassembling. Corpora cavernosa are separated from penile skin and glans with neurovascular bundle

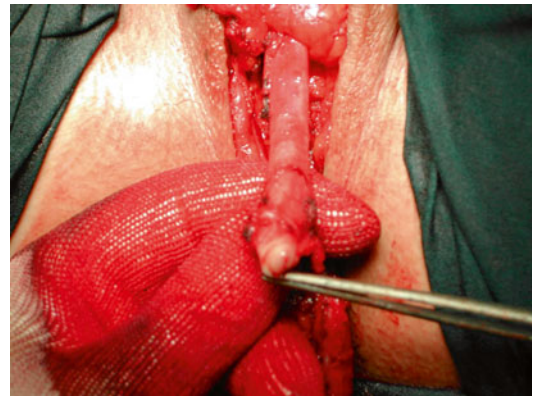


Fig. 2.7 Reconstruction of neoclitoris from penis glans

the penile glans. Through a bilateral incision of the Buck's fascia, a plane is created between the tunica albuginea and the dorsal neurovascular bundle whose connection to the glans is carefully preserved. The plane is initially developed at the level of the distal part of the penis. The glans can now be safely detached from the corpora cavernosa, and neurovascular bundle isolation can be carried out in a retrograde fashion. At this point all the anatomical components involved are now disassembled (Fig. 2.6). A double hemostatic stitch is passed through the crura of each corpus cavernosum. The corpora are then excised as proximally as possible, erectile tissue is cauterized, and residual bleeding controlled with a running suture. Before proceeding with the steps that follow, a bilateral orchidectomy is performed. A V-shape incision is performed on the glans, and a cuneus of glandular tissue is used for neoclitoris reconstruction (Fig. 2.7). In order to prevent inhestetism and uncomfortable bulging in the anterior vaginal wall, a reduction of the urethral bulb is performed with a nonabsorbable suture, taking care not to cause bladder outlet obstruction. After incision of the central tendon of the perineum, a plane is developed between the prostate and the rectum in order to expose the Denonvilliers fascia. The penile skin is then detubularized to obtain a pedicle flap, taking care to preserve vascularization. The penile and scrotal flaps are assembled together through an interrupted absorbable suture to constitute the neovagina (Fig. 2.8). The fixation

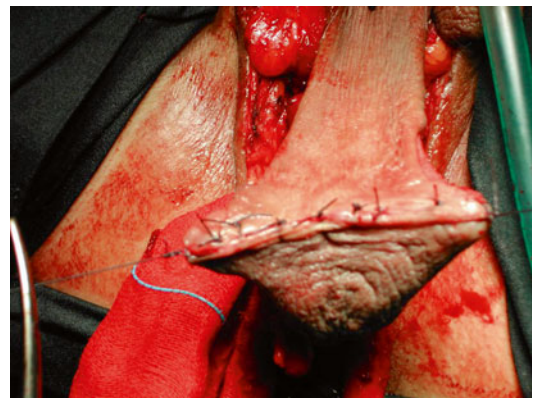


Fig. 2.8 The penile and scrotal flaps are assembled together through an interrupted absorbable suture to constitute the neovagina

of the cul-de-sac in the retroprostatic space is crucial to prevent the neovagina from prolapsing. A Prolene stitch is passed through the Denonvilliers fascia, and both ends of the suture are passed through the penoscrotal flap at the level of the cul-de-sac. The suture is then tied while a vaginal valve keeps the neovagina in position, obtaining optimal fixation (Fig. 2.9). A small incision on the anterior vaginal wall is performed to allocate the neoclitoris. The urethra is conveniently reduced and then is passed through a second incision which is performed more ventrally. The urethra is then spatulated. Possible bleedings can be controlled with a LigaSure device. The

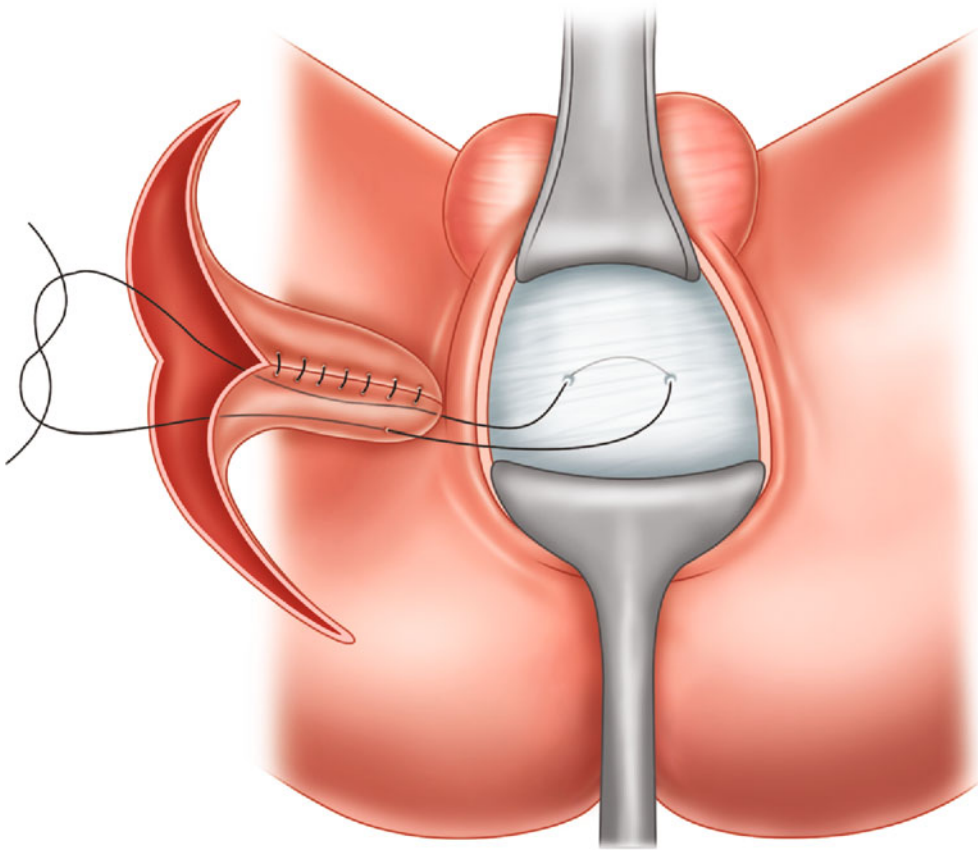


Fig. 2.9 A Prolene stitch is passed through the Denonvilliers fascia, and both ends of the suture are passed through the penoscrotal flap in order to obtain the fixation of the cul-de-sac in the retroprostatic space

urethrocutaneous anastomosis is then carried out with interrupted absorbable sutures. A hemostatic sponge is wrapped around the neomeatus to control residual bleeding. After reconstruction of the labia from the scrotal skin, a vaginal tutor is left in position (Fig. 2.10). The catheter is removed 5 days after surgery, and the patient is discharged after 7 days (Glenn 1980; Meyer et al. 2001; Small 1987).

2.8 Vaginoplasty According to Perovic's Technique

In the Perovic's vaginoplasty technique, the neovagina is created from an inverted pedicled island penile skin flap and a vascularized urethral flap. After a bilateral orchidectomy, as has been described for other techniques, the penis is disassembled into its anatomical components (corpora cavernosa, the glans cap with the urethra and its neurovascular bundle, and the vascularized penile skin). The corpora cavernosa are excised as proximally as possible, the erectile tissue is destroyed, and the tunica albuginea is sutured with 2-0 absorbable sutures. The glans is divided into two parts, ventral and dorsal, as the dorsal part of the glans will form the neoclitoris. To achieve this, the glans is reduced by severing the central ventral tissue and leaving the sides of the glans intact in order to avoid possible injuries to the neurovascular bundle. The sides of the dorsal half of the glans are then de-epithelialized and sutured to obtain a conical shape which is necessary for the construction

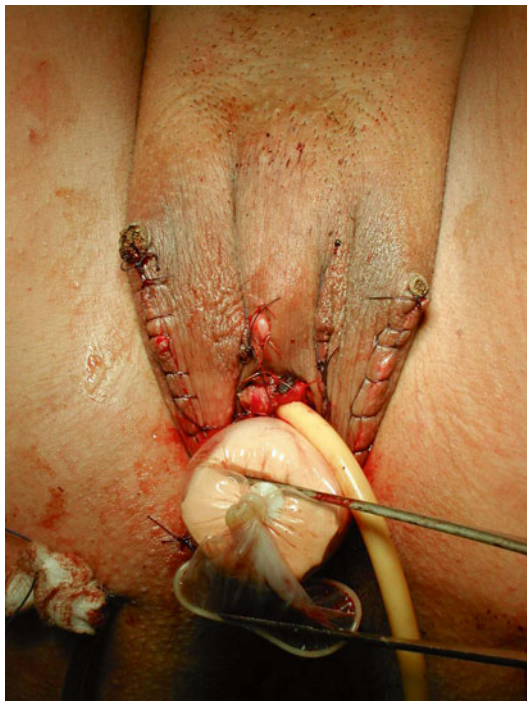


Fig. 2.10 At the end of operation, a vaginal tutor and a Foley catheter are placed

of the neoclitoris. The ventral part of the glans which is still connected to the urethra will become the neocervix at the base of the neovagina. The bulbospongiosus muscle must be carefully separated from the bulbar urethra to preserve the fascial sheath. The urethra is then spatulated and used to create the mucosal part of the neovagina. Any bleeding in the bulbar urethra during this phase can be controlled with hemostatic sutures without using electrocautery so as to preserve the vascularization of the urethral flap. The urethra is then shortened, and the neoclitoris is placed above the new urethral meatus. When reconstructing the neovagina, a vascularized island tube flap is molded from the skin of the penile body and prepuce. The incision is performed circa 2 cm above the base of the mobilized penile skin in order to obtain an extended vascularized pedicle for the tube. A hole is then made at the base of the pedicle to transpose the urethral flap. On the dorsal side of the skin tube flap, only the skin is incised, whereas the vascularized subcutaneous tissue remains intact. The urethral flap, which is transposed through

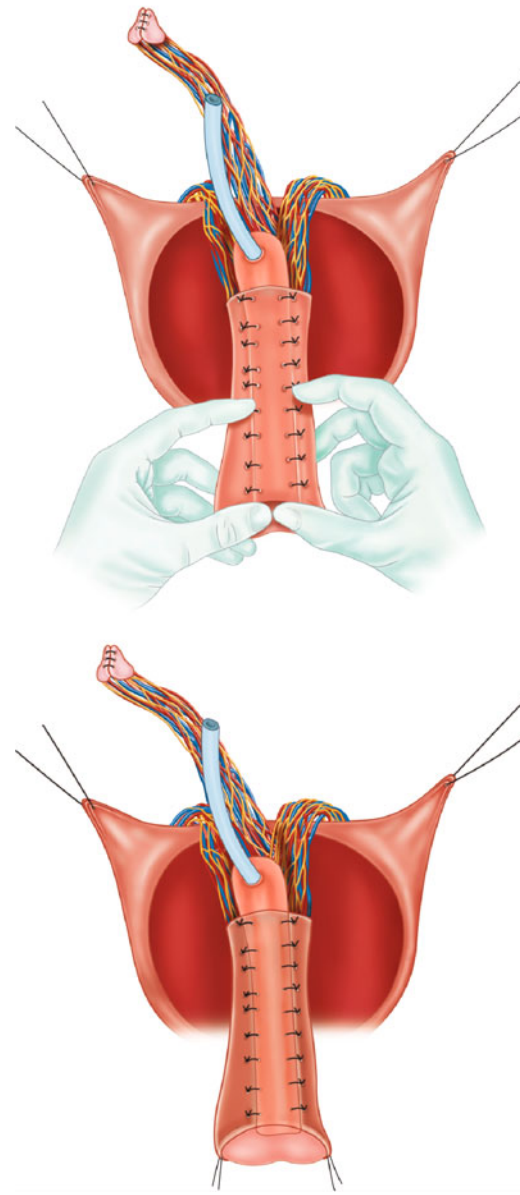


Fig. 2.11 Perovic's technique. The urethral flap is embedded into the skin tube and sutured

the pedicle hole, is embedded into the skin tube and sutured (Fig. 2.11). The bottom of the tube is closed with the distal part of the urethra and/or the remaining ventral half of the glans cap after the de-epithelialization of its inner side, as previously described. The tube, consisting of the skin and urethral flap, is then inverted thereby forming the

neovagina. If there is insufficient penile skin, the short skin tube and long urethral flap will not be in proportion. The vagina can then be formed in two ways. The proximal part at the base of the vagina is formed only by the urethral flap, which initiates secondary epithelialization. If the tube pedicle is too short to place the tube into the perineal cavity, the neovagina is created using the vascularized urethral flap and free penile skin grafts. In this case the vascularized urethral flap plays a key role in creating the new vagina. The space for the allocation of the neovagina is created in the perineum as has been described for the other techniques. The modified Stamey procedure is used to fix the neovagina within the perineal cavity. Two 15° angled Stamey needles penetrate through the rectus to the left and right of the midline at the upper border of the pubic symphysis. The needles then enter laterally into the neocavity from the bladder neck. In the empty bladder the Foley catheter balloon, which is easily palpable, enables the determination of the exact location of the bladder neck. A polypropylene U suture (0-0) in the middle lateral part of the neovagina is threaded through the eye of the needle, and the needle is withdrawn suprapubically. Both ends of the suture are pulled out of the skin of the prepubic area and knotted over bolsters under mild tension, so as to avoid necrosis of the penile flap where the sutures penetrate its wall. At this point the neovagina is placed deep in the perineal cavity. The next step consists of a vulvoplasty. The labia minora are formed by the remaining parts of the base of the penile skin which are sutured to the de-epithelialized area of the neoclitoris. The labia majora are created by the refinement of the original scrotal skin. A perivaginal Jackson-Pratt drain is left for 3 days. The urethral catheter and vaginal packing (a condom filled with soft material) are removed 7 days after surgery (Perovic et al. 2000).

2.9 Enterovaginoplasty

Enterovaginoplasty is a widely used technique in patients affected with vaginal aplasia caused by Mayer-Rokitansky-Kuster-Hauser syndrome but which can also be used in transsexual patients. The advantages of using this technique is the possibility of creating a neovagina of sufficient length and appearance that is similar to a natural vagina. Additionally, it is the only method that provides a vaginal lining with natural lubrication. This technique is the best choice for transsexual patients who had previously undergone a penectomy and orchidectomy as well as for patients with dissatisfactory vaginoplasty results.

2.9.1 Ileal Vaginoplasty

To create a neovagina from the ileum, the patient is put under general anesthesia and positioned in a supine lithotomic position in order to achieve a good intra-abdominal exposure as well as gain wide access to the perineum and introitus. A simultaneous abdominal perineal approach is used. A midline or Pfannenstiel approach is then performed, and the pouch of Douglas is accessed. A Hegar sound is inserted into the distal vaginal segment, and the peritoneal reflection is opened. The vaginal vault is then isolated and completely mobilized. When performed after prior surgery, this step of the operation is generally very difficult due to scars and fibrosis that obliterate the natural tissue planes. By way of a blunt dissection, a surgical plane is developed between the urethra and rectum. Careful attention must be paid to prevent damage to the surface of the rectum and the urethra. It is important to create a large enough space for the bowel segment to fit easily and to enable mobilization of the vaginal vault to allow a capacious, well-vascularized and tension-free anastomosis. The ileum is then extracted, and an ileal loop which more easily reaches the pelvis is formed at about 20 cm from the ileocecal valve. Vascularization of the loop is preserved using the standard transillumination technique. In most patients there is a normal distal vaginal segment that can be used for anastomosis to the bowel segment. In these cases a 12 cm segment is isolated, and intestinal transit is reestablished. The isolated segment is detubularized and transversally retubularized in order to configure the roof of the neovagina. The proximal end of the

conduit is closed with two layers of absorbable suture material. In patients with an inadequate distal vagina, the bowel segment must be longer in order to be anastomosed directly to the perineum. In such cases, two adjacent segments of 12 cm long ileum are isolated. Each segment is detubularized, and the resulting flaps are attached and retubularized transversally. In this way a 10–12 cm length tube with two long branches separated by two insertions of mesentery is created. The ileal segment is brought to the perineum with as little tension as possible in order to allow for a tension-free anastomosis. Ileo-cutaneous anastomoses with interrupted absorbable sutures (Monocryl 3-0) are then performed using a perineal approach. The laparoscopically assisted techniques are successfully used for isolation and mobilization of the vaginal vault, mobilization of the ileal segment, and to assist the vaginal anastomosis. An inflatable silicon vaginal tutor is then introduced into the vaginal cavity and is maintained all day long for 7 days. The catheter is removed after 5 days. It is important to avoid washing the neovagina with substances that can damage or irritate the ileum, and therefore sterile saline solution is recommended in the first postoperative month.

2.9.2 Rectosigmoidal Vaginoplasty

This operation can be performed with the help of a general surgeon. The general surgery team isolates the rectosigmoid intestinal flap, while the urologists create the vaginal cavity by dissecting the area between the penis and rectum. The blood supply of the rectosigmoid intestinal flap emanates from the superior hemorrhoidal artery from the inferior mesenteric artery. Innervation of the flap was from the autonomic system, with sympathetic (inferior mesenteric and hypogastric nerve) and parasympathetic components (hypogastric plexus). When isolating the rectosigmoid intestinal flap, an 8–12 cm length of rectosigmoid is resected, keeping the superior hemorrhoidal artery and then performing an end-to-side anastomosis between the remaining sigmoid colon and rectum using an intraluminal stapler. The proximal portion of the rectosigmoid flap was closed with 3-0 Vicryl sutures. In patients with the penis and scrotum intact, a penectomy and orchiectomy is executed, and a urethral opening is constructed at the proper site. A clitoroplasty using the penile glans is performed in patients who desire a clitoris; however, for patients who do not want a constructed clitoris as it is usually unsatisfactory due to its deformity, the remaining distal penile crura are sutured to each other and then attached to the anterior portion of the urethral orifice in substitution of a clitoris. This procedure offers patients excellent sexual sensitivity. The bulbospongiosus muscle is stripped of the bulky urethral portion and is used to augment the new labia majora. In the orchiectomy, the testes and epididymis are removed but the spermatic cord and surrounding tissue are preserved to provide sufficient volume in the labia majora. For the penectomy patients, a vaginal cavity is made by incising the transversus perinei superficialis muscle and fibrous connections. Bundles of puborectalis and rectovesicalis muscles must be cut to create a cavity of sufficient size. After complete blunt dissection of the Denonvilliers fascia (septum rectovesicale), the prepared rectosigmoid flap is transferred to the new vaginal cavity through the peritoneal opening of the peritoneal reflex region. The end of the rectosigmoid flap is then sutured to the skin of the new vaginal orifice. One or two Silastic drains are placed inside the new vaginal wall through the vaginal orifice, and a suction drain is inserted in the abdominal cavity. A sponge packing is inserted into the new vaginal cavity for a tight approximation of the rectosigmoid flap and the surrounding tissue (Trombetta et al. 2005).

2.10 Neovaginal Expanding Devices

The neocavity which is created in the perineal space among the rectum, the membranous urethra, and the anterior section of the prostate

Fig. 2.12 Expanding device constituted of a polyurethane foam body wrapped with an expanding silicone cylinder which may expand under atmospheric pressure

should be dilated and sustained by the introduction of an expanding device which often remains in place for many months after the operation. Usually these devices are constituted of a polyurethane foam body wrapped with an expanding silicone cylinder which may expand under atmospheric pressure (Fig. 2.12). A cylindrical shape with round edges is needed in order to avoid excessive compression in specific points and to ensure a uniform distribution of the forces. The volume of the device is regulated by an opening valve which ensures enough constant pressure to avoid contractions or stenosis. It is possible to drain eventual secretions and conduct washings through the central tube with sterile solutions in the postoperative care. The size of the device can vary from 3 to 5 cm in diameter and from 9.5 to 16 cm in length. The choice of a suitable size of the expanding device is crucial in allowing easy insertion and avoiding difficult removal.

2.11 Complications

Vaginoplasty surgical complications are common in all the techniques described above. All potential complications can be divided into intraoperative complications, short-term postoperative complications, long-term postoperative complications, and inhestetism (Table 2.3).

Table 2.3 Complications of vaginoplasty

Intraoperative complications	Rectal injuries
	Neurovascular bundle injuries
Short-term postoperative complications	Urethral perimeatal bleeding
	Neovagina-rectal fistula
	Penile or scrotal cutaneous cylinder necrosis
	Neoclitoris necrosis
	Vaginal abscess
	Wound infection
Long-term postoperative complications	Neovaginal stenosis
	Aditus
	Deep
	Neovaginal prolapse
	Urethral meatus stenosis
	Type 3 stress incontinence
Inhestetisms	Scrotiform aspect of main labia
	Neoclitoris hypertrophy
	Persistence of an exuberant fragment of corpus cavernosum
	Maintenance of bulbar urethra
	Superior or posterior neolabial commissural inhestetisms

References

Belgrano E, Fabris B, Trombetta C (1999) Il Transessualismo. Identificazione di un percorso diagnostico e terapeutico. Editrice Kurtis, Milano

Cohen-Kettenis PT, Gooren LJG (1999) Transsexualism: a review of etiology, diagnosis and treatment. J Psychosom Res 46(4):315–333

American Psychiatric Association (2000) Diagnostic and statistical manual of mental disorders, 4th edn, text rev. doi: 10.1176/appi.books.9780890423349

Glenn JF (1980) One stage operation for male transsexuals. J Urol 123:396–398

Meyer WIII, Bockting W, Cohen-Kettenis PT, Coleman E, Di Ceglie D, Devor H et al (2001) The standards of care for gender identity disorders – sixth version. http://www.symposion.com/ijt/soc_2001/index.htm. Feb 2001

Michel A, Mormont C, Legros JJ (2001) A psycho-endocrinological overview of transsexualism. Eur J Endocrinol 145:365–376

Perovic SV, Stanojevic DS, Djordjevic MLJ (2000) Vaginoplasty in male transsexuals using penile skin and a urethral flap. BJU Int 86:843–850

Ravenna AR (1998) Gender identity disorder (DSM IV 302.85) ratified by the "Osservatorio Nazionale sull'Identità di Genere – ONIG" in June 1998. IJT 2,4. http://www.symposion.com/ijt/ijtc0602.htm

Small MP (1987) Penile and scrotal inversion vaginoplasty for male to female transsexuals. Urology 22(6):593–597

Trombetta C, Liguoria G, Siracusano S, Bortul M, Belgrano E (2005) Transverse retubularized ileal vaginoplasty: a new application of the Monti principle – preliminary report. Eur Urol 48:1018–1024

Female to Male Transsexualism

3

Giulio Garaffa and David J. Ralph

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3.1 Introduction

Transsexualism (TS) or gender identity disorder (GID) can be defined as a condition of strong and persistent cross-gender identification that stems from a persistent patient's discomfort with his/her sex and a sense of inappropriateness in the gender role of that sex. This disturbance is not associated with any physical condition, chromosome abnormality or any mental disorder and is usually accompanied by the wish to make his or her body as congruent as possible with the preferred sex through surgery and hormone therapy (Diagnostic and statistical manual of mental disorders 1980, 1994; World Health Organization 1994; Cauldwell 1949; Hirschfeld 1923).

3.2 Female to Male Sex Reassignment Surgery

Gender reassignment surgery for the female to male transsexual involves breast surgery, total abdominal hysterectomy with salpingo-oophorectomy, vaginectomy and construction of the external male genitalia.

Ideally, the goal of total phallic construction is the creation in a few surgical steps and with minor donor site disfigurement of a cosmetically acceptable sensate phallus with incorporated neourethra, to allow patients to void while standing in a male urinal and with enough bulk to house the cylinder of a hydraulic erectile device

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V. Mirone (ed.), *Clinical Uro-Andrology*,
DOI 10.1007/978-3-662-45018-5_3,

in patients who wish to achieve the rigidity necessary to achieve penetrative sexual intercourse (Gilbert et al. 1987).

The main challenge for the reconstructive surgeon is that there is no good substitute for the unique corporeal tissue and that the anatomy of the penis is extremely complex and difficult to reproduce. This is why, despite a variety of surgical techniques of phallic reconstruction that have been described in the literature, none fulfils all the criteria and is currently accepted as gold standard method (Akoz and Kargi 2002).

3.3 Techniques of Total Phallic Construction

Among all phallic reconstruction techniques, metoidioplasty deserves a separate discussion, as this procedure should be only offered to patients in whom the androgen treatment has stimulated the growth of the clitoris to the point where the organ can serve as a penis. Due to the small size of the clitoris, the neophallus obtained with metoidioplasty usually does not allow patients to engage in penetrative sexual intercourse. This technique, first described in 1973, is carried out in one or two stages and consists in the release of the ventral clitoral chordee and ligaments with consequent straightening and lengthening of the clitoris and an advancement of the urethra up to the tip of the glans of the clitoris with the use of vaginal and labial flaps. The scrotum is then fashioned with the use of the labia majora's flaps (Hage 1996; Perovic and Sjordjevic 2003) (Fig. 3.1a, b).

Metoidioplasty, despite a high rate of complications such as fistulas and strictures, with up to 88 % of patients requiring revision surgery, is still considered by some authors the method of choice in a selected group of patients who are still in doubt about their need for phalloplasty (Hage and Van Turnhout 2003).

Patients who wish to engage in sexual intercourse cannot be served with a metoidioplasty and require total phallic construction.

3.4 Evolution of Phalloplasty Techniques

The development of total phallic construction techniques has paralleled the evolution of flap development in plastic surgery. At the moment more than 20 different types of flaps are available for phallic construction.

The first total phallic reconstruction was attempted in 1936 by Bogoraz, who used a random pedicled oblique abdominal tubularized flap with no incorporated neourethra to create a neophallus in patients who had previously experienced a traumatic amputation of the penis. A rib

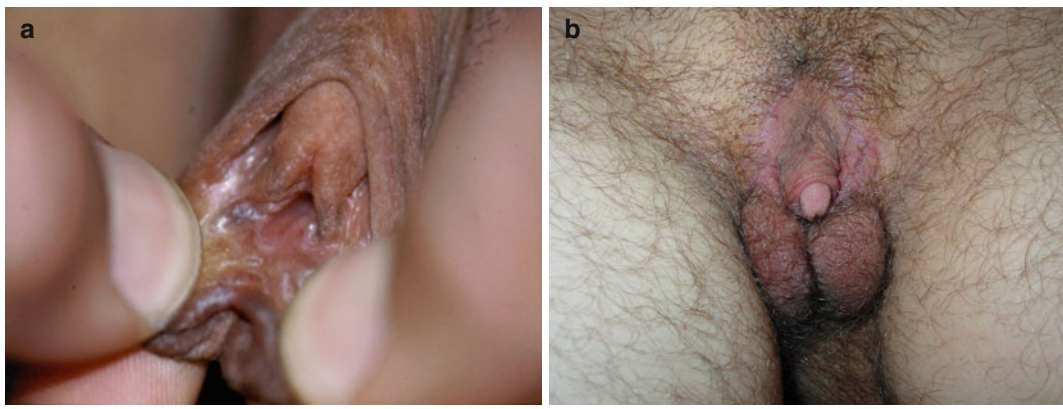


Fig. 3.1 The final result of a metoidioplasty. (**a**) The neourethra is advanced up to the tip of the clitoris' glans. (**b**) The scrotum is created with the use of labia majora's flaps, and the shaft is fashioned with the rotation of local skin flaps

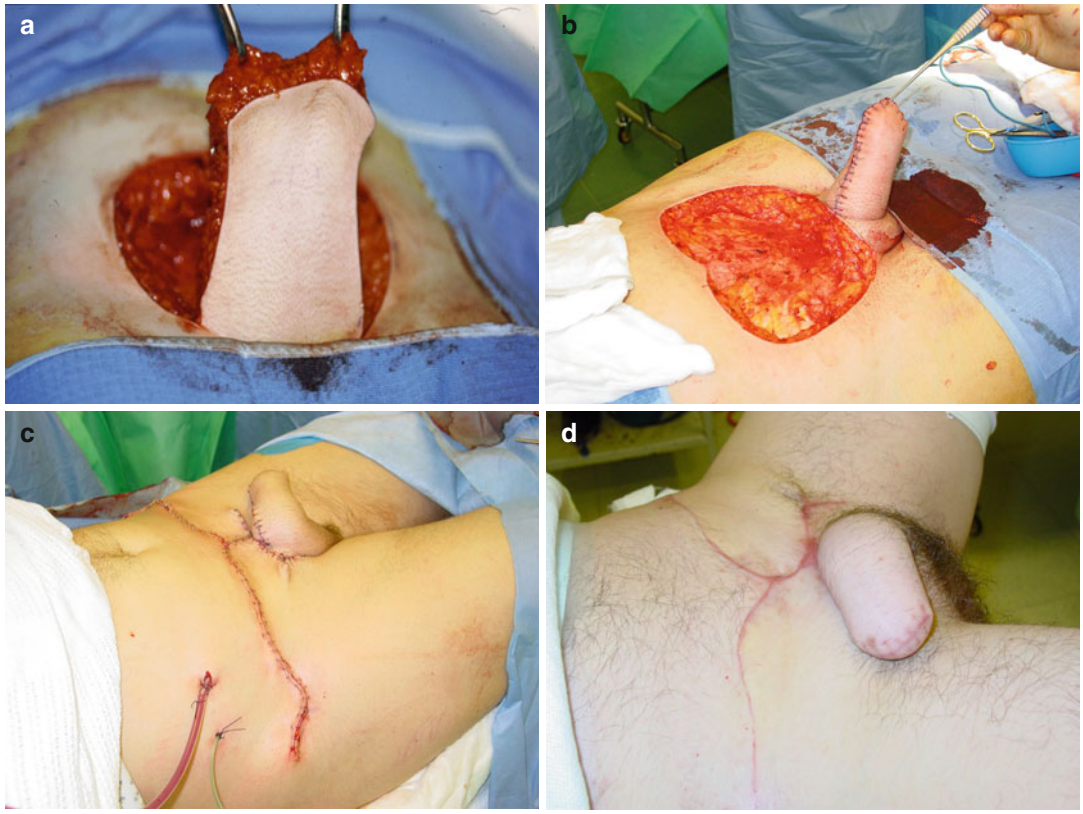


Fig. 3.2 The infraumbilical flap phalloplasty. (**a**) A 12×12 cm infraumbilical flap is raised. The dissection is carried out just above the rectus fascia. (**b**) The flap is tubularized to form a phallus. (**c**) The donor site defect is primary closed using abdominal flaps. (**d**) The final result at 3 months

cartilage was incorporated in the flap to guarantee the rigidity necessary for penetrative sexual intercourse (Bogoras 1936).

Bogoraz' technique was then improved by Gillies who fashioned a phallus with incorporated neourethra from a random pedicled abdominal flap using the 'tube within a tube' concept. This procedure involved a multistaged tissue transfer from the abdomen, resulted in extensive scarring and disfigurement of the donor area and produced a phallus without any tactile or erogenous sensation (Gillies and Harrison 1948).

The need for multistage tissue transfer has been overcome with the introduction of infraumbilical skin and groin flaps. Although the initial results were poor, as the phalluses obtained were non-sensate, wedge shaped and had no incorporated neourethra, the infraumbilical flap technique has been progressively refined, and now good cosmetic results can be achieved in more than 2/3 of patients (Fig. 3.2a–d). Moreover, patients who wish to be able to void while standing can be offered the creation of a neourethra made from a pedicled tube of labial skin or a free flap based on the radial artery, which is incorporated in the previously fashioned phallus (Bettocchi et al. 2004).

The use of musculocutaneous thigh flaps based on the gracilis muscle should instead be discouraged as the muscle component tends to contract with time, leading to poor cosmetic and functional results (Persky et al. 1983).

The advent of microsurgical and free tissue transfer techniques has represented the beginning of a new era for total phallic reconstruction with Song and Chang describing in the early 1980s the use of the radial artery free flap (RAFF) for the

creation of a neophallus in patients who had previously experienced a penile amputation (Chang and Hwang 1984; Song et al. 1982). This technique involved the creation of 'a tube within a tube' using a forearm skin flap with the urethra fashioned from the non-hair-bearing ulnar aspect and the whole flap based on the radial artery. This technique allowed the creation of a cosmetically acceptable phallus; sensation was also maintained due to the coaptation of the antebrachial nerves to the dorsal nerve of the clitoris or to the iliohypogastric and ilioinguinalis nerves.

Following the success of this series, many modifications in the flap design have been applied in order to improve the cosmesis of the neophallus and to minimize the overall complication rate, which can be as high as 45 %. Ulnar artery-based flaps have also been used to reduce the amount of hair-bearing skin incorporated (Gilbert et al. 1995).

The main drawback of forearm free flaps is donor site morbidity, which still represents a stigma and may be difficult to be accepted by patients. Therefore, free osteocutaneous fibular flaps, anterolateral thigh flaps and upper arm flaps have been used for total phallic construction, as they are associated with a less obvious donor site morbidity. However, due to the characteristics of the skin and subcutaneous tissues, using these flaps the neourethra cannot be fashioned with the tube within a tube technique. Therefore, in patients who wish to void while standing from the tip of the phallus, a prelaminated neourethra can be fashioned by tunnelling a skin graft or a mucosa graft inside the phallus (Rubino et al. 1993; Papadopulos et al. 2008).

An alternative in patients who wish to achieve cosmetic and functional results similar to the one provided by the RAFF phalloplasty but want to minimize the donor site morbidity is the incorporation of a 4 cm wide tubularized free forearm flap based on the radial artery in a pre-fashioned infra-umbilical flap phalloplasty. In a recent series of 27 patients, this technique yielded excellent cosmetic and functional results, and all patients who have completed the two-staged procedure were able to void from the tip of the phallus and had acceptable donor site morbidity, as the flap was relatively small (Garaffa et al. 2010a) (Figs. 3.3a–e and 3.4).

This chapter will concentrate on the radial artery-based forearm free flap phalloplasty since it is considered the technique that yields the best cosmetic and functional results.

3.5 The Radial Artery-Based Forearm Free Flap Phalloplasty

This procedure involves three stages, which are usually carried out at 4–6 months' distance from each other, and the overall process takes at least 1 year. The first stage consists in the creation of the phallus, which is transposed to the recipient site, and the insertion of a testicular prosthesis in one of the labia majora. The second stage involves the anastomosis of the native to the phallic urethra and the sculpture of the glans, while during the last stage, the cylinder(s), pump and reservoir of an inflatable penile prosthesis are inserted to guarantee the rigidity necessary for penetrative sexual intercourse. The testicular prosthesis is removed and transferred in the contralateral labia, and the pump is inserted in the capsule that had previously formed around the testicular prosthesis.

3.5.1 Stage 1

The phallus is created from a forearm free flap that is raised from the nondominant arm; to minimize blood loss the procedure is performed under tourniquet compression of a maximum of 2 h of inflation time. The size of the flap varies according to the dimensions of the forearm and to patient's expectations. The flap is separated longitudinally in two portions by a 1 cm wide strip of de-epithelialized dermis. The medial portion, obtained from the relatively hairless ulnar aspect of the forearm, is typically 4×15 cm and forms the neourethra, while the lateral portion, which is usually 15 cm long and has a width of 13–14 cm at the base and of 9 cm at the tip, will form the phallus. The flap is based on the radial artery, which is dissected to its origin from the brachial artery. The venous drainage is usually based on

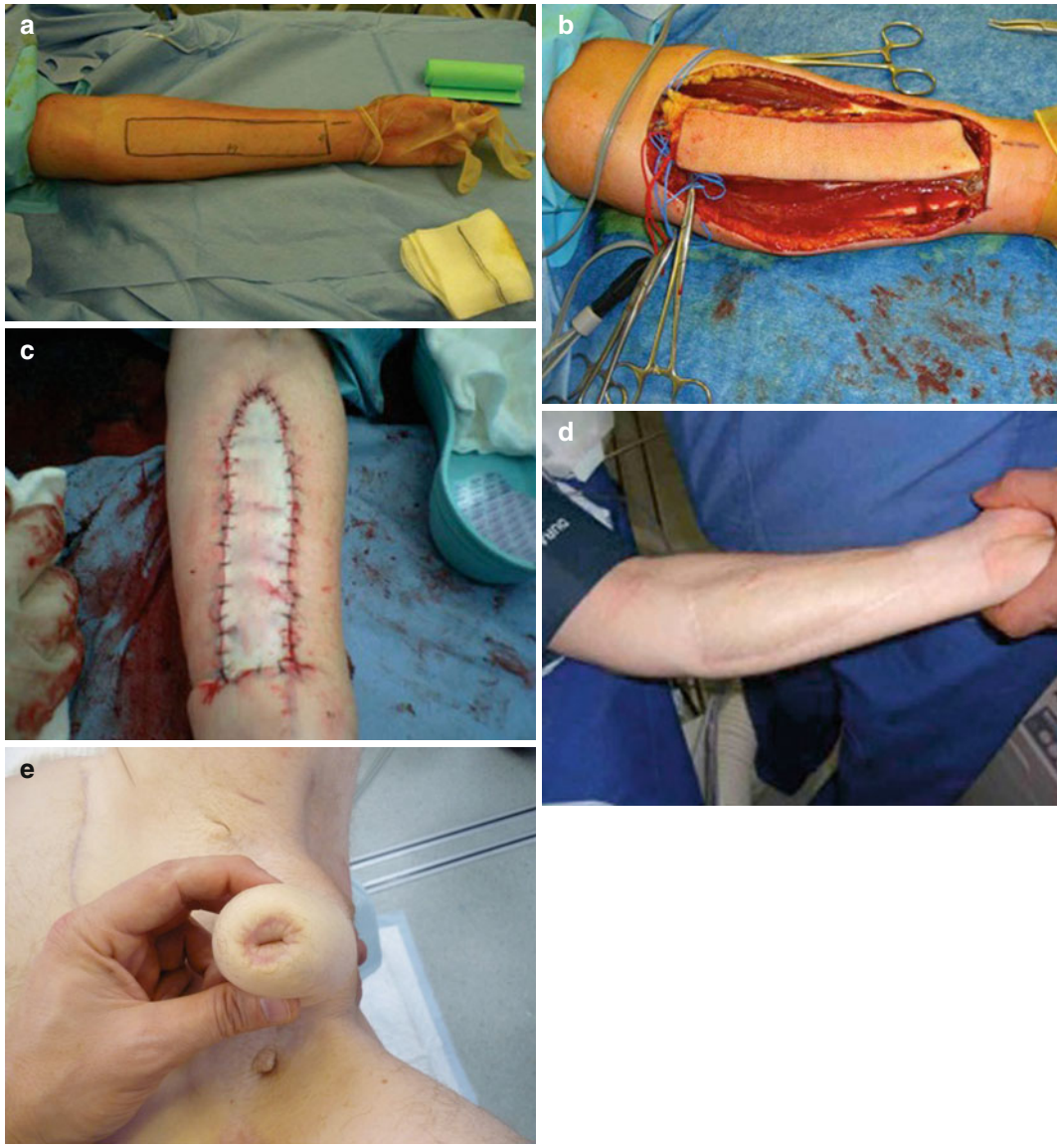


Fig. 3.3 The radial artery-based free flap urethroplasty. (**a**) The 4×17 cm flap is designed on the relatively less hairy medial aspect of the forearm. (**b**) The free flap is raised under tourniquet compression. (**c**) The donor site is repaired with a full-thickness skin graft harvested from the abdomen or buttock. (**d**) The donor site 6 months post-operatively. (**e**) The neourethra is incorporated in the infraumbilical flap phalloplasty

the cephalic vein, the venae comitantes of the radial artery and flap veins. Sensation of the flap is provided by the cutaneous nerves of the forearm (Fig. 3.5a, b).

Once the flap has been raised, the phallus is created in 'tube within a tube' fashion, and the urethral strip is tubularized around a 16-Fr catheter, and its proximal portion is left spatulated for 2 cm to allow a primary anastomosis to a labial flap. Once the neourethra has been completely fashioned, the lateral aspect of the flap is wrapped around the neourethra to form the bulk of the phallus (Fig. 3.6a, b).

Once the phallus is completed, its vascular pedicle is divided, and the free flap is transferred to the recipient site, which is located on the pubic

area, at the root of the clitoris (Fig. 3.7a–c). An inverted 'U'-shaped flap is created in one of the labia minora and is anastomosed to the proximal portion of the phallic urethra.

When the phallus is transposed to the recipient site, the following vascular, neural and urethral microsurgical anastomoses are performed with 8-0 Nylon® sutures:

1. Arterial: radial artery to inferior epigastric.
2. Venous: cephalic to long saphenous; usually the radial venae comitantes were incorporated with the cephalic. Other flap veins to smaller saphenous branches.
3. Neural: cutaneous nerves to ilioinguinal, iliohypogastric or dorsal nerve of the clitoris.

A mean of 2 venous and (range 1–5) and 2 neural (range 0–4) anastomoses is usually made.

After adequate preparation, the forearm donor site is covered with a full-thickness skin graft (FTSG) harvested from the buttock, axilla or abdomen. In general, FTSG are preferred to STSG since they harbour the hair follicles and tend to heal with less contracture providing superior cosmetic and functional results (Fig. 3.8a, b) (Garaffa et al. 2009, 2010b; Selvaggi et al. 2006).

At this stage a testicular prosthesis is usually inserted in one of the labia majora.

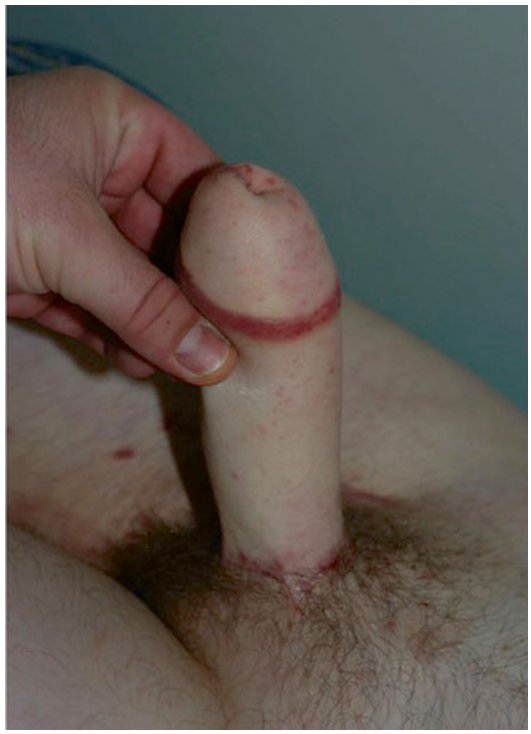
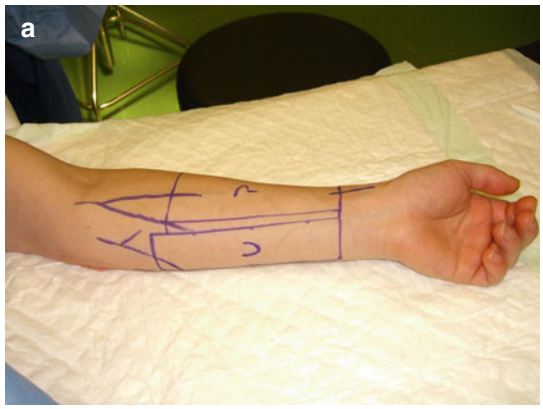


Fig. 3.4 Latissimus dorsi flap

3.5.2 Stage 2

The native urethra is connected with the phallic one with the use of local labial flaps usually 4–6 months after the first stage.

During this stage the distal aspect of the phallus is also sculptured using the Norfolk technique



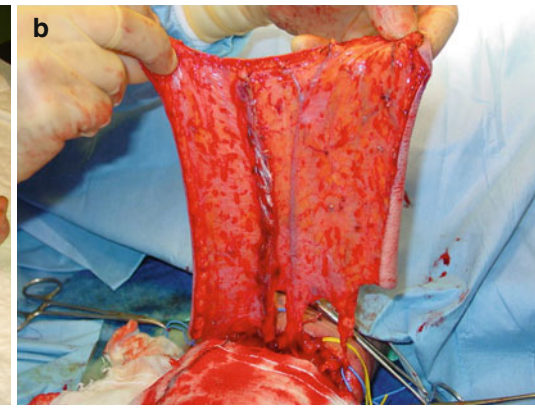


Fig. 3.5 The radial artery-based free flap phalloplasty. (**a**) The free flap is formed by two aspects: the inner one is a 4 cm wide strip that will form the neourethra, while the outer one will form the phallus. (**b**) The blood supply is guaranteed by the radial artery, while the venous drainage is provided by the cephalic vein, comitantes and flap veins

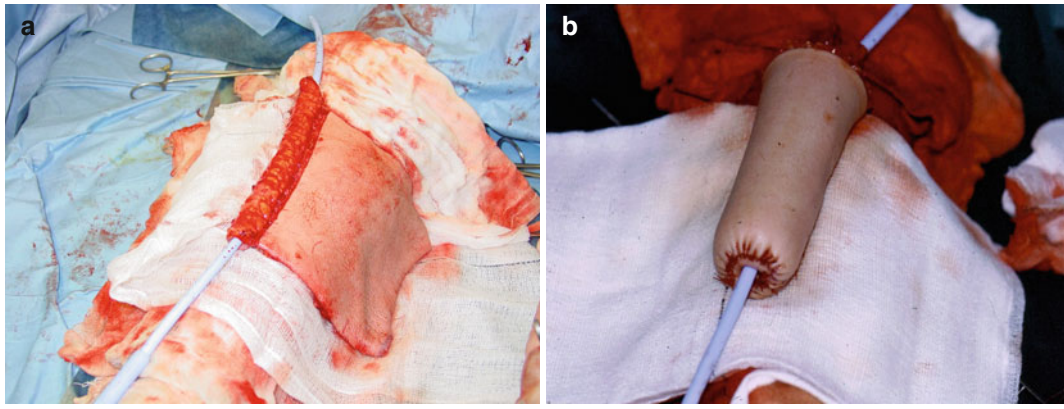


Fig. 3.6 The creation of the phallus. (**a**) The neourethra is tubularized on a 16-Fr stent. (**b**) The phallus is created according to the 'tube within a tube' technique

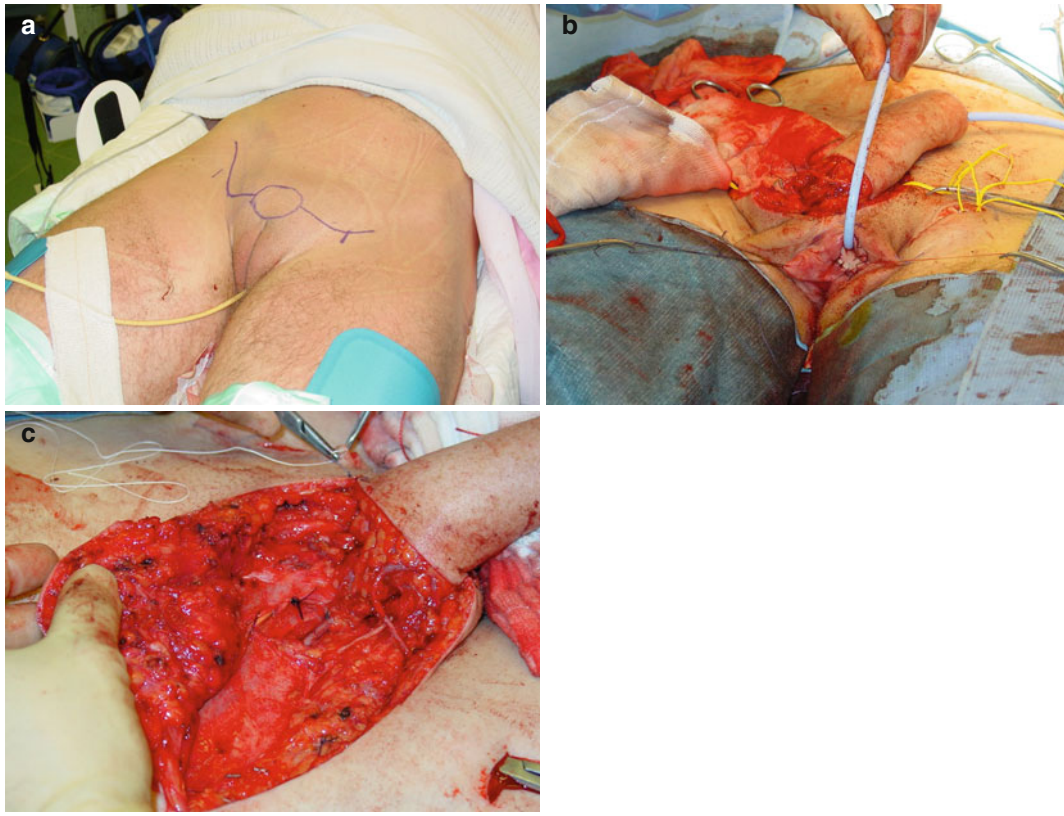


Fig. 3.7 (**a**) The recipient site. (**b**) The radial artery is anastomosed to the inferior epigastric artery, the flap veins are anastomosed to the long saphenous veins and the dorsal nerve of the clitoris and iliohypogastric and ilioinguinal nerves are coapted to the antebrachial nerves. (**c**) The neourethra is anastomosed to an inverted 'U' flap created from one of the labia minora

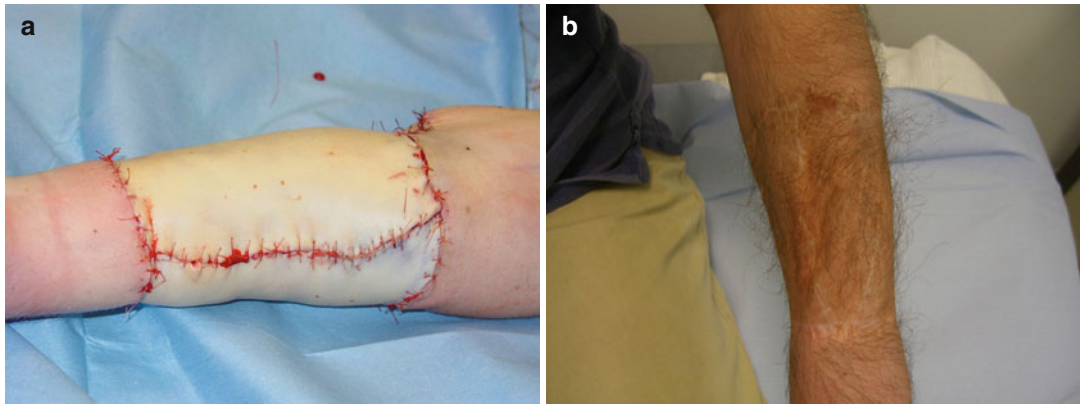


Fig. 3.8 The repair of the donor site. (**a**) The donor site is covered with a full-thickness skin graft harvested from the buttock or the abdomen. (**b**) The final result after 6 months

with the use of a FTSG harvested from a non-hair-bearing area in order to create a ridge and a grove that resemble the corona of a circumcised penis (Figs. 3.9a, b and 3.10a, b).

3.5.3 Stage 3

This stage is carried out approximately 1 year after phallus construction, to allow for cutaneous sensation to have developed.

Usually a single cylinder is implanted, but in bulky phalluses a second cylinder can also be used. Due to the absence of the tunica albuginea in the phallus, Dacron® or Gore-Tex® socks are fashioned to house the rear of the cylinder with incorporation of the exit tubing. The cylinders are then inserted in the phallus through a groin incision in the skin crease that is made on the side of the testis and reservoir. The incision is deepened to the pubic area, and the sock is anchored directly on the pubic bone with non-resorbable sutures. A Gore-Tex® or Dacron® cap is also fashioned and applied to the tip of the cylinder to prevent distal erosion. The previously inserted testicular prosthesis is removed and the pump placed into its capsule in order to allow for extra mobility, which is necessary to allow the patient to cycle the device. The pump is then connected with the cylinder's and reservoir's tubing and the testicular prosthesis transferred to the contralateral labia through a separate incision so that the neo-scrotum contains one pump and one testis (Figs. 3.11a–c and 3.12a, b).

Total phallic reconstruction with the use of the RAF is a reproducible technique. The most feared complication is acute venous thrombosis of the microsurgical anastomosis, which occurs in around 3 % of patients in postoperative day 3–4 and is characterized by a phallus that appears oozy and discoloured and by a progressive weakening of the pulse. Due to its subtle onset, it is recognized invariably too late and leads to the complete loss of the phallus. Acute thrombosis of the arterial anastomosis is instead immediate, easily identifiable and characterized by a pale cold phallus with no pulse; therefore, immediate re-exploration of the anastomosis with preservation of the phallus is almost always possible. Partial necrosis of the phallus due to arterial or venous ischemia may occur in up to 10 % of cases.

The most common complications are neourethral stricture and fistulas, which occur, respectively, in around 10 and 20 % of cases. Surgical correction is almost always possible, and after revision surgery, 99 % of patients are able to void standing from the tip of the phallus. Sensation on the phallus has been reported by 86 % of patients with an overall satisfaction rate after revision surgery of 97 % (Garaffa et al. 2010b).

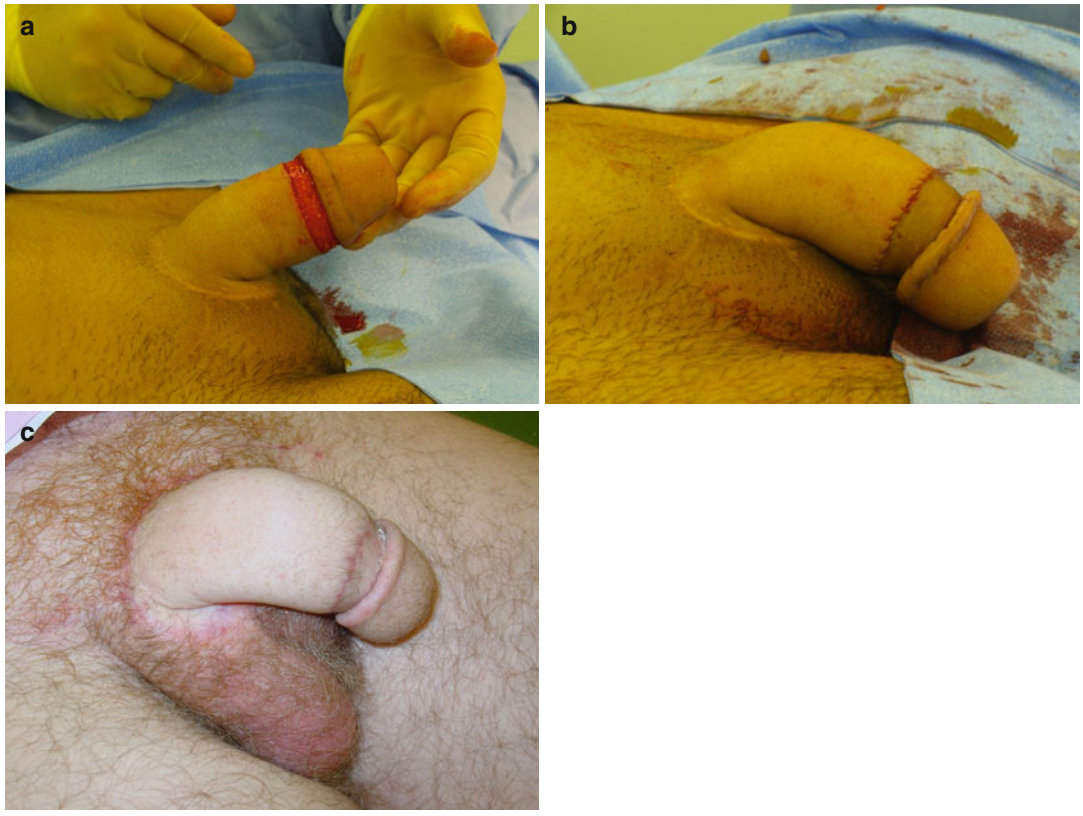


Fig. 3.9 The glans is sculptured according to the Norfolk technique. (**a**) A circumferential skin flap is raised to create the coronal ridge. (**b**) A full-thickness skin graft is applied to the de-epithelialized area to form the coronal groove. (**c**) The final result after 6 months

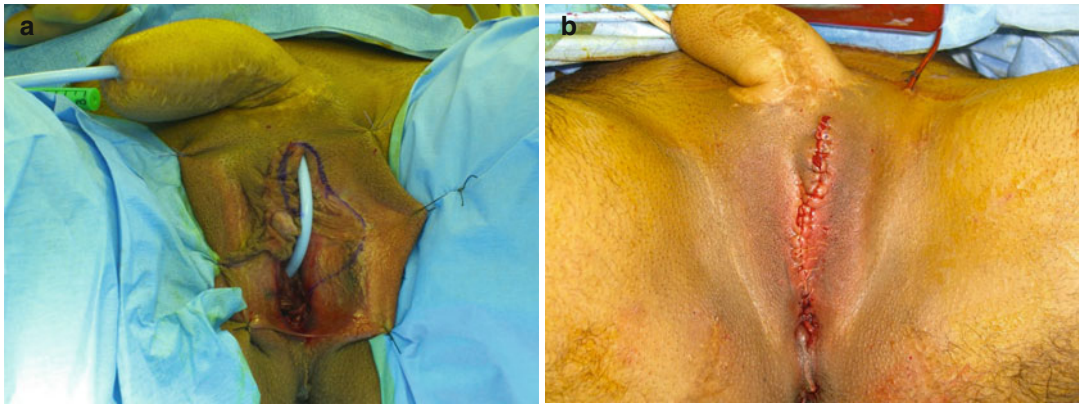


Fig. 3.10 The join up of the native urethra with the phallic one. (**a**) The native and phallic urethra are joined using local labial flaps. (**b**) The labia majora are fused together along the midline to form a pseudoscrotum

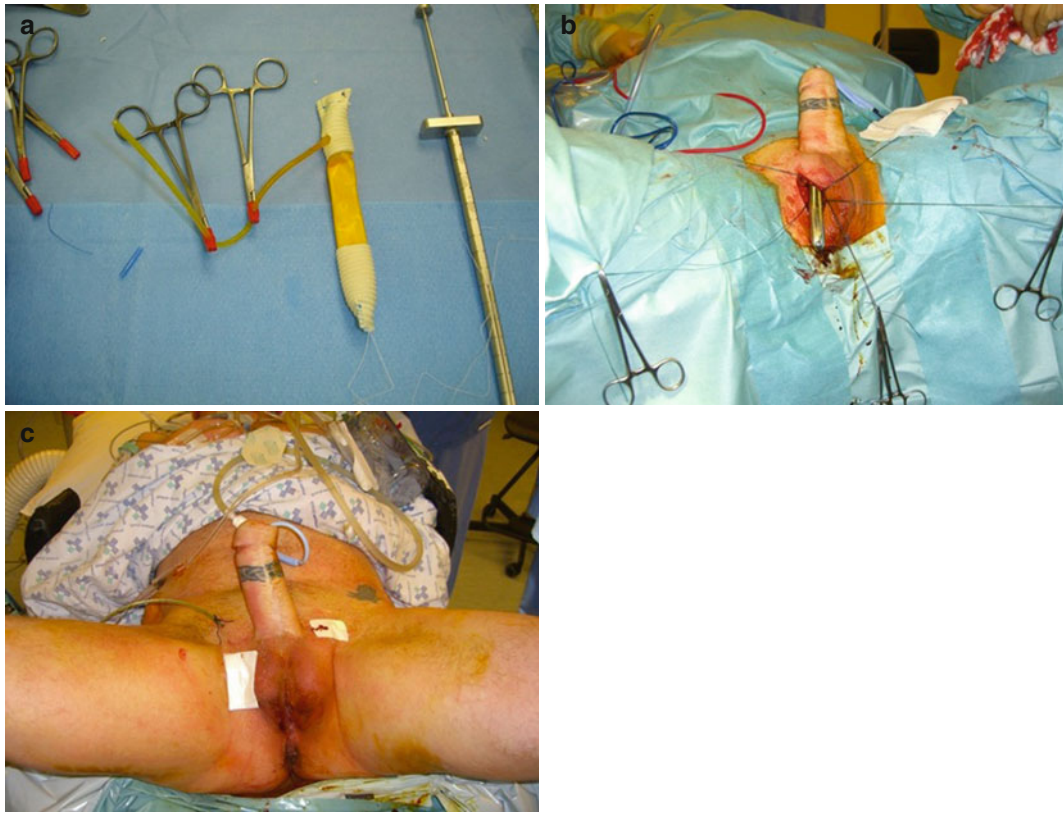


Fig. 3.11 (**a**) Dacron tip and sock. (**b**) A channel in the phallus is created with blunt dissection with Metzenbaum scissors and progressively dilated with Hegar's dilators up to 17 mm in order to house the cylinder with the Dacron or Gore-Tex cap. The sock is anchored to the pubic bone with 4 J needle 0 Ethibond sutures, applied in 2 parallel rows. (**c**) The final result after implantation of 2 cylinders

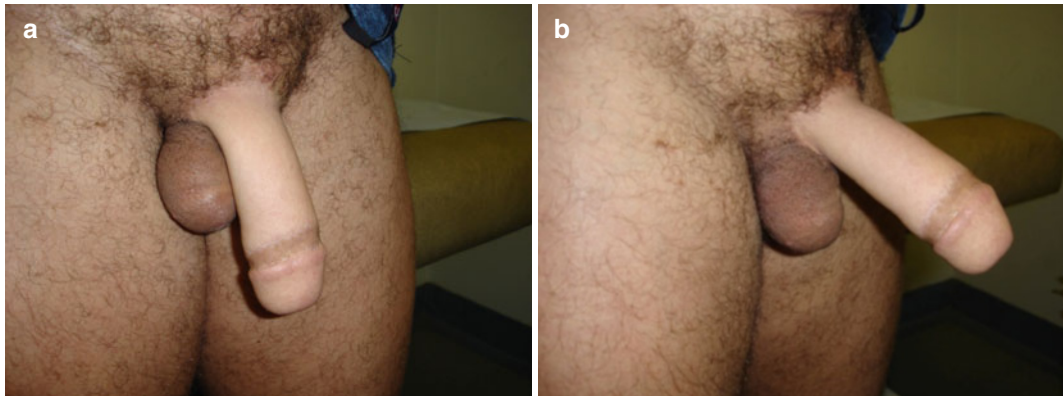


Fig. 3.12 (**a**, **b**) Inflation and deflation of the cylinders

Penile prosthesis insertion in a phalloplasty is associated with high risk of complications. This is due to the presence of the Gore-Tex® or Dacron® boot and sock and to the absence of the tunica albuginea that protects the cylinders from traumas and erosion.

In particular, infection rate, erosion rate and mechanical dysfunction of the device can be,

respectively, as high as 11.9, 8.1 and 22.2 % with an overall revision rate of 41 % at 5 years.

Overall, after stage 3, up to 60 % of patients have a normally functioning penile prosthesis, are able to cycle the device and, potentially, to have penetrative sexual intercourse (Hoebeke et al. 2010).

Conclusions

The process of gender reassignment is complex and requires the cooperation of a multidisciplinary team formed by mental health professionals, endocrinologists, gynaecologists, plastic surgeons and urologists. Although many of the phalloplasty techniques may achieve closely the goals of a neopenis with normal urination, none of them are perfect, and therefore none have achieved universal acceptance. Therefore, the choice of the most appropriate technique should be taken considering the patient's body habitus, concomitant diseases, surgeons' experience and the patient's desire to void in the standing position and to have penetrative sexual intercourse.

References

Akoz T, Kargi E (2002) Phalloplasty in a female to male transsexual using a double-pedicle composite groin flap. Ann Plast Surg 48(4):423–427

American Psychiatric Association (1980) Diagnostic and statistical manual of mental disorders 3rd edn, American Psychiatric Association, Washington, DC

American Psychiatric Association (1994) Diagnostic and statistical manual of mental disorders 4th edn, American Psychiatric Press, Washington, DC

Bettocchi C, Ralph DJ, Pryor JP (2004) Pedicled pubic phalloplasty in females with gender dysphoria. BJU Int 95:120–124

Bogoras N (1936) Uber die volle plastische wiederherstellung eines zum Koitus fahigen Penis (peniplastica totalis). Zentralbl Chir 63:1271

Cauldwell DC (1949) Psychopathia transexualis. Sexology 16:274–280

Chang TS, Hwang WY (1984) Forearm flap in one-stage reconstruction of the penis. Plast Reconstr Surg 74: 251–258

Garaffa G, Raheem AA, Christopher NA, Ralph DJ (2009) Total phallic reconstruction after penile amputation for carcinoma. BJU Int 104(6):852–856

Garaffa G, Ralph DJ, Christopher N (2010a) Total urethral construction with the radial artery based forearm free flap in the transsexual. BJU Int 106(8): 1206–1210

Garaffa G, Christopher NA, Ralph DJ (2010b) Total phallic reconstruction in female to male transsexuals. Eur Urol 57(4):715–722

Gilbert DA, Horton CE, Terzis JK, Devine CJ Jr, Winslow BH, Devine PC (1987) New concepts in phallic reconstruction. Ann Plast Surg 18:128–136

Gilbert DA, Schlossberg SM, Jordan GH (1995) Ulnar forearm phallic reconstruction and penile reconstruction. Microsurgery 16:314–321

Gillies HD, Harrison RJ (1948) Congenital absence of the penis with embryological consideration. Br J Plast Urol 1:8

Hage J (1996) Metoidioplasty: an alternative phalloplasty technique in transsexuals. Plast Reconstr Surg 97:161–167

Hage J, Van Turnhout A (2003) Metoidioplasty: a variant of phalloplasty in female transsexuals. BJU Int 92: 981–985

Hirschfeld M (1923) Die intersexuelle Konstitution [The intersexual state]. Jahrb sex Zwischenstufen 23:3–27

Hoebeke PB, Decaesteker K, Beysens M, Opdenakker Y, Lumen N, Monstrey SM (2010) Erectile implants in female-to-male-transsexuals: our experience in 129 patients. Eur Urol 57(2):334–340

Papadopulos NA, Schaff J, Biemer E (2008) The use of free prelaminated and sensate osteofasciocutaneous fibular flap in phalloplasty. Int J Care Injuried 39s: s62–s67

Perovic S, Sjordjevic M (2003) Metoidioplasty: a variant of phalloplasty in female transsexuals. BJU Int 92: 981–985

Persky L, Resnick M, Desprez J (1983) Penile reconstruction with gracilis pedicled grafts. J Urol 129:603–605

Rubino C, Figus A, Dessy LA, Alei G, Mazzocchi M, Trignano E, Scuderi N (1993) Innervated island pedicled anterolateral thigh flap for neo-phallic reconstruction in female-to-male transsexuals. J Urol 150(40): 1093–1098

Selvaggi G, Monstrey S, Hoebeke P, Ceulemans P, Van Landuyt K, Hamdi M, Cameron B, Blondeel P (2006) Donor-site morbidity of the radial forearm free flap after 125 phalloplasties in gender identity disorder. Plast Reconstr Surg 118(5):1171–1177

Song R, Gao Y, Song Y, Yu Y, Song Y (1982) The forearm flap. Clin Plast Surg 9:21

World Health Organization (1994) International classification of diseases, 10th edn. World Health Organization, New York

Peyronie's Disease (Induratio Penis Plastica)

4

Ates Kadioglu, Emre Salabas, and Faruk Küçükdurmaz

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4.1 Introduction

Peyronie's disease (PD), induratio plastica of the penis, has been a topic of debate with its complex pathologic pathways and ever developing treatment modalities since its initial report by François Gigot de la Peyronie in 1743. PD is an acquired fibrotic disease of the tunica albuginea (TA) of the penis characterized by the formation of fibrous plaques, which cause penile curvature and shortening, painful erection, loss of penile flexibility, and associated sexual dysfunction (Ralph et al. 2010). The incidence of PD is reported as 3.2 % in the Cologne Male Survey of 8,000 men (Schwarzer et al. 2001). Other epidemiological studies estimate the prevalence of PD to be 3–8.9 % with mean age of onset being 50–60 years (Smith et al. 2008; Mulhall et al. 2004). In addition, some studies reported up to

V. Mirone (ed.), *Clinical Uro-Andrology*,
DOI 10.1007/978-3-662-45018-5_4, © Springer-Verlag Berlin Heidelberg 2015

10.8 % prevalence of PD in men younger than the age of 40 who display a more acute onset and lower incidence of ED in comparison with PD encountered in older ages (Levine et al. 2003; Deveci et al. 2007; Kadioglu et al. 2007). PD is also encountered in a special subgroup, teenager population, with diversified qualities such as high HbA1c levels in 18 % of patients, noncontiguous plaques, and subsequent ED rate of 37 %, and they present earlier than their adult counterparts (Tal et al. 2012).

4.2 Etiology and Pathogenesis

The etiology of PD is considered to be multifactorial with the interplay of a genetic predisposition, trauma, and tissue ischemia (Mulhall et al. 2005). Although the exact pathogenesis is not understood, the most widely accepted theory is that PD is a wound-healing disorder, initiated by repetitive microtraumas to the penis, with subsequent scar formation. The source of the scar formation suggested by human penile sections and experimental animal PD models was extravasated fibrinogen during trauma of the penis with fibrin injections, but there is a general lack of clinical evidence pointing out the role of trauma in PD (Davila et al. 2003; Ralph et al. 2010). In a recent study, only two independent risk factors of PD have been identified as ED (%56–1.5 OR) and coital trauma (%22–2.69 OR), while DM increased the risk when accompanied by ED (Casabé et al. 2011). PD has also been associated with Dupuytren disease as 30–40 % of the patients with PD had manifested both diseases and 10 % of them had Dupuytren disease family history (Bjekic et al. 2006). These results may hint at the possible role of genetic and immune factors in PD, but more solid evidence should be acquired to verify it. Moreover, systemic vascular risk factors, such as diabetes mellitus (DM), hyperlipidemia, hypertension, and ischemic heart disease, smoking, and pelvic interventions have been hypothesized to play a role in the pathogenesis of PD (Pryor and Ralph 2002). Although the presence of the contradictory studies, diabetes mellitus has been accepted as an independent factor increasing the prevalence and the severity of PD.

The initiation of PD is an acute inflammatory process characteristically associated with increased tunical fibroblast proliferation, abnormal presence of myofibroblasts, followed by disproportionate deposition of collagen, persistence of fibrin, and elastin fragmentation in tunica albuginea of the penis. TGF-B 1 is a profibrotic factors which may be harvested from plaques or other fibrotic places in the body; may be injected directly, together with fibrin; or may be inducted with the help of adenoviral constructs to produce penile curvature and plaque in the animal models (Davila et al. 2003). Overexpression of myostatin, a member of TGF beta family, has been found in PD plaques, and it induced new plaque upon administration and condensed the already formed plaque of TGF-B1 (Cantini et al. 2008). Other profibrotic factors such as plasminogen activation inhibitor (PAI-1) and reactive oxygen species (ROS) as well as TGF-B 1 are released in the acute inflammation subsequent to trauma and may be aggravated after transition to chronic phase mean, while a dense fibrotic plaque is observed which might be accompanied with calcification and ossification of the plaque as well as the presence of osteoblasts (Gonzalez-Cadavid and Rajfer 2005; Gonzalez-Cadavid 2009; Ralph et al. 2010). Inducible nitric oxide syntheses (iNOS) leading to NO release has been proposed as a defensive mechanism against the profibrotic factors in studies because of their increased levels together with antioxidants in human and animal plaques leading to reduction of these in size. The fibrin clot in the tunica albuginea attracts monocyte chemotactic protein 1 (MCP-1) which itself probably induce iNOS. This postulate is supported by the reverse correlation of profibrotic factor levels and iNOS activity regulated by gene transfer and L-N-(1-iminoethyl)-lysine acetate (L-NIL) inhibition in animal experiments (Gonzalez-Cadavid 2009). It has been postulated that NO reduces ROS activity, leads myofibroblasts to apoptosis, and inhibits collagen synthesis together with its product cGMP (Vernet et al. 2002). Reduction in plaque size, oxidative stress, and alpha smooth muscle actin (ASMA) staining was observed in PD fibroblast cultures after PDE-5 inhibitor administration (Valente et al. 2003).

The inhibition and lack of metalloproteinase and collagenases contribute to the process while iNOS, MMPs 2 and 9, decorin (that binds TGFβ1), and thymosins are the active defense mechanisms against the disease (Ralph 2010). Recently, an overexpression of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) and its death receptor (DR5) has been demonstrated in PD plaque when compared to normal TA indicating the role of external apoptotic pathway in plaque formation (Loreto et al. 2011).

4.3 Course of the Disease

Generally, PD is thought to have an acute inflammatory phase followed by a chronic phase. The acute phase is characterized by a progressive increase in plaque size or penile curvature associated with penile pain. In most cases, the duration of this phase is 12 months from the onset of the disease. PD progressively deteriorates if left untreated in the acute phase of the disease. Accordingly, the results of 246 patients who were presented within 6 months from the onset of the disease and followed up for 1 year without treatment were reported (Mulhall et al. 2006). The authors demonstrated that penile curvature worsened in almost half of the cohort, while only 12 % of men improved in terms of mean degree of curvature, while 40 % remained stable and 48 % worsened during the follow-up period. On the other hand, the chronic phase is a stable period during which penile curvature and plaque size remain the same with the absence of penile pain which is generally accepted to be after 12 months from the onset of the disease (Hellstrom and Bivalacqua 2000).

4.4 Diagnosis and Evaluation of Peyronie

The diagnosis of PD should be based on a comprehensive medical and sexual history and a detailed physical examination (Ralph et al. 2010). In particular, symptoms of the acute phase and erectile dysfunction (ED) should be noted. Penile pain is present in the 35–45 % of the patients in the early phase (6 months) and resolve spontaneously for the 90 % of the patients in the first 12 months (Mulhall et al. 2006; Pryor and Ralph 2002). Dysmorphic penis causes significant distress in these patients documented by validated mental health questionnaires showing depression in the 48 % of the patients (Levine and Greenfield 2003). The Center for Epidemiological Studies Depression scale (CES-D) has been used to assess the correlation between depression and PD; rate of moderate and severe depression presence was observed as 26 and 21 %, respectively (Nelson et al. 2008). Significant improvement was recorded after PD surgery in sexual and overall relationship and confidence domains of the Self-Esteem and Relationship (SEAR) survey (Tal et al. 2010).

Correlation between ED and PD has been demonstrated in 55 % of the patients, and performance anxiety, deformity, flail penis, and impaired erection may be listed as the cause of this (Kadioglu et al. 2002). It should be assessed by IIEF-5 questionnaires and duplex ultrasonography may be performed in case of ED suspicion. Ultrasonography is also a useful tool for the plaque size and placement measurements but is not indicated in routine clinical practice (Ralph et al. 2010).

Since progressive penile shortening is common in patients with PD, measurement of stretched penile length is an important part of the physical examination (Smith et al. 2008). Men with PD have either a well-defined plaque or a palpable induration; for example, two-thirds of patients have a palpable induration on the dorsal aspect of the penis with a corresponding penile curvature. Meanwhile, plaques which are ventrally or laterally located are less common with an incidence of 10–20 % and 6–10 %, respectively, but cause more penetration difficulties (Pryor and Ralph 2002; Ralph et al. 2010). Assessment of curvature may be performed with the help of ICI, vacuum devices, or photographically, but there is a significant underestimation of curvature degree (10°) in the latter techniques when compared to ICI especially in patient with ED (Ohebshalom et al. 2007). Stable curvature

and a resolution of pain for at least 3 months are indicators of chronic phase, and this differentiation from acute phase is vital because only in this phase surgical intervention may be considered.

4.5 Medical Treatment

Medical therapy has been considered as an option since the definition of Peyronie's disease, but the plaucity in the explanation of the pathophysiological mechanism of the disease makes the final cure impossible for now. Medical therapy can be undertaken depending on the phase and severity of disease. Efficacy of the treatment should be assessed by the change in the curvature as plaque size and pain alterations are not objective criteria. A randomized and placebo-controlled trail (RPCT) is required for the review of the medical treatment option, and in the lack of this, a rate of success for a treatment modality should be much higher than 12 %, the rate of curvature reduction in untreated patient population.

4.6 Oral Treatment

4.6.1 Vitamin E

Vitamin E is the first and most commonly prescribed drug among PD medical therapy. It is a fat-soluble vitamin and a natural antioxidant and inhibits fibrosis by acting as a scavenger of ROS. Although it is an inexpensive drug with no side effects, it is not recommended because of the lack of efficacy proven in randomized controlled trials (Pryor and Farell 1983).

4.6.2 Potassium Para-aminobenzoate (Potaba)

Potaba is a part of vitamin B complex with a mechanism of action which involves three pathways: (1) increased oxygen uptake, (2) increased activity of MAO and decreases fibrogenesis by way of serotonin reduction, and (3) GAG (glycosaminoglycan) secretion. In two RPCTs with 41 and 103 patients who underwent a total of 12 mg Potaba daily treatment for 12 months, no significant reduction in penile curvature has been observed so it is not a recommended modality (Shah et al. 1983; Weidner et al. 2005).

4.6.3 Tamoxifen

Tamoxifen is a nonsteroidal estrogen receptor antagonist. Proposed mechanism in PD is modulation of TGF-ß secretion from fibroblasts. In a RPCTs with 25 patients who underwent a total of 40 mg tamoxifen daily treatment for 3 months, no benefit of the drug has been shown (Teloken et al. 1999).

4.6.4 Colchicine

Three hypothetic mechanism pathways of colchicine: (1) anti-inflammatory effect due to inhibition cytokine release from leukocytes by increasing intracellular cAMP, (2) antigout agent that inhibit collagen synthesis, and (3) subsequent fibrosis by inhibiting neutrophil microtubules which prevents chemotaxis of monocytes. Three prospective studies without control groups revealed that in 30–55 % of patient's penile curvatures had improved with oral colchicine treatment (Akkus et al. 1994; Prieto Castro et al. 2003). Although colchicines improved curvature significantly in comparison with placebo, it was administered with vitamin E combination. In a recent study colchicine treatment 2 mg daily for 3–6 months improved and stabilized curvature in 27 and 40 % of the patients, respectively. It is also worth mentioning that subgroup of patients with no ED, lesser curvatures (<30°), and at the early phase of the disease (<6 months) benefited more from the colchicine treatment (Akman et al. 2011).

4.6.5 Carnitine

Carnitine is a naturally occurring metabolic intermediate and facilitates entry of long-chain fatty acids into oxidative energy cycle, inhibiting acetyl coenzyme-A to help repair of damaged cells. One RCT compared carnitine 1 mg twice daily

with tamoxifen 20 mg daily treatment, and the former was shown to be significantly more effective than the latter in terms of curvature and pain improvement (Biagiotti and Cavallini 2001).

4.6.6 Pentoxifylline

Pentoxifylline is a nonspecific PDE inhibitor. It downregulates TGFβ1 and increases activity of fibrinolysis. Furthermore, an increase of nitric oxide levels may be effective in preventing progression of Peyronie's disease or reversing fibrosis. There is no PCRT for the assessment of pentoxifylline treatment in PD (Hatzimouratidis et al. 2012).

4.7 Intralesional Treatment

4.7.1 Steroids

There is only one PCRT with a small population, and no improvement has been observed in terms of neither curvature nor pain.

4.7.2 Topical Verapamil

It increases ECM collagenase secretion through fibroblast inhibition and decreases collagen and fibronectin synthesis and secretion and fibroblast proliferation. In spite of intriguing mechanism, it was demonstrated that topical verapamil could not penetrate and reach human tunica albuginea in normal conditions (Martin et al. 2002).

4.7.3 Verapamil

Verapamil is calcium channel blocker that inhibits its production of extracellular matrix proteins and decreases production of collagen and TGF-ß, and it also increases collagenase activity. Although the presence of several studies seems to establish the efficacy of verapamil 10 mg intralesional treatment for 3 months, there is no significant improvement of verapamil treatment modality for curvature reduction in the PCRT with 80 patients (Shirazi et al. 2009). The treatment seems more effective in young patients with lesser curvatures at an early phase.

In a recent study, the success predictors for verapamil were defined as younger age (<40 years) and greater curvature (>30°) contrary to other manuscripts (Moskovic et al. 2011). It also has been suggested that the inefficacy of verapamil in PCRT might be associated with the lesser treatment duration (3 vs. 6 months).

4.7.4 Collagenase

Collagenase is associated with specific matrix metalloproteinase 1, 8, and 13 and capable of collagen degradation. There is no PCRT to assess the efficacy of collagenase.

4.7.5 Interferon α-2b

It decreases fibroblast proliferation, extracellular matrix production, and collagen production from fibroblasts and improves the wound-healing process from Peyronie's disease plaques in vitro (Hatzimouratidis et al. 2012). In a PCRT with 103 patients who underwent interferon 5 M units/2 weeks for 12 weeks of treatment, a significant improvement in curvature has been observed (27 % vs. 9 %) as well as reduction in pain. Adverse effects such as sinusitis and flu-like symptoms had occurred. An important point is that a patient group had greater curvatures (>30°) at a late phase of the disease (>12 months) (Hellstrom et al. 2006). Interferon treatment seems to be best candidate in the medical treatment modalities for a solid alternative to surgical treatment.

4.8 Other Treatments

4.8.1 Penile Electroshock Wave Therapy (ESWT)

Although the exact mechanism for local ESWT treatment is obscure, several hypotheses have been suggested such as the improved vascularity

or macrophage activity following inflammation in the plaque or the fibrosis of the contralateral side of the curvature (Levine et al. 2003). In a PCRT for ESWT, no clinically significant improvement has been showed in terms of curvature and plaque size (Hauck et al. 2012).

4.8.2 Traction

Cell function is modulated by mechanotransduction over internal cytoskeleton and extracellular matrix. Collagen fibrils are reorganized parallel to the axis of stress, and antifibrotic upregulation was observed in response to stress. Two small noncontrolled studies have been performed with slight improvements in penile curvature and penile length and significant attenuation of pain (Larsen and Levine 2012).

4.8.3 Surgical Treatment

Surgical correction is the gold standard treatment option for PD, having the most reliable and sustained outcomes for correction of penile deformities. Surgery should only be considered in these conditions: (1) after stabilization of the disease (12 months after the onset of disease or once the deformity has been stable and painless for at least 3 months, preferably 6 months), (2) in the presence of severe penile shortening or severe deformity that causes difficulty in penetration, (3) in the presence of plaque calcification, and (4) after previously failed conservative treatment or when the patient wants the most definitive result (Ralph et al. 2010; Bella et al. 2007). Selection of the appropriate procedure for each patient depends on an accurate understanding of surgical outcomes and current status of the penile deformity. Erectile capacity should be assessed initially as it is the key determinant in the surgical technique preference between reconstructive surgery and penile prosthesis implantation. Other important qualities to be assessed are the direction and severity of the curvature, presence of destabilizing hinge effect caused by severe indentation or hourglass deformity, and patients' expectations related to the outcomes of surgical interventions (Ralph et al. 2010). Accepted reduction in penile length for every 30° of penile curvature is 1 cm so the preoperative size of the penis should be measured and lengthening operation should be preferred as reconstructive surgery for men with short penis and greater curvature degree.

The surgical treatment options available for PD involve different techniques which can be divided into two main categories:

1. Reconstructive surgeries are based upon either shortening the convex side or lengthening the concave side of the TA by incision or partial excision of plaque and use of different types of grafts for closure of defect.
2. Penile prosthesis implantation with or without additional procedures such as remodeling, plication, and grafting (Kadioglu et al. 2006, 2008).

4.9 Reconstructive Surgery

4.9.1 Tunical Shortening Procedures

Tunical shortening procedures are recommended for men with satisfactory erectile function and curvatures less than 60–70° without any destabilizing deformities or hinge effect and when the postoperative length loss is predicted to be less than 20 % of the erect penile length as the difference in length (cm) between the concave and convex sides of the penis, measured from penopubic junction to tip of the glans penis dorsally and from penoscrotal junction to tip of the glans ventrally (Ralph 2010; Mulhall et al. 2005; Levine and Lenting 1997). Thus, patients should be informed that penile length after surgery will be equal to the length of the concave side of the penis in all kinds of shortening procedures.

4.9.2 Nesbit Procedure

Originally described by Nesbit in 1965, this method involves excision of an ellipsoid area of tissue from the TA at the opposite side of the

Table 4.1 Outcomes of tunical shortening procedures

Study	*N*	Mean follow-up (months)	Outcomes (% of cohort)			
			Penile straightness	Penile shortening	Postoperative erectile dysfunction	Overall satisfaction
Nesbit procedure						
Savoca et al. (2004)	218	89	86.3	17.4	11.5	83.5
Bokarica et al. (2005)	40	81	87.5	100	5	NR
Licht and Lewis (1997)	28	22	79	37	4	79
Ralph et al. (1995)	359	21	89	100	2	NR
Horstmann et al. (2011)	16	70	97	72	9	62
Yachia procedure						
Yachia (1990)	1	NR	100	0	NR	100
Daitch et al. (1999)	14	24.1	93	57	7	79
Rehman et al. (1997)	26	22	73	100	7.6	78
Plication techniques						
Van Der Horst et al. (2004)	28	30	100	74	35.7	67.8
Greenfield et al. (2006)	68	29	99	7.3	7.3	98.5
Taylor and Levine (2008)	61	72	87	18	12	82
Gholami and Lue (2002)	132	31	85	41	3	96
Dugi and Morey (2010)	45	21	100	0	NR	93
Horstmann et al. (2011)	16	70	97	72	9	62
Adibi et al. (2012)	102	15	96	14	4	92

Abbreviation: *NR* not reported

penis to the most prominent point of curvature (Nesbit 1965). Naturally, shortening of the convex side of the penis is expected after closure of the defect. Depending on direction of the curvature, mobilization of the dorsal neurovascular bundle (NVB) or ventral corpus spongiosum is required.

Mobilization of the NVB for the correction of ventral deformities can be achieved by medial or lateral dissection of NVB depending on the experience of the surgeon. In the latter, mobilization of the NVB is performed by two longitudinal lateral incisions on Buck's fascia above the urethra at 5 and 7 o'clock positions. Alternatively, medial dissection is performed in the bed of the previously resected deep dorsal vein (Giammusso et al. 2004). The meticulous medial dissection should be preferred with the help of surgical loupes preserving NVB.

Studies evaluating outcomes of the Nesbit procedure for different kinds of curvatures have reported success rates of penile straightening between 79 and 100 %, with an overall patient satisfaction rate of 67–100 % (Savoca et al. 2004; Bokarica et al. 2005; Licht and Lewis 1997; Ralph et al. 1995) (Table 4.1). In these series, penile shortening up to 2.5 cm was reported in 17.4–100 % of patients by Giammusso et al. In the largest series to date, 359 men who had undergone the Nesbit procedure, difficulty achieving penetration after surgery had been reported in less than 2 % of the patients. All men experienced penile shortening, with an 82 % overall satisfaction rate (Ralph et al. 1995).

4.9.3 Yachia Procedure

The Yachia procedure is a modification of the Nesbit technique that utilizes the Heineke-Mikulicz principle, where a single long incision or multiple small incisions are made longitudinally in the TA and subsequently closed horizontally to shorten the convex side of the penis (Yachia 1990). Reported patient satisfaction rates after the Yachia procedure range between 80 and

100 % (Daitch et al. 1999; Rehman et al. 1997) (Table 4.1). Despite this procedure is not commonly used depending on the surgical experience, this operation should be within the surgical armamentarium of urologists dealing with sexual medicine. The major reasons for dissatisfaction of Nesbit and Yachia procedures were the loss of penile tactile sensation (24 %) and ED (12 %) owing to elevation of the NVB and disruption of cavernosal integrity, respectively (Essed and Schroeder 1985).

4.9.4 Plication Procedures

The penile plication technique, originally described by Essed-Schroeder is the least invasive and thus the most commonly used surgical option for tunical shortening. No absorbable sutures are placed over the convex side of the TA, without the need for excision of TA tissue or mobilization of NVB in order to achieve a straight penis (Essed and Schroeder 1985). Plication procedures result in penile shortening similar to Nesbit and Yachia procedures and therefore recommended only in patients with adequate penile length and good baseline erectile function without any destabilizing deformity. Since NVB is not mobilized, fewer complications, such as reduced penile sensation and retarded ejaculation, are seen in comparison with aforementioned techniques.

In a quality of life assessment performed by Van der Horst et al., 28 men with PD who underwent plication were retrospectively evaluated after 30 months (Van Der Horst et al. 2004). Patients reported penile straightening, penile shortening, postoperative ED, and sensory changes at rates of 100, 74, 35.7, and 28 %, respectively, with an overall satisfaction rate of 67.8 % (Table 4.1). Similarly, Kadioglu et al. reported penile straightening in 14 of 15 men who had a preoperative mean penile curvature of 51° after a mean follow-up of 24 months (Kadioglu et al. 2008). All patients reported penile shortening, and none complained of ED. In another series, more than 90 % of patients reported penile straightening with a postoperative ED rate of approximately 10 % (Greenfield et al. 2006; Taylor and Levine 2008). Gholami and Lue reported a 16-dot (two pairs of plication) or 24-dot (three pairs of plication) plication technique depending on the severity of the curvature with minimal tension using multiple parallel plications (Gholami and Lue 2002). After a mean follow-up of 2.6 years, 93 % of 116 patients had straight erections, and only 4 % of them complained of decreased erectile function. However, recurrence of the curvature was observed in 15 % of patients and approximately 41 % of them complained of penile shortening—the most commonly encountered adverse outcome of plication surgery.

The penoscrotal plication technique had been described for reconstruction of penile curvature in 45 men with PD (Dugi and Morey 2010). The technique was performed with a 2 cm longitudinal incision at the penoscrotal junction opposite the direction of maximal curvature and carried down through Buck's fascia to expose the TA, where parallel sutures are placed in vertical mattress fashion parallel to the urethra. Penile straightening was achieved in all patients with an overall satisfaction rate of 93 %. Despite evaluating relatively small cohort of patients with limited follow-up (only 34 were performed within 2 years), the technique described by the authors is promising since it is applicable for almost all curvatures, including severe or biplanar ones. The major advantage of the technique is the avoidance of circumcision to prevent distal ischemic and lymphatic complications. This technique has been performed recently for a larger patient population ($n = 102$) with a severe or biplanar curvature in 43 % of them and a similar follow-up time, 15 months. The results of this study look promising with only 4 % residual curvature and erectile dysfunction rates and penile shortening of 14 % (Adibi et al. 2012).

Tunica albuginea plication (TAP), modification of the Baskin-Duckett procedure, is another procedure that merit mentioning. In this technique, plication was performed by using suturing in an inverted fashion after tunical shaving. Meanwhile the plication is subsequently reinforced with several additional interrupted sutures in a Lembert fashion. Levine et al. evaluated the outcomes of TAP technique in a cohort including 100 patients with a median curvature angle of 49° and reported that 93 % of the patients had

curvatures less than 30° after a median follow-up of 72 months (Taylor and Levine 2008).

In summary, the major advantages of plication procedures are that they are simple, less invasive than other tunical shortening techniques, and associated with better preservation of erectile function. However, penile shortening (especially after correction of curvatures greater than 60° which may lead to shortening up to 2 cm), the need for mobilization of NVB that may lead to NVB injury and more length loss in ventral curvatures, and augmentation of an existing hourglass deformity or hinge effect due to the need for longer plications are potential disadvantages of these procedures (Ralph et al. 2010; Greenfield et al. 2006). Consequently, plication techniques are currently more utilized because extensive surgical experience except ventral curvatures is not needed.

4.9.5 Tunical Lengthening Procedures

Generally, penile lengthening surgery is reserved for men with adequate erectile capacity having severe penile length loss, curvatures greater than 60°, or prominent hourglass deformities (Ralph et al. 2010). These procedures involve incision of the plaque at the point of maximum concavity and insertion of a graft to repair the defect, with resultant penile lengthening. Gelbard and Hayden recommend plaque incision rather than full plaque excision because PD affects the entire TA and excision of the plaque might cause irreversible dysfunction of the veno-occlusive mechanism of the penis (Gelbard and Hayden 1991).

The operative procedure is similar for all grafting techniques. After performing a circumcising incision and degloving the skin to the base of the penis to provide exposure of the entire shaft, an artificial erection is created with an intracorporal injection of vasoactive agent. As a side note, degloving of penile skin without the circumcision incision has been defined by using a 5 cm ventral incision from the scrotal raphe to penile base, and it has been performed for over 80 patients with either congenital curvature or PD and erectile dysfunction (Austoni et al. 2012). For dorsally located plaques, Buck's fascia is opened from the dorsal side of the penis, and the deep dorsal vein is removed at the most prominent area of curvature. The NVB on the dorsolateral aspect of the corpora cavernosa is carefully dissected up to the healthy tissue (approximately 1 cm) with medial or lateral dissection off the underlying TA under loupe magnification (Pryor and Ralph 2002). For dorsally located plaques, medial dissection performed through the bed of the dorsal vein is probably more suitable than lateral dissection for dorsally located plaques. However, adequate lateral exposure is important for patients with severe lateral curvatures or hourglass deformities and might not be obtained with the medial approach.

Subsequently, plaque incision is performed, and graft material is positioned and sutured to restore tunical tissue integrity. Egydio et al. described the use of a single, almost complete circumferential-relaxing incision instead of traditionally used H incision, applying geometrical principles and suitable for all kinds of curvatures (Egydio et al. 2004). Tripod-shaped forks of 120° produce a simpler configuration of the tunical defect, which allows for easy suturing of the graft during the procedure. This technique has the potential to be the standard technique for plaque incision in the future.

4.9.6 Graft Materials

Historically, three types of grafts have been described: autologous grafts, allografts (or xenografts), and synthetic grafts (Ralph et al. 2010). Synthetic materials, including polyester and polytetrafluoroethylene, are not used anymore owing to increased rates of infection, fibrosis resulting from significant inflammation around the graft site, contracture owing to inelasticity of the material used, and risk of allergic reactions (Kadioglu et al. 2007).

The ideal graft material should be readily available, pliable, inexpensive, resistant to infection, and able to preserve erectile capacity. In addition, experience of the physician, patient preference, and type of deformity can influence the selection of graft type (Kadioglu et al. 2007).

Table 4.2 Outcomes of tunical lengthening surgery with autologous grafts

Study	*n*	Mean follow-up (months)	Graft material	Outcomes (% of cohort)			
				Penile straightening	Postoperative erectile dysfunction	Penile shortening	Patient satisfaction
Gelbard and Hayden (1991)	12	NA	Temporal fascia	100	0	NR	100
Wild et al. (1979)	50	17	Dermal	80	12	NR	70
Levine and Lenting (1997)	48	19.6	Dermal	100	100	NR	0
Goyal et al. (2008)	11	9.6	Dermal	81.8	18.2	NR	81.8
O'Donnell (1992)	25	42.2	Tunica vaginalis	88	68	96	NR
Kargi et al. (2004)	12	10	Fascia lata	100	0	0	100
Shioshvili and Kakonashvili (2005)	26	38.4	Buccal mucosa	92.3	7.7	15.4	NR
Cormio et al. (2009)	15	13.1	Buccal mucosa	100	0	0	93.3
Teloken et al. (2000)	7	6	Tunica albuginea	85.7	0	0	85.7
Da Ros et al. (2005)	27	NA	Crural tunica albuginea	96.2	3.7	NR	70.4
Hsu et al. (2003)	24	31.2	Deep dorsal vein	96	4	NR	100
Craatz et al. (2006)	12	4–10	Rectus sheath	83.3	NA	NR	58.3
Radopoulos et al. (2009)	14	12	Preputial skin	91	16	NR	75
Simonato et al. (2010)	26	95	Preputial skin flap	64	32	NR	40

Abbreviation: *NR* not reported

Currently, investigations to determine the ideal graft material continue, and there are no robust data from comparative studies. In this search for a novel graft, an absorbable sealant patch for topical application consisting collagen, fibrin glue, fibrinogen, and human thrombin was tried as a grafting material. In a study with 43 patients who underwent tunical incision/excision and patch application, postoperative penile straightness, shortening, ED, and satisfaction rates were reported as 93, 93, 21, and 51 %, respectively, with similar satisfaction to tunical shortening procedures (Horstmann et al. 2011). Preoperative erectile status of the patient and the type of intervention are more significant predictors of postoperative ED than graft type (Levine et al. 2005). In 46 % of the patients who underwent grafting surgery with cadaveric pericardium had significant reductions in erectile capacity (>6 point IIEF score reduction) and degree of preoperative curvature (>60°), the type of plaque incision (Egydio), patient age (>55), and presence of venous leak were demonstrated to be independent predicators of this reduction (Flores et al. 2011). Similar to these results, in a study with 218 patients who underwent plication or grafting, no correlation was found between postoperative ED and comorbid diseases except DM (Chung et al. 2011). Although a higher ED rate in grafting procedure was shown in comparison with plication (21 % vs. 10 %), this distinction did not reach statistical significance (Taylor and Levine 2012).

4.9.7 Autologous Grafts

Autologous grafts are derived from the recipient of the graft. These grafts can provide the advantage of easy incorporation into host tissue with decreased incidence of local inflammatory reaction. Since Lowsley and Boyce first used autologous grafts for patients with PD in 1950, there have been many studies assessing the outcomes of autologous materials, including the buccal mucosa, saphenous vein, preputium, dermis, TA, tunica vaginalis, fascia lata, and rectus sheath (Table 4.2).

Replacement of the plaque with buccal mucosa was first reported in 2005 (Shioshvili and Kakonashvili 2005). In animal experiments, they found that buccal mucosa was better than the vein, dermis, aponeurosis, and peritoneum in terms of elasticity, lengthening, and morphological properties of the graft. In their prospective cohort of 26 men, 24 achieved complete penile straightening within 2–6 months after surgery, and only 4 patients complained of penile shortening after a mean follow-up of 3.2 years. The authors concluded that the rich vascular blood supply of buccal mucosa provides good graft nourishment. In a recent study, Cormio et al. evaluated 15 patients who underwent plaque incision and buccal mucosa grafting and reported 100 % penile straightening with no postoperative ED after 13 months (Cormio et al. 2009). However, significant disadvantages of the procedure such as oral numbness (16 %) and tightness (32 %) caused by tissue harvesting still persisted after 1-year follow-up (Dublin and Stewart 2004). Despite the use of the buccal mucosa as a potential graft material due to its favorable graft properties, its side effects due to tissue harvesting are a major concern that probably limits its wide acceptance. Moreover, there are some concerns that buccal mucosa may produce inclusion cysts requiring secondary surgery (Levine et al. 2009).

Subsequently, Teloken used TA harvested from patients' own proximal crura for avoiding immunogenic problems of adopting another organ tissue to TA such as retraction of the graft due to fibrosis and decrease cosmetic alterations (Teloken et al. 2000). Schwarzer reported satisfactory penile straightening in 26 of 31 patients; 4 patients had minimal residual curvatures (Schwarzer 2005). In another study, a surgical technique combining the Nesbit procedure with TA-free grafting to decrease the penile shortening caused by the Nesbit procedure by grafting the opposite site has been defined (Hatzichristou et al. 2002). The authors noted no recurrence except one with mild curvature in 13 patients after a mean follow-up of 39.5 months. Despite being based on a rational idea, it should be noted that only small grafts can be obtained with this method and surgery related to the proximal crura might lead to problems such as narrowing of the proximal corpus cavernosum that might be a problem for the future implantation of penile prosthesis and weaken the support of the penis.

The use of dermal grafts has become less popular because of high rate of de novo veno-occlusive dysfunction due to decreased tunical wall tension on the graft site. Historically, Krishnamurti reported the results of the first use of penile dermal flap for defect reconstruction in 17 PD patients with a follow-up of 3 months to 4 years (Krishnamurti 1995). All patients had adequate erectile function, and none of them had penile shortening or graft contracture during the follow-up. Recently, Radopoulos et al. (2009) reported the preliminary results of penile curvature correction with preputial skin graft in 14 patients. After 12-month follow-up, eight patients were evaluated, and six of them had complete penile straightening; whereas the remaining two patients had a residual curvature less than 20°. Despite two patients reported worsening of erections in comparison with preoperative situation, no patients mentioned any complications including de novo ED at the end of follow-up. The authors mentioned that the tight structure of the foreskin's keratinized squamous epithelium functions to prevent venous leakage owing to the unfavorable outcomes of dermal grafts and the small number of patients in these studies, and the preputial skin is not a first-line option for graft material.

The saphenous vein is the most commonly used graft material for tunical lengthening owing to ease and reliability of harvesting, large surface area, and increased compliance with thin vascular walls that can be perfused from corporal bodies (Chang et al. 2012). Moreover, it is hypothesized that the nitric oxide secreted from endothelium might prevent hematoma formation and improve erectile function (Nowicki et al. 2004; Tsui et al. 2002). After the first report of saphenous vein grafting by Brock et al. in 1993, El-Sakka et al. reported the outcomes of 112 patients with a mean follow-up of 18 months (El-Sakka et al. 1998). Penile straightening was achieved in 95.5 % of patients with a 92 % satisfaction rate, while 12 % of the patients reported decreased potency, and 17 % had penile shortening. In another study, Kalsi et al. reported the

Table 4.3 Outcomes of tunical lengthening surgery with saphenous vein grafting

Study	*n*	Mean follow-up (months)	Outcomes (% of cohort)			
			Penile straightening	Penile shortening	Postoperative erectile dysfunction	Patient satisfaction
El-Sakka et al. (1998)	112	18	96	17	12	92
Kalsi et al. (2005)	113	12	86	25	15	96
Adeniyi et al. (2002)	51	16	82	35	8	92
Akkus et al. (2001)	50	32	80	40	6	88
De Stefani et al. (2000)	8	13	87.5	0	0	100
Kadioglu et al. (2008)	70	41	75.7	0	8.5	86.2
Kalsi et al. (2005)	40	60	80	35	22.5	86
Montorsi et al. (2004)	50	>60	72	100	22	60
Hsu et al. (2007)	48	NR	90	NR	5	90

Abbreviation: *NR* not reported

results of 113 patients with PD and a mean penile curvature of 64.5°. After a mean follow-up of 12 months, penile straightness was observed in 86 % of patients. Postoperative ED and penile shortening were present in 15 and 25 % of the patients, respectively. The authors noted the risk factor for de novo ED as greater angle (mean angle 76°) of deformity and concomitant risk factors for ED such as diabetes, hypertension, and ischemic heart disease (Kalsi et al. 2005). Similarly, we used the same technique in 75 patients with a mean angle of curvature of 61° and reported the outcomes of 70 patients after a mean follow-up of 41.7 months (Kadioglu et al. 2008).

In this series, penile curvature was completely straightened in 53 (75.7 %) patients, while 9 (12.8) patients and 8 (11.4 %) patients had residual curvature less than 20° and greater than 20°, respectively. Other studies performed with saphenous vein grafting reported overall rates for successful penile straightening, penile shortening, and patient satisfaction ranging between 72–96 %, 17–40 %, and 88–100 %, respectively (Adeniyi et al. 2002; Akkus et al. 2001, 2012; De Stefani et al. 2000) (Table 4.3).

Although midterm outcomes of venous grafting studies are satisfactory, the success of surgery decreases in the long run. In 2004, Montorsi et al. reported the results of 50 men after 5 years. All patients noted penile length loss and 6 of them had persistent or recurrent curvatures. Postoperative ED was present in 11 patients and diminished orgasmic function in 41 % of the cohort (Montorsi et al. 2004). Only 60 % of the patients were satisfied with the outcomes of the operation. Kalsi et al., reported 40 patients with vein grafting followed for 5 years and demonstrated a postoperative ED rate of 22.5 %, and a length loss was observed in 35 % of the patients (Kalsi et al. 2005). In these studies, decreased penile rigidity and penile shortening were the reasons of dissatisfaction. It is worth mentioning that the unfavorable outcomes of the former studies are generally attributed to the large vein grafts leading to de novo veno-occlusive dysfunction. In addition, worsening of erectile capacity due to risk factors in time may also contribute to ED which is the main dissatisfaction of these patients. By contrast, Hsu et al. reported the outcomes of 48 patients who underwent plaque incision and vein grafting with long-term follow-up.

Accordingly, the authors noted that objective measurement of the angle of curvature revealed a decrease from a preoperative mean of 52.6–7.8° with over 90 % of the patients satisfied with the postoperative outcomes (Hsu et al. 2007). The authors addressed some issues for preventing fibrotic complications that might lead to better satisfaction. These are using strong nonabsorbable monofilament sutures, avoidance of applying electrocautery and suction as well as using meticulous use of hydropressure and caution against too much separation of the tissue layers of the penile shaft.

Although patient satisfaction rates are high with autologous grafts, their use is often associated with harvest-site comorbidities, labor-intensive preparation, and penile complications. The major disadvantage of the vein grafting

procedure is the need for a second incision. Harvest-site comorbidities include leg wound infection, hypoesthesia of the legs, and lymphocele. Penile complications that might be encountered include decreased penile sensation, retarded ejaculation, penile edema, bulging of the graft, and hematoma under the graft site (Kalsi et al. 2005; Adeniyi et al. 2002). Generally, it is accepted that the nature of the graft is the least important determining factor with respect to complications, such as recurrent penile curvature and de novo ED. For this reason, surgeons' experience, patient preference, and cost-effectiveness are the main determining factors for choosing the graft type among autologous materials. However, it is worth to underline that experience with the saphenous vein is far beyond others and the abovementioned favorable tissue properties of veins and its well-established surgical technique makes it the mostly preferred one among the autologous materials.

4.9.8 Allografts and Xenografts

Allografts are extracellular matrix tissues isolated from the same species as host such as human cadaveric pericardium or dermis, whereas xenografts are processed from animal tissues such as bovine pericardium or porcine small intestinal submucosa (SIS). They allow host cell ingrowth with minimal inflammatory response.

Midterm outcomes of allograft surgery are similar to those of autologous grafts, with the advantages of a decreased operation time, and the absence of tissue harvesting means no harvest-site complications (Ralph 2010). For this reason, there is a current tendency for surgeons to use allografts. Among these materials, the pericardium is the most commonly used graft type.

Egydio et al. grafted bovine pericardium in 78 men and reported successful correction of deformity in 88 % of patients, with a 2.21 cm mean increase in penile length after a mean follow-up of 17.5 months (Egydio et al. 2004). In the assessment of long-term results (20 months) in 157 patients with 12 % mild residual curvature and 3 % glans hypoesthesia, no erectile dysfunction and 2.5 cm penile length increase was reported (Sansalone et al. 2011). In 23 patients with ED and PD, Sansalone inserted penile prostheses and circumferential grafts and achieved 2.8 cm length increase with 85 % penile straightening, 90 % satisfaction, and 20 % glans hyposensitivity (Sansalone et al. 2012). Studies with cadaveric pericardium reported similar penile straightening success rates of 56–98 % with penile shortening rates of 0–33 %. Overall satisfaction rates in these studies ranged between 73 and 98 % (Table 4.4). Recently, Taylor and Levine reported the results of 101 patients undergoing partial plaque excision with processed cadaveric pericardial grafting after a mean follow-up of 5 years (Taylor and Levine 2008). Only 8 % of the patients reported persistent or recurrent curvatures greater than 20°. Stretched penile length loss was observed in 47 %, postoperative ED in 24 % of the patients, while 31 % of them reported diminished penile sensation with an overall satisfaction rate of 76 %. Thus, the pericardium either bovine or cadaveric is the most widely used off-the-shelf biomaterial with satisfactory short- to midterm outcomes.

Small intestinal submucosa (SIS) is another acellular biomaterial consisting of the stratum compactum of the tunica mucosa, tunica muscularis mucosa, and submucosa of the porcine jejunum. Knoll was the first to use lyophilized porcine SIS graft in 12 patients with PD and reported complete straightness in 92 % of patients after a mean follow-up of 11 months (Knoll 2001). More-recently, Knoll reported the results of 162 patients with PD who underwent plaque incision and porcine 4-layer SIS grafting (Knoll 2007). After a mean of 38 months after surgery, similar to the initial report 91 % of the patients achieved penile straightening, 79 % of patients were fully potent, and only 5 % of the patients complained of penile shortening with no report of long-term pain, infection, and local immunogenic reaction. Similar results were obtained by Lee et al. in a small cohort of patients (Lee et al. 2008). However, unfavorable outcomes and complications were reported by Breyer et al. with porcine SIS 1-layer grafting in 19 patients with severe curvatures (>60°) (Breyer et al. 2007). In this cohort, 37 % of the patients developed recurrent curvatures, and 26 % of them had recurrence

Table 4.4 Outcomes of tunical lengthening surgery with allograft or xenografts

Study	*N*	Graft material	Mean follow-up (months)	Outcomes (% of cohort)			
				Penile straightening	Penile shortening	Postoperative erectile dysfunction	Satisfaction
		Allografts					
Taylor and Levine (2008)	81	Pericardial graft	58	92	33	35	75
Chun et al. (2011)	9	Cadaveric pericardium	6	55.5	NR	66.7	88.8
Usta et al. (2003)	19	Cadaveric pericardium	21.9	78.9	0	15.7	73.7
Levine and Estrada (2003)	40	Cadaveric pericardium	22	98	33	30	98
Kalsi et al. (2006)	14	Cadaveric fascia lata	31	78.5	28.5	7.1	92.8
Flores et al. (2011)	52	Cadaveric pericardium	6	100	0	46	NR
Chung et al. (2011)	23	Cadaveric pericardium	73	87	17	63	35
Sampaio et al. (2002)	40	Dura mater	12–72	87	0	15	95
Adamakis et al. (2011)	5	Acellular dermal tissue	6	100	NR	0	100
		Xenografts					
Egydio et al. (2004)	78	Bovine pericardium	17.5	88.4	0	0	NR
Knoll (2007)	162	Porcine 4-layer SIS	38	91	0	21	NR
Lee et al. (2008)	13	Porcine 4-layer SIS	14	100	NR	54	NR
Breyer et al. (2007)	19	Porcine 1-layer SIS	15	63	63	53	NR
Staerman et al. (2010)	28	Porcine 4-layer SIS	28	67	25	11	79
Chung et al. (2011)	17	Porcine 4-layer SIS	75	76	29	63	35

Abbreviation: *NR* not reported

of Peyronie's plaque after a mean follow-up of 15 months. Moreover, 26 % of the patients had graft-site hematomas, and one patient had graft infection. Consequently, despite a limited experience with 4-layer SIS grafting, it is a promising option for grafting. Recently, the results of long-term outcomes of xenografting have been published in a study of 86 PD patients with a follow-up longer than 5 years. Patients underwent surgery with dermal (n=20), pericardium (n=33) and Stratasis grafts (n=33) recurrence and persistence of curvature have been manifested 21 % and 11 of patients. Additionally, the initial satisfaction rate of 80 % decreased into 35 % in the long-term follow-up of these patients, casting doubt on the expected success of these grafts (Chung et al. 2011).

Cadaveric fascia lata is another biologically stable graft material with enough mechanical strength which is available in a range of sizes. It is used by Kalsi et al. in 14 PD patients with a mean follow-up of 31 months (Kalsi et al. 2006). Penile straightness was achieved in 11 patients, 4 patients complained of penile shortening, and only one patient reported de novo ED after the operation. The outcomes of autologous dermal,

cadaveric pericardial and 4-layered SIS grafting were compared in another study (Kovac and Brock 2007). Self-reported resolution of penile curvature was noted in 60 % of dermal, 100 % of cadaveric fascia lata, and 76.9 % of 4-layer SIS graft recipients. Meanwhile, patient satisfaction was higher in cadaveric fascia lata (92 %) and 4-layer SIS (84.6 %) in comparison with dermal grafts. Thus, the authors suggested using cadaveric fascia lata based on their comparative study. Accordingly, among allografts/xenografts, the pericardium, 4-layer SIS, and fascia lata are currently available options with satisfactory clinical outcomes. Of note, among allograft materials, the use of the dura mater, despite its high success rates, has been abandoned due to the probability of development of slow viral and prion infections (Sampaio et al. 2002).

4.9.9 Postoperative Care

There are a number of penile rehabilitation options to promote the recovery of erectile function after PD surgery, which might also serve to reduce penile shortening. Massage and stretch therapy, performed by grasping and pulling the glans penis away from the body while gently massaging the graft site, can be initiated 2 weeks after the surgery and applied twice a day for 4 weeks (Ralph et al. 2010). This therapy may be performed by the patients' themselves or their partners. Besides, bedtime phosphodiesterase (PDE5) inhibitors might be recommended commencing 7–10 days after surgery and maintained for 6 weeks to enhance nocturnal erections to stretch the tissue. Levine et al. reported the rate of postoperative ED as 26 % in a group of patients using nightly PDE5 inhibitors, whereas this rate was 36 % in patients who did not received this treatment (Levine et al. 2005). In addition, external penile traction therapy might be advised to reduce postoperative penile shortening. Traction therapy should be initiated 2–3 weeks after reconstructive surgery and performed for at least 2–8 h daily for 3 months (Moncada-Iribarren). Accordingly, despite having limited data, postoperative penile rehabilitation including massaging the graft side, using bedtime PDE5 inhibitors and penile traction therapy may be helpful to the patient for prevention of penile shortening and de novo ED.

4.9.10 Penile Prosthesis Implantation

Penile prosthesis implantation (PPI) is the standard procedure for men with PD and concomitant ED who do not respond to medical treatment (Ralph et al. 2010; Smith et al. 2008). Both malleable and inflatable prostheses are available, although inflatable prostheses are associated with higher functional satisfaction and lower persistent curvature rates. Indeed, Montorsi et al. reported a patient satisfaction rate of only 48 % in 48 men 5 years after they underwent malleable prosthesis surgery (Montorsi et al. 2003), whereas there are several studies in the literature of inflatable penile prostheses reporting success rates ranging between 84 and 100 % (Wilson and Delk 1994; Levine and Dimitriou 2000; Carson 2000; Chaudhary et al. 2005; Levine et al. 2010).

Generally, pubic or penoscrotal incisions are preferred for insertion of inflatable penile prosthesis according to the surgeons' experience. After cavernotomy, Hegar dilatators and, in fibrotic corpora, Rosillo cavernotomes can be used to dilate the corpora prior to the insertion of prosthesis. In patients with mild curvatures (<30°), penile straightening can be achieved with the implantation of prosthesis alone. If a considerable penile curvature (>30°) persists after PPI, there are several further options, including manual modeling, and plaque incision with or without grafting (Ralph 2010; Kadioglu et al. 2007). If residual curve is less than 30°, it is believed that no further treatment is needed because the prosthesis itself acts as a tissue expander and will presumably correct the deformity in 6–9 months (Ralph et al. 2010) However, results of a recent study challenge this assumption. Recently, Levine et al. reported the results of 90 patients with PD with drug-resistant ED and PD who underwent inflatable penile prosthesis implantation (Levine et al. 2010). Complete penile

straightening was achieved with prosthesis implantation alone in only 4 % of patients, whereas 79 % of men reported complete straightening after implantation with manual modeling. During a mean follow-up of 49 months, mechanical failure rate was 7.7 %, and device infection was reported in only one case. Overall patient satisfaction rate was 84 %, but specific patient questioning regarding satisfaction with curvature correction was disappointingly at only 73 %. More important point is that 84 % of patients felt that their deformity had reached maximum straightening at 3 months postoperatively. Although, authors conclude that inflatable penile prosthesis implantation with additional maneuvers is a durable and successful treatment option in men with medication-resistant ED and PD, this finding is contrary to previously accepted opinion that the penis could straighten progressively over time due to the tissue-expanding nature of the prosthesis.

Manual modeling, first described by Wilson and Delk, can be performed for patients with persistent curvature over 30° following PPI (Wilson and Delk 1994). After the prosthesis is inflated to its maximum distension, the penis is grasped with both hands and bent over the inflated cylinders at the point of maximum curvature but in the opposite direction. Pressure is sustained for at least 30–60 s. The tubing between the pump and the cylinders should be occluded with rubber shod hemostats to protect the pump high-pressure damage. This technique requires a high-pressure cylinder such as the AMS 700™ series (American Medical Systems, Minnetonka, Minnesota, USA) or Mentor Alpha 1® cylinders (Mentor Corp., Santa Barbara, California, USA). Wilson and Delk reported successful straightening in 86 % of patients with this maneuver; however, 8 % of men required subsequent plaque surgery. In a recent study with 209 patients who underwent penile prosthesis implantation operation, 29 % required additional intervention for remaining curvatures greater than 10–20°. Success rates of manual modeling with malleable and inflatable penile prostheses were 54 and 84 %, respectively, and five patients required remodeling surgery (Garaffa et al. 2011). The stress on prosthesis both through and after the surgery was claimed to damage the durability of the device as increased mechanical malfunction of 4 % was seen in PD patients with PPI (Diblasio et al. 2010).

Another option is to use a penile plication technique when implanting the prosthesis. In this technique, plication sutures are not tied before the implantation of prosthesis, but instead sutures are tied one by one with assessment of the curvature each time to achieve a straight penis (Hakim et al. 1996). Instead of plication, Nesbit procedure may also be used to correct the deformity after implantation of penile prosthesis.

PPI combined with manual modeling can provide penile straightness in more than half of patients, but up to 20–30 % of men with significant residual curvature require additional plaque surgery (incision with or without grafting) in order to achieve a straight penis (Kadioglu et al. 2008). Incision of the plaque over a Mentor Alpha 1® inflatable penile prosthesis using electrocautery (35 W) is the simplest plaque surgery that can be performed (Mulcahy and Wilson 2002). Grafting is generally recommended if the incision creates a tunical defect after incision of the plaque greater than 2 cm in order to decrease the risk of contracture owing to fibrosis. However, tunical defect may be closed with grafted tissue regardless of its size in order to prevent formation of hematoma, infection, and herniation of the cylinders (Wilson and Delk 1994).

As a novel approach, Shaeer et al. reported the transcorporal incision (TCI) followed by penile prosthesis implantation in 16 PD patients with refractory ED (Shaeer 2011). TCI is a minimally invasive endoscopic approach for plaque incision from within the corpora. The technique is performed at the point of maximum deformity to provide straightness and length to the penis before calibration of the corpora cavernosa, allowing implantation of a longer prosthesis in a straight penis with no need of mobilization of the NVB and a secondary incision. At the end of 14-month follow-up, penile straightness was achieved in all cases. Post-TCI, both corpora were of equal length with an average increase of 2.5 (11.9 %) cm on the right side and 1.9 (9.1 %) cm on the left. All patients were satisfied with the

surgical outcome, and none of them reported sensory deficit or residual curvature.

Autologous and allograft/xenograft tissues such as the dermis and pericardium can be used in prosthetic surgery, but autologous rectus fascia is most widely used material. Pathak et al. reported a patient satisfaction rate of 93.3 % 18 months after PPI in 15 patients with incision and autologous rectus fascia graft (Pathak et al. 2005). Similarly, we used autologous rectus fascia in 18 men undergoing incision of plaque and grafting after PPI and reported curvature recurrence in an acceptable rate of 5 % (Kadioglu et al. 2008). The major advantages of autologous rectus fascia are its resistance to ischemia owing to low metabolic demands, and tissue harvesting can be performed without an additional incision if a pubic incision is used for implantation of the prosthesis. Austoni et al. reported the outcomes of 145 patients undergoing three-piece inflatable PPI using a relaxing incision and grafting with the saphenous vein (Austoni et al. 2005). After 13 months, 80 patients reported their situation as stable in terms of penile straightening and satisfactory sexual function. Usta et al. reported a 78.9 % penile straightness rate using combination of prosthesis and pericardial graft (Usta et al. 2003). Consequently, the preference of graft materials while using penile prosthesis in PD surgery mostly depends on the experience of the surgeon and cost-effectiveness.

Conclusions

Medical therapy may be administered for Peyronie's disease in the early phase (<12 months), and the primary efficacy of the treatment should be evaluated by the curvature improvement. No significant improvement in curvature has been demonstrated in placebo-controlled studies for the oral treatment. While interferon treatment seems to be the best alternative in the nonsurgical treatment group with significant improvements in curvature, intralesional verapamil treatment, iontophoresis, and other options require further investigation.

Surgical treatment is the gold standard treatment option for men in the chronic phase of PD with disabling penile deformity and/or concomitant ED. Surgical approaches can be categorized as reconstructive surgeries (penile shortening or penile lengthening) or PPI. Erectile capacity should be assessed initially as it is the key determinant in the surgical technique preference followed by the direction and severity of the curvature, presence of destabilizing hinge effect caused by severe indentation or hourglass deformity, penis size, and patients' expectations related to the outcomes of surgical interventions. Among tunical shortening procedures, penile plication is a more minimally invasive option which is relatively easy to perform in comparison with Nesbit and Yachia procedures. Lengthening procedures should be reserved for severe curvatures and complex deformities; the saphenous vein and cadaveric pericardium are the most reliable graft materials.

For patients with PD and associated ED who are nonresponsive to medical treatment, PPI is the standard of care. However, additional interventions such as manual modeling, tunical placation, plaque incision, and grafting might be required to obtain complete penile straightness. If these maneuvers fail to correct the deformity, grafting with the autologous rectus fascia and cadaveric pericardium or 4-layer SIS can be considered. Although it is well known that PD is a heterogenous condition and no single procedure applies to all patients, the surgeon must choose the type of the operation according to his or her own individual experiences as well as the preference of the patient.

References

Adamakis I, Tyritzis SI, Stravodimos KG (2011) A novel approach for the surgical management of Peyronie's disease using an acellular, human dermis tissue graft: preliminary results. World J Urol 29(3):399–403

Adeniyi AA, Goorney SR, Pryor JP, Ralph DJ (2002) The Lue procedure: an analysis of the outcome in Peyronie's disease. BJU Int 89:404–408

Adibi M, Hudak SJ, Morey AF (2012) Penile plication without degloving enables effective correction of complex Peyronie's deformities. Urology 79(4): 831–835

Akkus E, Carrier S, Rehman J et al. (1994) Is colchicine effective in Peyronie's disease? A pilot study. Urology 44(2):291–295

Akkus E, Ozkara H, Alici B et al (2001) Incision and venous patch graft in the surgical treatment of penile curvature in Peyronie's disease. Eur Urol 40(5): 531–536; discussion 537

Akkus E, Ozkara H, Alici B et al (2012) Incision and venous patch graft in the surgical treatment of penile curvature in Peyronie's disease. Eur Urol 40:531–536

Akman T, Sanli O, Uluocak N et al (2011) The most commonly altered type of Peyronie's disease deformity under oral colchicine treatment is lateral curvature that mostly shifts to the dorsal side. Andrologia 43:28–33

Austoni E, Colombo F, Romano AL, Guarneri A, Kartalas Goumas I, Cazzaniga A (2005) Soft prosthesis implant and relaxing albugineal incision with saphenous grafting for surgical therapy of Peyronie's disease: a 5-year experience and long-term follow-up on 145 operated patients. Eur Urol 47:223–229

Austoni E, Altieri VM, Tenaglia R (2012) Trans-scrotal penile degloving, a new procedure for corporoplasties. Urologia 79:200–1012

Bella AJ, Perelman MA, Brant WO, Lue TF (2007) Peyronie's disease (CME). J Sex Med 4:1527–1538

Biagiotti G, Cavallini G (2001) Acetyl-L-carnitine vs tamoxifen in the oral therapy of Peyronie's disease: a preliminary report. BJU Int 88(1):63–67

Bjekic MD, Vlajinac HD, Sipetic SB, Marinkovic JM (2006) Risk factors for Peyronie's disease: a case–control study. BJU Int 97:570–574

Bokarica P, Parazajder J, Mazuran B, Gilja I (2005) Surgical treatment of Peyronie's disease based on penile length and degree of curvature. Int J Impot Res 17:170–174

Breyer BN, Brant WO, Garcia MM, Bella AJ, Lue TF (2007) Complications of small intestine submucosa grafts for Peyronie's disease. J Urol 177:589–591

Brock G, Kadioglu A, Lue TF (1993) Peyronie's disease: a modified treatment. Urology 42:300–304

Cantini LP, Ferrini MG, Vernet D, Magee TR, Quian A, Gelfand RA, Rajfer J, Gonzalez-Cadavid N (2008) Pro-fibrotic role of myostatin in Peyronie's disease. J Sex Med 5:1607–1622

Carson CC (2000) Penile prothesis implantation in the treatment of Peyronie's disease and erectile dysfunction. Int J Impot Res 12:122–126

Casabé A, Bechara A, Cheliz G (2011) Risk factors of Peyronie's disease. What does our clinical experience show? J Sex Med 8(2):518–523

Chang JA, Gholami SS, Lue TF (2012) Saphenous vein grafts. Int J Impot Res 14:375–378

Chaudhary M, Sheikh N, Asterling S, Ahmad I, Greene D (2005) Peyronie's disease with erectile dysfunction: penile modelling over inflatable penile prosthesis. Urology 65:760–764

Chun JL, McGregor A, Krishnan R, Carson CC (2011) A comparison of dermal and pericardial grafts in the modified Horton-Devine procedure for Peyronie's disease. J Urol 166:185–188

Chung E, Clendinning E, Brock G (2011) Five-year follow-up of Peyronie's graft surgery: outcomes and patient satisfaction. J Sex Med 8:594–600

Cormio L et al (2009) Surgical treatment of Peyronie's disease by plaque incision and grafting with buccal mucosa. Eur Urol 55(6):1469–1475

Craatz S, Spanel-Borowski K, Begemann JF, Olianas R, Fisch M, Hohenfellner R (2006) The dorsal lamina of rectus sheath. A suitable grafting material for the penile tunica albuginea in Peyronie's disease? BJU Int 97:134–137

Da Ros C, Graziottin M, Riberio E, Bonfanti A, Sogari P, Teloken C (2005) Graft of crural tunica albuginea for the treatment of Peyronie's disease. J Urol 173:202, A:V743

Daitch JA, Angermeier KW, Montaque DK (1999) Modified corporoplasty for penile curvature: long-term results and patient satisfaction. J Urol 162: 2006–2009

Davila H, Ferrini M, Rajfer J et al (2003) Fibrin induction of a Peyronie's-like plaque in the rat penile tunica albuginea. A new model for Peyronie's disease. Br J Urol 91:830–838

De Stefani S, Savoca G, Ciampalini S, Gattuccio I, Scieri F, Belgrano E (2000) Saphenous vein harvesting by "stripping" technique and 'W'-shaped patch covering after plaque incision in the treatment of Peyronie's disease. Int J Impot Res 12:299–301

Deveci S, Hopps CV, O'Brien K, Parker M, Guhring P, Mulhall JP (2007) Defining the clinical characteristics of Peyronie's disease in young men. J Sex Med 4(2): 485–490

DiBlasio CJ, Kurta JM, Botta S et al (2010) Peyronie's disease compromises the durability and component-malfunction rates in patients implanted with an inflatable penile prosthesis. BJU Int 106(5):691–694

Dublin N, Stewart LH (2004) Oral complications after buccal mucosa graft harvest for urethroplasty. BJU Int 94:867–869

Dugi DD, Morey AF (2010) Penoscrotal plication as a uniform approach to reconstruction of penile curvature. BJU Int 105(10):1440–1444

Egydio PH, Lucon AM, Arap S (2004) A single relaxing incision to correct different types of penile curvature: surgical technique based on geometrical principles. BJU Int 94:1147–1157

El-Sakka AI, Rashwan HM, Lue TF (1998) Venous patch graft for Peyronie's disease. Part II: outcome analysis. J Urol 160:2050–2053

Essed E, Schroeder F (1985) New surgical treatment for Peyronie's disease. Urology 25:582–587

Flores S, Choi J, Alex B et al (2011) Erectile dysfunction after plaque incision and grafting: short-term assessment of incidence and predictors. J Sex Med 8: 2031–2037

Garaffa G, Minervini A, Christopher NA (2011) The management of residual curvature after penile prosthesis implantation in men with Peyronie's disease. BJU Int 108(7):1152–1156

Gelbard MK, Hayden B (1991) Expanding contractures of the tunica albuginea due to Peyronie's disease with temporalis fascia free grafts. J Urol 145:772–776

Gholami SS, Lue TF (2002) Correction of penile curvature using the 16-dot plication technique: a review of 132 patients. J Urol 167:2066–2069

Giammusso B, Burrello M, Branchina A, Nicolosi F, Motta M (2004) Modified corporoplasty for ventral penile curvature: description of technique and initial results. J Urol 171:1209–1211

Gonzalez-Cadavid NF, Rajfer J (2005) Mechanisms of disease: new insights into the cellular and molecular pathology of Peyronie's disease. Nat Clin Pract Urol 2(6):291–297

Gonzalez-Cadavid NF (2009) Mechanisms of penile fibrosis. J Sex Med 6(suppl 3):353–362

Goyal NK, Kumar A, Das SK et al (2008) Experience with plaque excision and dermal grafting in the surgical treatment of Peyronie's disease. Singapore Med J 49(10):805–808

Greenfield JM, Lucas S, Levine LA (2006) Factors affecting the loss of length associated with tunica albuginea plication for correction of penile curvature. J Urol 175: 238–241

Hakim LS, Kulaksızoglu H, Hamill BK, Udelson D, Goldstein I (1996) A guide to safe corporotomy incisions in the presence of underlying inflatable penile cylinders: results of in vitro and in vivo studies. J Urol 155:918–923

Hatzichristou DG, Hatzimouratidis K, Apostolidis A, Tzortzis V, Bekos A, Ioannidis E (2002) Corporoplasty using tunica albuginea free grafts for penile curvature:surgical technique and long-term results. J Urol 167(3):1367–1370

Hatzimouratidis K, Eardley I, Giuliano F et al (2012) EAU guidelines on penile curvature. Eur Urol 62(3):543–552

Hauck EW, Altinkilic BM, Ludwig M et al (2012) Extracorporeal shock wave therapy in the treatment of Peyronie's disease. First results of a case controlled approach. Eur Urol 38:663–670

Hellstrom WJ, Bivalacqua TJ (2000) Peyronie's disease: etiology, medical and surgical therapy. J Androl 21:347–354

Hellstrom WJ, Kendirci M, Matern R et al (2006) Single-blind, multicenter, placebo controlled, parallel study to assess the safety and efficacy of intralesional interferon alpha-2B for minimally invasive treatment for Peyronie's disease. J Urol 176(1):394–398

Horstmann M, Kwol M, Amend B (2011) A self-reported long-term follow-up of patients operated with either shortening techniques or a TachoSil grafting procedure. Asian J Androl 13(2):326–331

Hsu YS, Huang WJ, Kuo YJ, Chung HJ, Chen KK, Chang LS (2003) Experience of surgical treatment of peyronie's disease with deep dorsal venous patch in Taiwanese men. J Chin Med Assoc 66:487–491

Hsu GL, Chen HS, Hsieh CH et al (2007) Long-term results of autologous venous grafts for penile morphological reconstruction. J Androl 28:186–193

Kadioglu A, Tefekli A, Erol B et al (2002) A retrospective review of 307 men with Peyronie's disease. J Urol 168(3):1075–1079

Kadioglu A, Akman T, Sanli O, Gurkan L, Cakan M, Celtik M (2006) Surgical treatment of Peyronie's disease: a critical analysis. Eur Urol 50(2):235–248

Kadioglu A, Sanli O, Akman T, Ersay A, Guven S, Mammadov F (2007) Graft materials in Peyronie's disease surgery: a comprehensive review. J Sex Med 4:581–595

Kadioglu A, Sanli O, Akman T, Cakan M, Erol B, Mammadov F (2008) Surgical treatment of Peyronie's disease: a single center experience with 145 patients. Eur Urol 53:432–440

Kalsi J, Minhas S, Christopher N, Ralph D (2005) The results of plaque incision and venous grafting (Lue procedure) to correct the penile deformity of Peyronie's disease. BJU Int 95:1029–1033

Kalsi JS, Christopher N, Ralph DJ, Minhas S (2006) Plaque incision and fascia lata grafting in the surgical management of Peyronie's disease. BJU Int 98(1): 110–114

Kargi E, Yesilli C, Hostuner M, Akduman B, Babuccu O, Mungan A (2004) Relaxation incision and fascia lata grafting in the surgical correction of penile curvature in Peyronie's disease. Plast Reconstr Surg 113:254–259

Knoll LD (2001) Use of porcine small intestinal submucosal graft in the surgical management of Peyronie's disease. Urology 57:753–757

Knoll LD (2007) Use of small intestinal submucosa graft for the surgical management of Peyronie's disease. J Urol 178:2474–1478

Kovac JR, Brock GB (2007) Surgical outcomes and patient satisfaction after dermal, pericardial and small intestinal submucosal grafting for Peyronie's disease. J Sex Med 4(5):1500–1508

Krishnamurti S (1995) Penile dermal flap for defect reconstruction in Peyronie's disease: operative technique and four years' experience in 17 patients. Int J Impot Res 7:195–208

Larsen SM, Levine LA (2012) Review of non-surgical treatment options for Peyronie's disease. Int J Impot Res 24(1):1–10

Lee EW, Shindel AW, Brandes SB (2008) Small intestinal submucosa for patch grafting after plaque incision in the treatment of Peyronie's disease. Int Braz J Urol 34(2):191–196

Levine LA (2009) Editorial comment on: surgical treatment of Peyronie's disease by plaque incision and grafting with buccal mucosa. Eur Urol 55:1475–1476

Levine LA, Dimitriou RJ (2000) A surgical algorithm for penile prosthesis placement in men with erectile failure and Peyronie's disease. Int J Impot Res 12:147–151

Levine LA, Estrada CR (2003) Human cadaveric pericardial graft for the surgical correction of Peyronie's disease. J Urol 170:2359–2362

Levine LA, Greenfield JM (2003) Establishing a standardized evaluation of the man with Peyronie's disease. Int J Impot Res 5:103–112

Levine LA, Lenting EL (1997) A surgical algorithm for the treatment of Peyronie's disease. J Urol 158: 2149–2152

Levine LA, Estrada CR, Storm DW, Matkov TG (2003) Peyronie's disease in younger men: characteristics and treatment results. J Androl 24(1):27–32

Levine LA, Greenfield JM, Estrada CR (2005) Erectile dysfunction following surgical correction of Peyronie's disease and a pilot study of the use of sildenafil citrate rehabilitation for postoperative erectile dysfunction. J Sex Med 5:241–247

Levine LA, Benson J, Hoover C (2010) Inflatable penile prosthesis placement in men with Peyronie's disease and drug-resistant erectile dysfunction: a single center study. J Sex Med 7(11):3775–3783

Licht MR, Lewis RW (1997) Modified Nesbit procedure for the treatment of Peyronie's disease: a comparative outcome analysis. J Urol 158:460–463

Loreto C, Barbagli G, Djinovic R et al (2011) Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) and its death receptor (DR5) in Peyronie's disease. A biomolecular study of apoptosis activation. J Sex Med 8(1):109–115

Lowsley OS, Boyce WH (1950) Further experiences with an operation for the cure of Peyronie's disease. J Urol 63:888–902

Martin DJ, Badwan K, Parker M et al (2002) Transdermal application of verapamil gel to the penile shaft fails to infiltrate the tunica albuginea. J Urol 168(6): 2483–2485

Montorsi F, Guazzoni G, Bergamaschi F, Rigatti P (2003) Patient-partner satisfaction with semirigid penile prostheses for Peyronie's disease: a 5-year followup study. J Urol 150:1819–1821

Montorsi F, Salonia A, Briganti A, Deho F, Zanni G, Luigi DP, Rigatti P (2004) Five year follow up of plaque incision and vein grafting for Peyronie's disease. [Abst 1256]. Annual Meeting of the American Urological Association, San Francisco

Moskovic DJ, Alex B, Choi JM, Nelson CJ et al (2011) Defining predictors of response to intralesional verapamil injection therapy for Peyronie's disease. BJU Int 108(9):1485–1489

Mulcahy JJ, Wilson SK (2002) Management of Peyronie's disease with penile prostheses. Int J Impot Res 14: 384–388

Mulhall JP, Creech SD, Boorjian SA et al (2004) Subjective and objective analysis of the prevalence of Peyronie's disease in a population of men presenting for prostate cancer screening. J Urol 171:2350–2353

Mulhall JP, Anderson M, Parker M (2005) A surgical algorithm for men with combined Peyronie's disease and erectile dysfunction: functional and satisfaction outcomes. J Sex Med 2:132–138

Mulhall JP, Schiff J, Guhring P (2006) An analysis of the natural history of Peyronie's disease. J Urol 175: 2115–2118

Nelson CJ, Diblasio C, Kendirci M, Hellstrom W, Guhring P, Mulhall JP (2008) The chronology of depression and distress in men with Peyronie's disease. J Sex Med 5(8):1985–1990

Nesbit RM (1965) Congenital curvature of the phallus: report of three cases with description of corrective operation. J Urol 93:230–232

Nowicki M, Buczkowski P, Miskowiak B, Konwerska A, Ostalska-Nowicka D, Dyszkiewicz W (2004) Immunocytochemical study on endothelial integrity of saphenous vein grafts harvested by minimally invasive surgery with the use of vascular mayo stripers. A randomized controlled trial. Eur J Vasc Endovasc Surg 27:244–250

O'Donnell PD (1992) Results of surgical management of Peyronie's disease. J Urol 148:1184–1187

Ohebshalom M, Mulhall J, Guhring P et al (2007) Measurement of penile curvature in Peyronie's disease patients: comparison of three methods. J Sex Med 4(1):199–203

Pathak AS, Chang JH, Parekh AR, Aboseif SR (2005) Use of rectus fascia graft for corporeal reconstruction during placement of penile implant. Urology 65: 1198–1201

Prieto Castro RM, Leva Vallejo ME, Regueiro Lopez JC et al (2003) Combined treatment with vitamin E and colchicine in the early stages of Peyronie's disease. BJU Int 91(6):522–524

Pryor JP, Farell CF (1983) Controlled clinical trial of vitamin E in Peyronie's disease. Prog Reprod Biol 9:41–45

Pryor JP, Ralph DJ (2002) Clinical presentations of Peyronie's disease. Int J Impot Res 14:414–417

Radopoulos D, Vakalopoulos I, Thanos P (2009) Preputial graft in penile curvature correction: preliminary results. Int J Impot Res 21(1):82–87

Ralph DJ, al-Akraa M, Pryor JP (1995) The Nesbit operation for Peyronie's disease: 16-year experience. J Urol 4:1362–1363

Ralph D et al (2010) The management of Peyronie's disease: evidence-based 2010 guidelines. J Sex Med 7: 2359–2374

Rehman J, Benet A, Minsky LS, Melman A (1997) Results of surgical treatment for abnormal penile curvature: Peyronie's disease and congenital deviation by modified Nesbit plication (tunical shaving and plication). J Urol 157:1288–1291

Sampaio JS, Fonseca J, Passarinho A, Cristino J, Mendes J (2002) Peyronie's disease: surgical correction of 40 patients with relaxing incision and dura mater graft. Eur Urol 41:551–555

Sansalone S, Garaffa G, Djinovic R (2011) Long-term results of the surgical treatment of Peyronie's disease with Egydio's technique: a European multicentre study. Asian J Androl 13(6):842–845

Sansalone S, Garaffa G, Djinovic R (2012) Simultaneous penile lengthening and penile prosthesis implantation in patients with Peyronie's disease, refractory erectile dysfunction, and severe penile shortening. J Sex Med 9(1):316–321

Savoca G, Scieri F, Pietropaolo F, Garaffa G, Belgrano E (2004) Straightening corporoplasty for Peyronie's

disease: a review of 218 patients with median follow-up of 89 months. Eur Urol 46:610–614
Schwarzer JU (2005) The tunica-albuginea-patch-technique: a new technique of an autologous grafting procedure for patients with Peyronie's disease. J Urol 173:202, A: V742
Schwarzer U, Sommer F, Klotz T, Braun M, Reifenrath B, Engelman U (2001) The prevalence of Peyronie's disease: results of a large survey. BJU Int 7:727–730
Shaeer O (2011) Transcorporal incision of Peyronie's plaques. J Sex Med 8(2):589–593
Shah PJR, Green NA, Adib RS et al (1983) A multicentre double-blind controlled clinical trial of potassium para-amino-benzoate (POTABA1) in Peyronie's disease. Prog Reprod Biol Med 9:61–67
Shioshvili TJ, Kakonashvili AP (2005) The surgical treatment of Peyronie's disease. Replacement of plaque by free autograft of buccal mucosa. Eur Urol 48:129–135
Shirazi M, Haghpanah AR, Badiee M et al (2009) Effect of intralesional verapamil for treatment of Peyronie's disease: a randomized single-blind, placebo-controlled study. Int Urol Nephrol 41(3):467–471
Simonato A, Gregori A, Varca V (2010) Penile dermal flap in patients with Peyronie's disease: long-term results. J Urol 183(3):1065–1068
Smith JF, Walsh TJ, Lue TF (2008) Peyronie's disease: a critical appraisal of current diagnosis and treatment. Int J Impot Res 20:445–459
Staerman F, Pierrevelcin J, Ripert T et al (2010) Medium-term follow-up of plaque incision and porcine small intestinal submucosal grafting for Peyronie's disease. Int J Impot Res 22(6):343–348
Tal R, Nabulsi O, Nelson CJ, Mulhall JP (2010) The psychosocial impact of penile reconstructive surgery for congenital penile deviation. J Sex Med 7(1 Pt 1):121–128
Tal R, Hall MS, Alex B, Choi J, Mulhall JP (2012) Peyronie's disease in teenagers. J Sex Med 9(1):302–308
Taylor FL, Levine LA (2008) Surgical correction of Peyronie's disease using tunica albuginea plication or partial plaque excision with pericardial graft. Long-term follow-up. J Sex Med 5:2221–2228
Taylor FL, Abern MR, Levine LA (2012) Predicting erectile dysfunction following surgical correction of Peyronie's disease without inflatable penile prosthesis placement: vascular assessment and preoperative risk factors. J Sex Med 9:296–301
Teloken C, Rhoden EL, Grazziotin TM et al (1999) Tamoxifen versus placebo in the treatment of Peyronie's disease. J Urol 162(6):2003–2005
Teloken C, Grazziotin T, Rhoden E et al (2000) Penile straightening with crural graft of the corpus cavernosum. J Urol 164:107–108
Tsui LC, Souza DS, Filbey D, Karlsson MG, Dashwood MR (2002) Localization of nitric oxide synthase in saphenous vein grafts harvested with a novel "notouch" technique: potential role of nitric oxide contribution to improved early graft patency rates. J Vasc Surg 35:356–362
Usta MF, Bivalacqua TJ, Sanabria J, Koksal IT, Moparty K, Hellstrom WJ (2003) Patient and partner satisfaction and long-term results after surgical treatment for Peyronie's disease. Urology 62:105–109
Valente EG, Vernet D, Ferrini MG, Qian A, Rajfer J, Gonzalez-Cadavid N (2003) F L-arginine and PDE inhibitors counteract fibrosis in Peyronie's plaque and related fibroblast cultures. Nitric Oxide 9:229–244
Van Der Horst C, Martinez Portillo FJ, Seif C, Alken P, Juenemann KP (2004) Treatment of penile curvature with Essed-Schroeder tunical plication: aspects of quality of life from the patients' perspective. BJU Int 93:105–108
Vernet D, Ferrini MG, Valente E, Magee TR, Bou-Gharios G, Rajfer J, Gonzalez-Cadavid NF (2002) Effect of nitric oxide on the differentiation of fibroblasts into myofibroblasts in the Peyronie's fibrotic plaque and in its rat model. Nitric Oxide 7:262–276
Weidner W, Hauck EW, Schnitker J (2005) Potassium paraaminobenzoate (POTABA) in the treatment of Peyronie's disease: a prospective, placebo-controlled, randomized study. Eur Urol 47(4):530–535
Wild RM, Devine CJ, Horton CE (1979) Dermal graft repair of Peyronie's disease: survey of 50 patients. J Urol 121:47–50
Wilson SK, Delk JR 2nd (1994) A new treatment for Peyronie's disease: modelling the penis over an inflatable penile prosthesis. J Urol 152:1121–1123
Yachia D (1990) Modified corporoplasty for the treatment of penile curvature. J Urol 143:80–82

Part III

Sexual Dysfunctions

Erectile Dysfunction

5

Dimitris Hatzichristou

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5.1 Introduction

It has been well established that sexual health not only reflects an integral part of overall health, but equally important, sexual activity is a predictor of general health (Lindau and Gavrilova 2010) and longevity (Davey Smith et al. 1997). According to recent data, more than half of people aged 57–85 and about one third of those aged 75–85 are sexually active; moreover, physical health is significantly correlated with sexual activity and many aspects of sexual function, irrespective of age (Lindau et al. 2007). Erectile dysfunction (ED), on the other hand, has been indicated not only as the most bothersome sexual dysfunction in men (Evangelia et al. 2010; Papaharitou et al. 2006) but also as an independent marker of cardiovascular health (Montorsi et al. 2010a, b; Nehra et al. 2012). Such data demonstrate that ED is a severe medical condition.

During the last 30 years, basic and clinical research has led to tremendous improvement in our knowledge on erection physiology and pathophysiology and has offered multiple novel, effective, and safe treatment options for ED patients (Andersson 2011; Hatzimouratidis et al. 2010; Montorsi et al. 2010b). Only the first 7 years following its market launch, sildenafil was prescribed by more than 750,000 physicians to more than 23 million men worldwide (Martin et al. 2013). Urologists played a key role in such developments, although the availability of phosphodiesterase type-5 inhibitors (PDE5i) in the market has unfortunately transformed ED management into a "prescribing work" (Martin Morales et al. 2013). Even though prescribing PDE5i can be an easy and effective way for restoring erections, the possible underlying causes of ED and associated life-threatening comorbidities remain undiagnosed (Dinsmore et al. 2007). Even in urology settings, limitations in the physicians' education lead to inadequate ED management (Hatzichristou et al. 2010). In fact, how many urologists nowadays do actually perform intracavernosal injections, color duplex Doppler ultrasonography of the penis or penile prosthesis implantation? Even more crucial, how many urologists have followed a Sexual Medicine course in order to gain the primary knowledge on sexuality and the communication skills to deal with patients with sexual problems? It is a fact that the knowledge gap between developments in Sexual Medicine and the clinical skills of practicing physicians is growing (Reisman et al. 2013). This chapter does not provide either an evidence-based overview or guidelines for ED management; there are several high-quality books, review articles, and the EAU guidelines to cover such needs (Porst 2012; Wespes et al. 2013). Evidence-based medicine is integration of the best available evidence from basic and clinical research, clinical expertise, and patient's preferences (Haynes et al. 1996). The goal of this chapter therefore is to "translate" research evidence in the field of ED into clinical practice guidance, based on the clinical experience earned practicing Sexual Medicine for more than two decades.

5.2 Which Are the Essential Skills for Treating ED Patients?

Urologists are the only physicians who can offer every available treatment option for ED to their patients, besides psychosexual therapy. Therefore, urologists are the experts on the condition, despite the fact that specialized training is mandatory. The

primary knowledge and the essential skills for a practicing urologist are the following:

- Knowledge of the epidemiology/risk factors, physiology/pathophysiology of the erectile mechanism
- Knowledge on prevention strategies
- Communication skills to provide a comfortable and relaxing atmosphere, without cultural/ethical constraints
- Sexual history taking, including psychosexual history
- Clinical examination, including basic cardiovascular assessment and basic neurological exam
- Mandatory laboratory test interpretation
- Duplex ultrasonography of the penis/cavernosal arteries
- Knowledge on the evidence of different treatment options
- Recommendations on the best use of oral pills
- Technical aspects of the intracavernosal injection program, including types and characteristics of vasoactive agents' injection technique and practical knowledge on priapism management
- Technical aspects on vacuum device use
- Technical aspects on the types of penile prosthesis devices
- Treatment strategies for nonresponders to pharmacotherapy
- Need for referrals

5.3 What Information Should We Share with Patients Regarding ED Epidemiology?

There are several reports on the numerous epidemiological studies (Eardley 2013; Lewis et al. 2010; Selvin et al. 2007). Informing a patient with ED about the high prevalence and incidence of ED worldwide, the role of the age and severity of the condition may make him feel that "he is not the only one" and that ED is a common medical condition. The key epidemiological findings that should be delivered to the patients are the following:

- The overall prevalence of ED is between 20 and 30 %.
- ED prevalence is age-dependent: at the age of 20 years, the prevalence is about 2–3 % and increases with age up to 50–80 % at the age of 80 years.
- 1 out of 5 men may experience inadequate rigidity, although managing to perform most of the times.
- 1 out of 4 men may experience inadequate rigidity and maintenance capability, rendering sexual intercourse problematic.
- Overall, 1 out of 10 men is not able to have sex due to erectile dysfunction.
- There are about 19–26 new ED cases per 1,000 men/year.

5.4 What Should We Know on ED Risk Factors?

Epidemiological and clinical studies have demonstrated consistent and compelling evidence for several risk factors or disorders associated with ED (Table 1).

Risk factors can be identified through the patient's medical history and laboratory tests; however, in several cases ED happens to be either the first symptom that will unmask a systemic disease (e.g., diabetes mellitus, cardiovascular disease) or overlaps with other medical conditions.

A brief review on conditions of special interest for urologists will be presented.

5.4.1 Lifestyle and ED

Lack of exercise, obesity, the metabolic syndrome, and smoking are lifestyle factors negatively affecting potency. According to "The 45 and Up Study" – a cross-sectional population-based trial conducted in Australia in a sample of 101,674 men – the risk of moderate/complete ED was higher among men with low socioeconomic status, high body mass index, sedentary lifestyle, and current smokers, compared to men without these risk factors. Moderate alcohol consumption was associated with a significantly reduced risk of ED in men aged 45–54 years, while increased physical activity was associated with lower risk of ED in men aged 75 or older (Weber et al. 2013). Compared to nonsmokers, the adjusted odds ratio for erectile dysfunction

was found to be 1.24 (95 % confidence interval (CI) 1.01–1.52, $p=0.04$) for those smoking ≤20 cigarettes per day and 1.39 (95 % CI 1.05–1.83, $p=0.02$) for those smoking >20 cigarettes per day, after adjusting for other confounding factors.

In the MMAS, men who began exercising in midlife had a 70 % reduced risk for ED compared to sedentary men and a significantly lower incidence rate over an 8-year follow-up period of regular exercise (Derby et al. 2000). According to the European Male Ageing Study, men with high waist circumference, including those who are "non-obese" with body mass index (BMI) <30 kg/m^2, have poor quality of life with symptoms of impaired physical, psychological, and sexual functions (Han et al. 2011). Data collected from a multicenter, cross-sectional, observational study conducted in Spain among men with a confirmed diagnosis of testosterone deficiency, the prevalence of ED and metabolic syndrome were 97.6 and 69 %, respectively, both increasing with age. Bivariate analysis showed that moderate or severe ED, obesity, and peripheral vascular disease were the variables associated with the greatest odds of metabolic syndrome (OR = 2.672 and 2.514, respectively), followed by alcohol intake (OR = 1.911) (Garcia-Cruz et al. 2013). Such data clearly demonstrate that identifying the patient's lifestyle factors while taking his medical history is highly significant, as their modification may constitute part of our treatment plan.

5.4.2 The Correlation Between Cardiovascular Disease (CVD) and ED

Numerous studies have documented that ED and CVD should be regarded as two different manifestations of the same systemic disorder (Gandaglia et al. 2013). A brief description of the key points of the correlation between ED and CVD follows.

5.4.2.1 ED Is an Indicator of Systemic Endothelial Dysfunction: "The Size Theory"

ED and CVD rarely become evident at the same time. This difference in rate of occurrence of different symptoms is proposed to be caused by the different size of the arteries supplying the penis and the heart (Montorsi et al. 2005). Because the size of penile arteries is smaller (1–2 mm) compared with that of coronary arteries (3–4 mm), the same level of endothelial dysfunction and atherosclerosis may lead to a more significant reduction of blood flow in erectile tissues compared with that in coronary arteries. The "size theory" therefore explains why the penile vascular bed could be a sensitive indicator of systemic vascular diseases. In support of this hypothesis, COBRA trial revealed that ED occurs prior to cardiac symptoms in virtually all patients with chronic coronary syndrome with a time interval of 3 years, whereas patients with acute coronary syndrome have a low prevalence of sexual dysfunction (Montorsi et al. 2006).

Thus ED could be an indicator of systemic endothelial dysfunction that can be used to identify men at higher risk of CVD events (Gandaglia et al. 2013).

5.4.2.2 CV Risk Is Higher in Younger Men with ED

The latest document of the Princeton Consensus for the Management of Erectile Dysfunction and Cardiovascular Disease (Nehra et al. 2012) included three important statements:

- ED not only shares risk factors with CVD but also constitutes itself an independent marker of increased risk for CVD.
- ED is a marker of significantly increased risk for coronary artery disease (CAD), stroke, and all-cause mortality.
- ED provides an opportunity for CVD risk reduction.

Multiple published studies have shown that ED has a similar or greater predictive value for cardiovascular events than traditional risk factors including smoking, hyperlipidemia, and family history of myocardial infarction; therefore, ED is an independent marker of increased CVD risk and mortality, particularly in men aged 30–60 years (Gandaglia et al. 2013). According to a meta-analysis of 12 prospective cohort studies involving 36,744 participants, ED significantly increases the risk of CVD, coronary heart disease, stroke, and all-cause mortality, while this

increase is probably independent from conventional cardiovascular risk factors (Dong et al. 2011). Furthermore, a more recent meta-analysis of 14 studies revealed that the relevant CV risk is higher in younger men with ED (Vlachopoulos et al. 2013). Similarly, another study showed that ED is a particularly significant harbinger of CVD in 2 populations: men <60 years of age and those with diabetes (Miner et al. 2012). In addition, men 40–49 years of age with ED had much higher incidence of new incidents of coronary artery disease than those without ED, while ED was found to be a particularly powerful predictor of CVD in diabetic men as well.

Regarding the common underlying pathophysiology of ED and CVD, the most recent systematic review on the topic reports that the link between these conditions might reside in the interaction between androgens, chronic inflammation, and cardiovascular risk factors that determines endothelial dysfunction and atherosclerosis, resulting in disorders of penile and coronary circulation (Gandaglia et al. 2013).

ED and CVD also share mutually reinforcing associations and predictors with depression (Goldstein 2000). In one study conducted in patients with coronary artery disease, ED was associated with age ($p < 0.0001$) and depressive symptoms ($p = 0.007$), but not with the number of obstructed coronary arteries, history of diabetes mellitus, hypertension, or smoking (Mulat et al. 2010). Therefore, treatment of all three conditions is recommended.

5.4.2.3 CVD Risk Assessment

According to the Third Princeton Consensus (Nehra et al. 2012), the following risk assessments are recommended for identifying men with ED and unknown CVD who may require additional cardiologic work-up to prevent a major cardiac event including MI, acute coronary syndromes, angina pectoris, heart failure, and death:

- Patient history including information on patient's age, presence or absence of comorbid conditions (e.g., abdominal obesity, hypertension, dyslipidemia, prediabetes, and symptoms suspicious for obstructive sleep apnea), family history of premature atherothrombotic CVD (father aged <55 years or mother aged <65 years; ACCF/AHA class I, LOE B), and lifestyle factors (e.g., diet, excessive use of alcohol, limited physical activity, and smoking).
- Physical examination noting blood pressure, waist circumference, BMI, fundal arterial changes, cardiac auscultation, carotid bruits, and palpation of femoral and pedal pulses.
- ED severity (International Index of Erectile Function score or Sexual Health Inventory of Men) and duration.
- Resting electrocardiogram (ACCF/AHA class IIa, LOE C in asymptomatic adults with hypertension or diabetes and ACCF/AHA class IIb, LOE C in asymptomatic adults without hypertension or diabetes)
- Fasting plasma glucose level
- Serum creatinine level (estimated glomerular filtration rate) and albumin to creatinine ratio
- Total testosterone (TT) level (before 11 am)
- Plasma lipid levels (total, low-density lipoprotein, HDL cholesterol, and triglyceride values)

As urologists may be the first experts that men with erectile dysfunction will contact, they have the responsibility to identify those who require early intervention to prevent cardiovascular disease.

5.4.2.4 The Princeton Consensus Algorithm on Sexual Function and Cardiovascular Health

The Princeton Consensus (Expert Panel) Conference is a multispecialty collaborative tradition dedicated to optimizing sexual function and preserving cardiovascular health (DeBusk et al. 2000; Kostis et al. 2005; Nehra et al. 2012). The Third Princeton Consensus recommendations are based upon those developed during the first and second Princeton Consensus Conferences (DeBusk et al. 2000; Kostis et al. 2005). In the updated recommendations, special emphasis is placed upon (Nehra et al. 2012): (a) the use of exercise ability and stress testing to ensure that each man's cardiovascular health is consistent with the physical demands of sexual activity before prescribing treatment for ED and (b) the link between ED and the cardiovascular disease, which may be asymptomatic, and the benefit deriving from cardiovascular risk reduction.

The Third Princeton Consensus stratified patients with ED into three cardiovascular risk categories (Nehra et al. 2012):

Low-Risk Patients
Low-risk group means that sexual activity does not represent significant cardiac risk. Low-risk patients include successfully revascularized individuals (e.g., via coronary artery bypass grafting, stenting, or angioplasty), patients with asymptomatic controlled hypertension or mild valvular disease, as well as patients with left ventricular dysfunction/heart failure (NYHA classes I and II) who achieved five metabolic equivalents of the task (Mets) without ischemia on recent exercise testing.

High-Risk Patients
High-risk patients are those with cardiac conditions severe or unstable enough to pose a significant risk when resuming sexual activity. Common high-risk patient profiles include unstable or refractory angina pectoris, uncontrolled hypertension, congestive heart failure (NYHA class IV), recent MI without intervention (<2 weeks), high-risk arrhythmia (exercise-induced ventricular tachycardia, implanted internal cardioverter defibrillator with frequent shocks and poorly controlled atrial fibrillation), obstructive hypertrophic cardiomyopathy with severe symptoms, and moderate to severe valve disease, particularly aortic stenosis.

Indeterminate-Risk Patients
Stress test evaluation is required for indeterminate-risk patients before resuming sexual activity. Completing 4 min of the standard Bruce treadmill protocol (5–6 Mets) without symptoms, arrhythmias or a drop in systolic BP identifies the safety of sexual activity. Based on the results, they will be reclassified to low- or high-risk patients. Indeterminate-risk patients include those with mild or moderate stable angina pectoris, past MI (2–8 weeks) without intervention awaiting exercise electrocardiography, congestive heart failure (NYHA class III), and non-cardiac sequelae of atherosclerotic disease (e.g., PAD and history of stroke or transient ischemic attack).

This stratification can be used as the basis for a treatment algorithm with the aim of initiating or resuming sexual activity (Fig. 5.1). It is also possible for the clinician to estimate the risk of sexual activity in most patients according to their level of exercise tolerance, which can be determined when taking the patient's history.

5.4.2.5 Sexual Counselling for Individuals with Cardiovascular Disease and Their Partners

Cardiac rehabilitation programs typically neglect the role of sexual function. Health professionals approach management of these disorders from a disease-centered perspective, which often fails to integrate the patient's needs and perspectives (Hatzichristou and Tsimtsiou 2005). The trajectory, however, of a cardiovascular event and the comorbid ED may demand continuous adjustment from both patients and their partners as they adapt to the chronicity of heart disease. In turn, patients frequently complain about lack of sensitivity or awareness on the part of their physicians. Recently, a joint position statement from the American Heart Association and the European Society of Cardiology Council on Cardiovascular Nursing and Allied Professions has been published (Steinke et al. 2013), in order to address the barriers for successful sexual counselling interventions in CV patients and emphasize the significant value of including sexual counselling content in healthcare providers' educational programs. The document includes recommendations for sexual activity in patients with congenital heart disease, coronary artery disease, angina and MI, coronary artery bypass surgery, cardiac transplantation and left ventricular assist device, heart failure, implantation of cardioverter-defibrillator, and stroke (Steinke et al. 2013).

5.4.3 The Relationship of Benign Prostatic Hyperplasia (BPH) and ED

BPH-associated lower urinary tract symptoms (LUTS) are the most common non-vascular risk factor for ED. Community-based and clinical studies demonstrate a strong and consistent

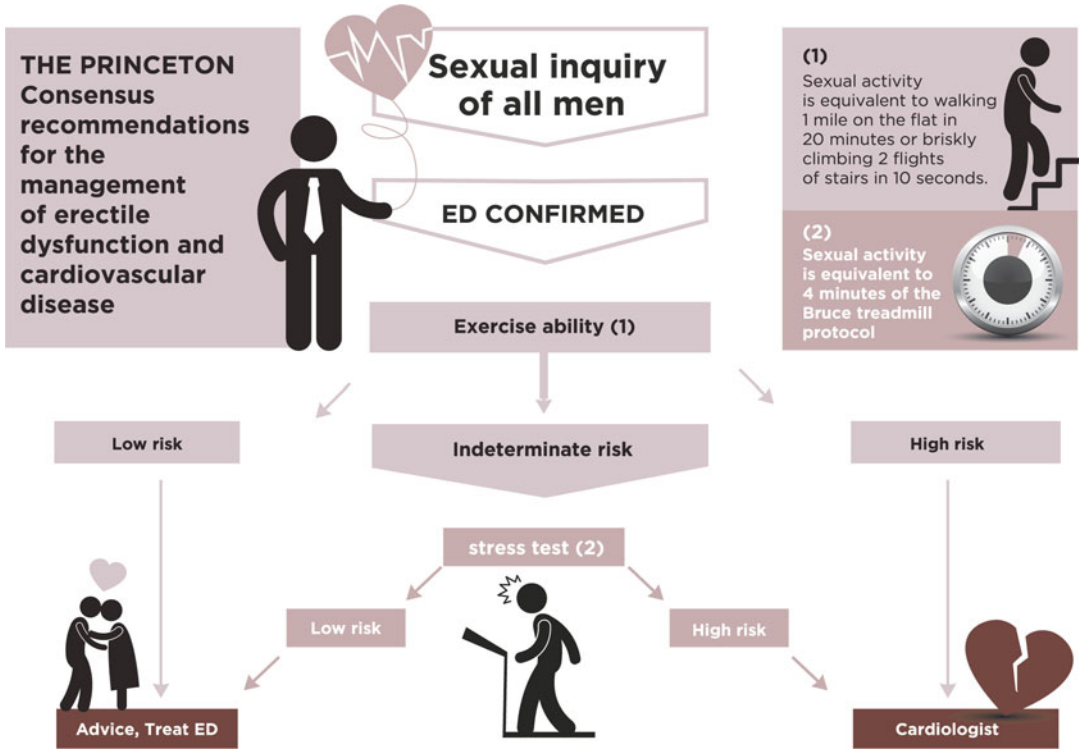

Fig. 5.1 The Princeton Consenus Recommendations for the management of erectile dysfunction and cardiovascular and cardiovascular disease (DeBusk et al. (2000), Kostis et al. (2005), Nehra et al. (2012); Source: www.imop.gr)

association between LUTS and ED, suggesting that elderly men with LUTS should be evaluated for ED and vice versa (Gacci et al. 2011).

5.4.3.1 LUTS Is a Strong Predictor of ED

According to the first published study in men with LUTS due to BPH (Rosen et al. 2003), the overall prevalence of ED was 49 %; severity of LUTS was a strong predictor of erectile dysfunction with odds ratio 8.90 (95 % CI: 6.85–11.55). Presence of severe LUTS, as well as changing LUTS severity category (from mild to moderate, or moderate to severe LUTS), had a greater impact on ED than aging by 10 years. Results from the large EpiLUTS study in 2,954 men revealed that 24.8 % had reduced or no sexual activity because of LUTS (Wein et al. 2009). In a systematic review of 12 studies that used both the International Prostate Symptom Score (IPSS) and International Index of Erectile Function (IIEF) as assessment tools, the overall prevalence of coexistent LUTS and ED of any severity was 71–80 % among men seeking treatment for LUTS. In the 2011 US National Health and Wellness Survey, a cross-sectional, self-administered online survey in men ≥40 years old, the prevalence of ED alone and ED/BPH (ED/BPH) was 24.6 and 4.9 %, respectively (Foster et al. 2013). Overall, 37.3 % of men with ED and 74.6 % with ED/BPH reported moderate-severe urinary (IPSS ≥8). About 23 % of either group reported currently using ED medication, compared to 31.1 % with ED/ BPH; BPH medication was used by 51.7 % of men (Foster et al. 2013). These findings suggest that ED in patients with BPH-associated LUTS is underdiagnosed and undertreated.

5.4.3.2 The Interplay of the Four Common Pathophysiologic Mechanisms

It has been well established that ED and BPH share common pathophysiologic mechanism. Actually, four mechanisms have been proposed,

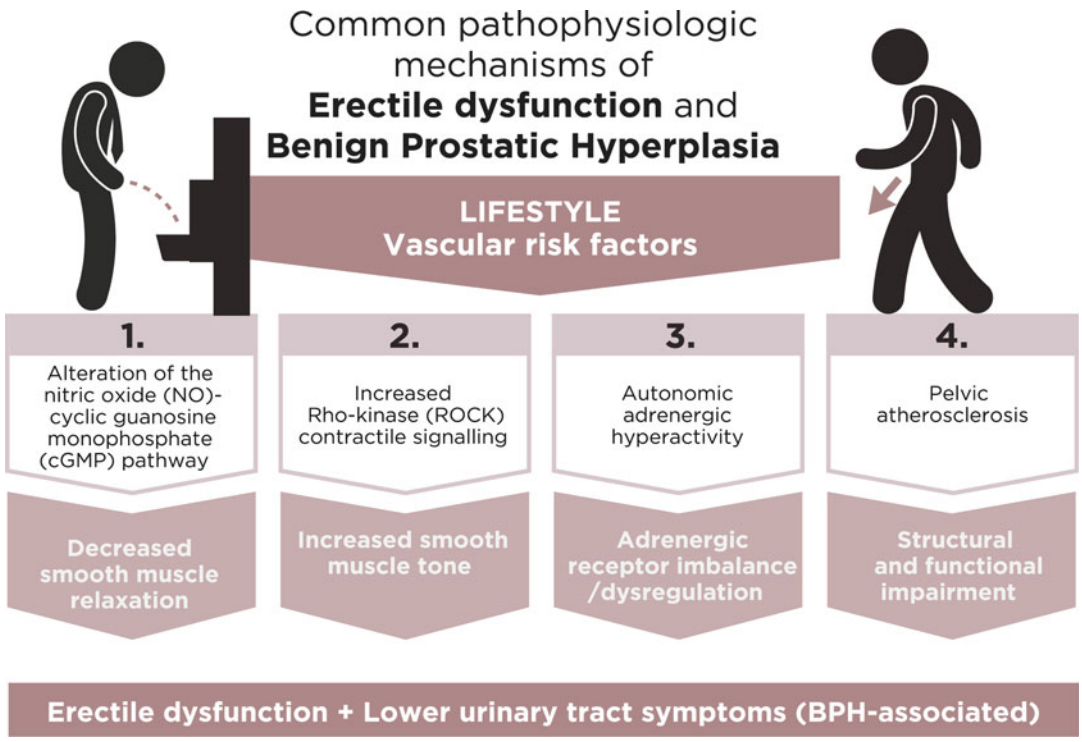

Fig. 5.2 Common pathophysiologic mechanisms of erectile dysfunction and benign prostatic hyperplasia (Gacci et al. (2011); Source: www.impo.gr)

and available data support interplay between those mechanisms in both comorbidities. The four pathophysiologic mechanisms of BPH-associated LUTS and ED are shown in Fig. 5.2 and can be summarized as follows (Gacci et al. 2011; Giuliano et al. 2013):

1. Alteration of the nitric oxide (NO)–cyclic guanosine monophosphate (cGMP) pathway. Production of NO synthase (NOS) and NO in the corpora cavernosa, the prostate, and the bladder is reduced in the presence of vascular risk factors, decreasing the level of smooth muscle relaxation of the corpora cavernosa, the bladder neck, and urethra and may stimulate prostatic smooth muscle cell proliferation that results in increased outlet resistance (Giuliano et al. 2013).
2. Enhancement of RhoA–rho-kinase (ROCK) contractile signalling. The ROCK pathway is a major mechanism regulating calcium sensitivity and, hence, contraction of smooth muscle. Increased smooth muscle tone, observed in LUTS and ED, exerts its effects via rho-kinase (Chang et al. 2005).
3. Autonomic adrenergic hyperactivity. Autonomic nervous system hyperactivity is well known to be associated with ED, but is also associated with BPH/LUTS in humans, as a significant association between increased sympathetic tone and the level of LUTS has been observed (McVary et al. 2005).
4. Pelvic atherosclerosis. Risk factors for vascular disease and ED (e.g., hypertension, smoking, diabetes, and hypercholesterolemia) have been proposed to contribute to LUTS by reducing pelvic arterial blood flow and, thus, resulting in smooth muscle loss from the bladder, prostate fibrosis, and increased urethral resistance. Actually, pelvic atherosclerosis may also induce autonomic nervous system hyperactivity, reduce NOS expression, and upregulate rho-kinase (Gacci et al. 2011).

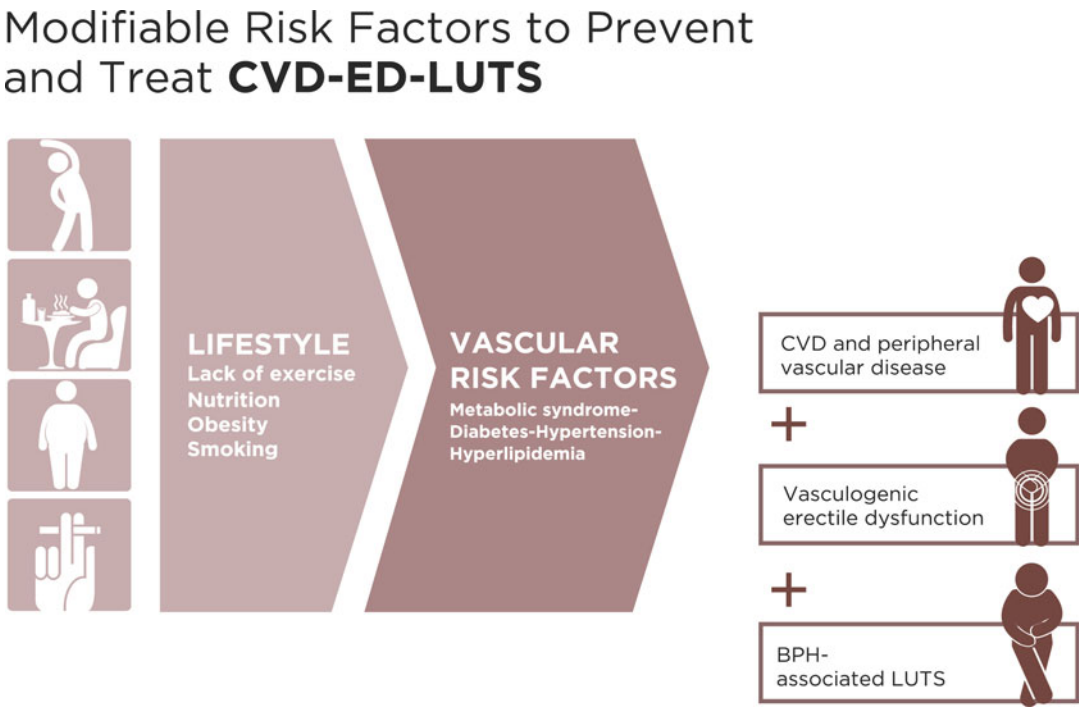

Fig. 5.3 Modifiable risk factors to prevent and treat CVD-ED-LUTS (Parsons (2007), Glina et al. (2013); Source: www.impo.gr)

5.4.3.3 The Need for Common Management of ED, LUTS, and CVD

The necessity for common management of ED and LUTS is well established, and urologists may diagnose and manage both conditions appropriately (Kirby et al. 2013). Factors that potentially increase the risk of benign prostatic hyperplasia and lower urinary tract symptoms include obesity, diabetes, and lack of physical activity (Parsons 2007). Furthermore, the metabolic syndrome is associated with the risk predictors for clinical progression of BPH in men with moderate to severe lower urinary tract symptoms (Kwon et al. 2013). However, patients with BPH-associated LUTS have a considerably higher prevalence of CVD than the general population in old age. Several studies have documented that CV risk factors are also risk factors for BPH. On the other hand, BPH may be an insidious risk factor for CVD by causing nocturia-induced sleep disturbances, blood pressure variability, increased sympathetic activity, and non-dipping BP variations (Karatas et al. 2010).

On the other hand, as ED and CVD share risk factors, a common prevention strategy has been proposed (Hatzichristou and Tsimtsiou 2005). Currently, the evidence recommends that ED patient education should aim at increasing exercise, reducing weight to achieve a body mass index less than 30 kg/m(2), and stopping smoking to improve or restore erectile function. When comorbidities are present, lifestyle modifications may include precise glycemic control in diabetic men and the use of pharmacologic therapies for hypertension and depression, which are less likely to cause sexual side effects (Glina et al. 2013).

As all common risk factors for ED and BPH are risk factors for CVD, the optimal clinical practice would integrate a common prevention and management strategy for all three conditions (Fig. 5.3). Such clinical practice is further endorsed by data showing that waist circumference – as a main sign of the metabolic syndrome – is positively

associated with prostate volume, serum prostate-specific antigen, and IPSS (Lee et al. 2012). Furthermore, statins have a beneficial effect on erectile function (La Vignera et al. 2012), while a retrospective cohort study has suggested that the use of statins may delay the development of LUTS by 6.5–7 years (St Sauver et al. 2011).

5.4.3.4 BPH Therapies and ED

Clinical trials with 5ARI report prevalence rates of de novo erectile dysfunction of 5–9 %, while decreased circulating dihydrotestosterone (DHT) in diminished sexual desire and/or orgasm (Gacci et al. 2011; Gur et al. 2013). Prolonged adverse effects on sexual function such as erectile dysfunction and diminished libido are reported by a subset of men, raising the possibility of a causal relationship (Traish et al. 2011).

A systematic review of 33 randomized controlled trials and cohort studies showed that minimally invasive surgeries for BPH have comparable effects to those of TURP on erectile function (Frieben et al. 2010). From a technical perspective, the comparative effects of bipolar versus monopolar TURP on overall sexual function have been investigated in an international, multicentre double-blind RCT using a true bipolar system and IIEF. No difference was found between the two arms of the trial in relation to any aspect of the sexual function (Mamoulakis et al. 2013).

5.4.3.5 The Role of PDE5i in LUTS

Several randomized controlled trials on PDE5i have demonstrated significant improvements in both lower urinary tract symptoms (LUTS) and erectile dysfunction (ED) in men affected by the one or both conditions, without significant adverse events. A recent meta-analysis showed that the use of PDE5i was associated with a significant improvement of the IIEF score (+5.5; $p<0.0001$) and the International Prostate Symptom Score (IPSS) (−2.8; $p<0.0001$), but not the maximum flow rate compared to placebo. On the other hand, combination of PDE5i and alpha-1 adrenergic blockers improved the IIEF score (+3.6; $p<0.0001$), IPSS score (−1.8; $p=0.05$), and Q(max) (+1.5; $p<0.0001$) at the end of the study as compared with alpha-blockers alone (Gacci et al. 2012).

Thus, evidence and our everyday clinical practice suggest that PDE5i can improve LUTS as alpha-blockers do, in addition to the erectile function improvement.

5.4.4 Drug-Induced Erectile Dysfunction

ED is a common side effect of medication and should be interpreted with caution. Several drug categories have been associated with ED, including beta-adrenoreceptor antagonists, digoxin, thiazide diuretic, older antipsychotics and risperidone, selective serotonin reuptake inhibitors (SSRIs) and venlafaxine, lithium, gabapentin, carbamazepine, as well as antiandrogens (U 2010). However, two drug categories are the most widely used and associated with ED: antihypertensives and antidepressants. Although ED treatments are efficacious in such patients, strategies to prevent ED are absent. Regarding antihypertensives, sexually related side effects may not only compromise the patient's and partner's quality of life, but may also lead to withdrawal or poor compliance with severe consequences: abnormal blood pressure and associated life-threatening morbidity. Unfortunately, only a minority of the existing clinical practice guidelines (CPGs) for the treatment of hypertension consider ED or other sexual issues to be either an adverse outcome or a factor to consider in treatment (Karavitakis et al. 2011). This is partly due to the lack of randomized trials assessing the effects of switching to currently available antidepressant agents with lower rates of adverse sexual effects, the role of psychological or mechanical interventions or of techniques such as "drug holidays" (Taylor et al. 2013). From a clinical practice point of view, the only way to identify the effect of a drug is to order a drug holiday, if indicated: in other words, if erectile function is restored when the prescribed medication is interrupted for some period of time, this easily leads to the conclusion that ED was drug induced. In such case, a change of the prescribed drug to one with similar action without sexual side effects may be worthy. In cases that this is not feasible,

the following aspects should be discussed with the physician who prescribed the drug:

- Dose reduction, if indicated.
- Dose schedule after sexual activity.
- Scheduling a drug holiday periodically, e.g., a 2-day drug holiday each week (usually weekends) of an antidepressant, may restore sexual function without the drug losing its efficacy.

5.4.5 Urological Surgery and ED: What Kind of Information Should Be Provided to Patients?

From a urologist's perspective, ED associated with other urological diseases or treatments is of major interest, particularly post-radical prostatectomy ED, as well as penile surgery-associated ED.

5.4.5.1 Nerve-Sparing Radical Prostatectomy and Rehabilitation Program: A Fairy Tale?

According to the Merriam Webster dictionary, fairy tale is defined as a story in which improbable events lead to a happy ending. Is preservation of erectile function a fairy tale? In order to give an evidence-based answer, two distinct questions have to be addressed: if the nerve-sparing surgery preserves potency in most men and if rehabilitation programs are able to restore erections.

Nerve-Sparing Radical Prostatectomy: Myth or Reality?

Many issues regarding radical prostatectomy and erectile function (EF) remain under discussion (Hatzichristou 2012). Post-radical prostatectomy ED prevalence varies in different studies between 25 and 75 % (Sanda et al. 2008). Given that there are no randomized prospective, well-designed head-to-head, comparative studies to show that the outcome in erectile function (EF) is significantly different between open and laparoscopic or robotic radical prostatectomy (Salonia et al. 2012b), the International Consultation for Sexual Medicine Committee statement recommends: "Patients should be given individualised outcomes based on surgical technique, patient and surgeon factors, thus including accurate data on erectile function recovery from their own patient population" (Mulhall et al. 2010). This last aspect, which seems polemic against a certain type of behavior, actually allows clinicians to bypass the errors of the scientific literature, eventually providing patients with more realistic expectations (Hatzichristou 2012). Therefore, a comprehensive discussion with the patient about the true prevalence of postoperative erectile dysfunction (ED), the concept of spontaneous or pharmacologically assisted erections, and the difference between "back to baseline" EF and "erections adequate enough to have successful intercourse," clearly emerge as key issues in ultimately understanding ED prevention and promoting satisfactory postoperative recovery of erectile function. Patient factors (including age, baseline EF, and comorbid conditions), cancer location (unilateral vs bilateral nerve-sparing), technical aspects (i.e., intra- vs inter- vs extrafascial technique), surgical approach (i.e., open, laparoscopic, and robot-assisted RP), and surgeon factors (i.e., surgical volume and surgical skill) represent the primary parameters contributing to EF recovery (Salonia et al. 2012b).

Rehabilitation Program: Is It Time to Forget About It?

There has been a lot of discussion in the literature regarding the use of penile rehabilitation to ensure cavernous oxygenation, but the results of the well-designed studies are discouraging. Despite the great number of possible rehabilitation approaches proposed, these approaches should be regarded only as strategies, since incontrovertible evidence for their effectiveness in improving natural EF recovery is limited. Conversely, numerous effective therapeutic options are available for treating post-radical prostatectomy ED (Salonia et al. 2012b).

Regarding rehabilitation programs, two double-blind studies have found no difference between nightly vs on-demand use of vardenafil or sildenafil after nerve-sparing radical prostatectomy (Montorsi et al. 2008; Pavlovich et al. 2013). A goal-oriented treatment paradigm has been recently proposed for

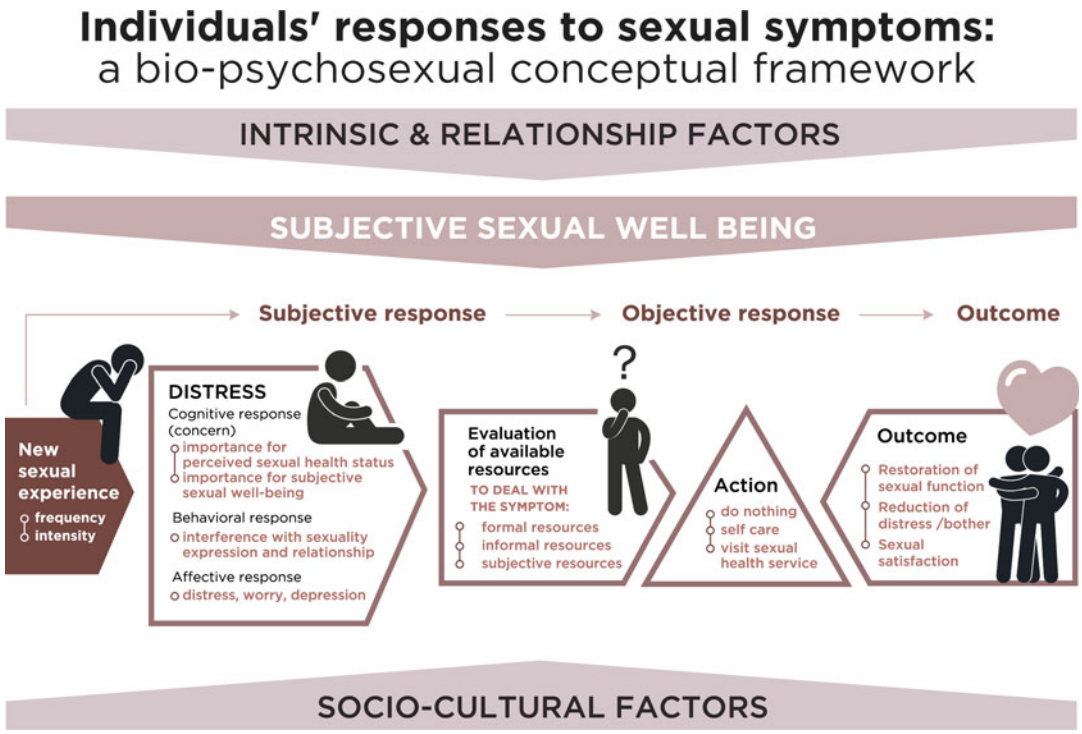

Fig. 5.4 Individuals' responses to sexual symptoms: a bio-psychosexual conceptual framework (Adapted from Kirana et al. (2009); Source: www.impo.gr)

our daily practice, where any chosen treatment may actually induce erections that allow sexual intercourse (Fode et al. 2013). Such treatments should be offered as early as possible, to minimize the potential adverse effects regarding both low tissue oxygenation and detrimental psychological effects. The authors stated that "One must be very careful not to repeat the statement that penile rehabilitation regimens improve erectile function after radical prostatectomy so many times that it becomes a truth, even without the proper scientific backing" (Fode et al. 2013).

5.4.5.2 Nerve-Sparing Radical Cystectomy: Is It Feasible?

Cystectomy permanently deteriorates the erectile capacity; results of the newly applied nerve-sparing procedure (NS) are still questioned as limited data are available. In one study, 12 patients (57.8 %) had spontaneous complete tumescence and five patients (21 %) had partial tumescence using PDE5i (Hekal et al. 2009). In contrast, all patients who underwent non-nerve-sparing cystectomy did not improve even with sildenafil and used alprostadil intracavernosal injection postoperatively. In another study, cystectomy was performed with a prostatic capsule- and seminal-sparing approach. A total of 20/21 (95 %) were sexually active following prostate-sparing cystectomy and orthotopic neobladders (Thorstenson et al. 2009). The recent first report on penile rehabilitation post-nerve-sparing radical cystectomy in a small group of patients has shown positive results (Hekal et al. 2011), but the experience from similar programs after radical prostatectomy does not support enthusiasm (Fig. 5.4).

5.4.5.3 Peyronie's Disease: Grafting Procedures Are Not Friendly to Erectile Function

Peyronie's disease is associated with ED, having also major negative impact in the patient's quality of life (Levine 2013). In the largest, single-center study, a total of 1,001 patients with PD

were evaluated retrospectively and 58.1 % reported preoperative ED, while penile color Doppler ultrasound revealed some degree of penile vascular disease in 76.8 %: mixed vascular disease in 41.1 %, cavernosal disease in 23.2 %, and arterial disease in 12.5 % of the patients (Kadioglu et al. 2011).

Regarding postoperative ED, it is clear that the risk of erectile dysfunction seems to be greater for penile lengthening procedures, compared to plication/tunica excision procedures (Hatzimouratidis et al. 2012). The risk of new ED with plication/tunica excision techniques is 0–13 %, compared to 5–53 % for grafting techniques (Hatzimouratidis et al. 2012). Furthermore, diminished sensation is reported in 4–21 % for plication/tunica excision, with limited data for grafting procedures (Levine and Burnett 2013).

Patients should be aware of grafting major drawbacks before surgery. The use of grafts harvested from the patient seems to cause potential complications of healing, scarring, and possible lymphedema. Synthetic grafting is not recommended, due to the potential risk of infection localized inflammation, fibrosis, and reaction to the presence of the synthetic material. Finally, allografts and xenografts (including processed pericardium from a bovine or human source, porcine intestinal submucosa, and porcine skin) have also moderate long-term results. The recurrence of penile curvature, penile length loss, and the new-onset of ED are not uncommon. In one study, although the 6-month postoperative follow-up showed excellent resolution or significantly less penile curvature, this figure significantly decreased in the 5-year follow-up: 50 % in dermal graft, 87 % in Tutoplast graft group, and 76 % in Stratasis graft group patients. Based on IIEF-5 scores, progression of ED was observed and more than 65 % of patients were dissatisfied with the outcome of graft surgery at 5 years (Chung et al. 2011). In patients with Peyronie's disease and ED that are nonresponders to erectogenic pharmacotherapy, penile prosthesis implantation is the first-line treatment option. However, responders to pharmacotherapy may also be regarded as candidates for corporoplasty, but not for grafting surgery due to the poor outcome (Mulhall et al. 2005).

Based on the above, all proposed guidelines recommend tunica plication procedures for curvature <60° and absence of extreme deformities (hourglass, hingle), while the anticipated loss of length would be less than 20 % of total erect or stretched length. Importantly, what has clearly emerged in the literature is that these men should have strong sexually induced rigidity preoperatively, in order to reduce the likelihood of postoperative ED (Hatzimouratidis et al. 2012; Levine and Burnett 2013).

5.4.5.4 Penile Fracture: Conservative Treatment Leads to ED

Penile fracture is a rare condition in western world; however, the incidence in the Western and Southern Asia countries is higher due to a tradition that involves bending the top part of the erect penis while holding the lower part of the shaft in place, until a click is heard and felt (Taqaandan) (Al Ansari et al. 2013; Zargooshi 2009). In the largest published study in 373 patients, surgical treatment restored erectile function in 98.6 %, while conservative treatment in 20 % (Zargooshi 2009). Other series has shown similar results for surgery, but erectile function in the conservative treatment group was higher (up to 50 %) (Bar-Yosef et al. 2007; Gamal et al. 2011). Penile nodules are the most common postoperative complication, without any impact of erectile function. Despite the fact that dorsal vein tears may mimic penile fracture (Bar-Yosef et al. 2007), surgical exploration is mandatory in every case suspicious for penile fracture in order to preserve potency.

5.4.5.5 Hypospadias Repair: High Incidence of Erectile Dysfunction and Premature Ejaculation

Hypospadias repair is also associated with ED. In a single-center study, 119 patients who underwent hypospadias repair 20–35 years ago responded to questionnaires on penile appearance and sexual life; 8.9 % with glanular hypospadias, 50 % with distal hypospadias, and 72.2 % with proximal hypospadias reported mild ED. Furthermore, it is extremely disappointing that 83.2 % of all patients complained about

premature ejaculation and all patients treated for proximal hypospadias reported impaired sexual quality of life (Chertin et al. 2013). Such data clearly show not only the high incidence of erectile dysfunction and premature ejaculation in hypospadias repair surgery and the necessity for appropriate parents'/patients' counselling before surgery but also the urgent need for the development of new, erection-preventive surgical techniques for the condition.

5.4.5.6 Urethroplasty: Pelvic Fracture and Not Surgery Is the Cause of ED

In a recent meta-analysis of 36 retrospective studies of anterior urethroplasty results, with a total of 2,323 patients, de novo ED was rare, with an incidence of 1 %. Transient ED was resolved within a 6–12- month period in 86 % of cases (Goel et al. 2013). Transperineal bulboprostatic anastomosis for posterior urethral strictures after pelvic structures has not a major effect on erectile function, as the incidence of preoperative ED in such cases is about 85 % (Fu et al. 2013). Three factors are significant and independent predictors of ED after pelvic fractures: diastasis of pubic symphysis, lateral displacement of prostate, and long urethral gap with odds ratios of 15.9, 6.9, and 2.0, respectively (Koraitim 2013). Appropriate patients' counselling regarding the likelihood of developing transient or permanent ED following urethroplasty procedures is advised.

5.5 Principles in ED Management

5.5.1 The Problem of Limited Treatment Seeking of Men with ED

Despite major advances in ED management, many patients remain untreated, as they don't feel comfortable to talk to a physician. The first step, therefore, is to make our patients talk about their problem. However, we should keep in mind that sexual dysfunctions are not always associated with increased bother or dissatisfaction, a condition that influences treatment-seeking behavior (Evangelia et al. 2010). Many patients have difficulty discussing their sexual problems or concerns with a physician. It is the responsibility of the physician to both develop a relationship of trust and intimacy with the patient and analytically discuss all key elements necessary for adequate treatment. The acronym "TALK," which has been proposed in order to help people ask for help, refers also to what every patient with a sexual problem may consider in his/her appointment with the expert:

- *T*rust your doctor.
- *A*sk about your sexual problem.
- *L*earn available treatment options.
- *K*eep your partner involved.

5.5.2 A Conceptual Framework to Explain Treatment-Seeking and Outcome Behavior

Individuals' responses to symptoms are not limited to common health behaviors, such as treatment-seeking or problem identification. In reality, patients respond to symptoms and treatment regimens within the context of life goals, priorities, health issues, partners' demands, and other personal concerns that make up their sexual well-being. Based on a previously described model (Hatzichristou 2008; Kirana et al. 2009), a conceptual framework has been developed for better understanding the process from sexual symptom identification to sexual health outcome as occurring in a series of linked phases.

Phase 1: Experience of a New Sexual Problem

A symptom may have different characteristics, including frequency and severity.

Phase 2: Distress

To elicit behavioral responses from a man, ED needs to be perceived as a *source of distress*. Cognitive appraisal will determine the patient's perception of ED that is influenced by beliefs and convictions (e.g., sexual myths) about the cause and significance, as well as by anticipated consequences and outcomes. Finally, affective response refers to the impact that ED may have on the individual's emotions, affect, and mood. If ED causes

fear or anxiety and the patient does not seek medical advice, it may result in depression.

Phase 3: Assessment of Available Resources
Individuals' assessment of the availability and potential effectiveness of available sexual healthcare resources (urological societies may play a key role raising awareness on the condition) will determine the likelihood of treatment seeking for ED. Of even greater importance is the patient's perception of their availability and effectiveness. Among the potential resources to be considered are the following:

- Formal resources (i.e., availability of sexual health services, andrological clinics)
- Informal resources (i.e., partner, friends)
- Subjective resources (i.e., coping style, previous experiences with healthcare/urological services)

If the individual perceives himself to have access to the required formal or informal resources, then an intention to take action may be evident.

Phase 4: Objective Response
This is the behavioral phase in the process and typically results in the individual choosing between one or more of the following actions:

- Help seeking (visit a general practitioner or a urologist)
- Self-care (e.g., via Internet)
- Avoidance (learn how to live without sex)

Phase 5: Outcome
In the final phase, the patient assesses the outcome of the process, defined as the reduction of symptom distress. According to this model, the outcome of the process should not be defined solely on the basis of objective criteria (e.g., IIEF) but also on the level of sexual satisfaction or reduction in subjective distress achieved. In situations where the patient is satisfied with the outcome (e.g., restoration of erection by using pharmacotherapy), the process may be terminated. Conversely, if there is no satisfactory outcome, the individual may reinitiate the process again. This will likely include reassessment of the level of subjective distress, evaluation of available resources, and selection of an alternative health behavior, e.g., discontinuing PDE5i treatment or visiting another urologist for second opinion.

In conclusion, this model reminds us Jung's quote: "The shoe that fits one person pinches another." Keeping this model in our mind, it helps us to better understand our patients in our everyday clinical practice and guides us to identify the best treatment option on individual basis.

5.5.3 Discussing ED in a Urology Office

Sexual health problems are often neglected in clinical practice (Tsimtsiou et al. 2006). Many patients have difficulty discussing their sexual problems or concerns with a physician, as they experience a sense of frustration, confusion, embarrassment, or distress; moreover, patients often feel that physicians are reluctant, disinterested, or unskilled in sexual problem management. On the other hand, clinicians are often reluctant to ask about sexual issues due to their negative attitude towards sexual issues and concerns, time constraint, as well as a growing knowledge gap between developments in Sexual Medicine and clinical skills of practicing physicians (Athanasiadis et al. 2006; Parish and Rubio-Aurioles 2010; Shabsigh et al. 2009).

Talking about sexual problems, the urologist should keep in mind to abide by the following (Hatzichristou et al. 2010):

- Create an atmosphere of sensitivity and respect.
- Be culturally sensitive.
- Respect every individual's sexual preferences.
- Consider status of relationship.
- Present evidence-based treatment options.
- Organize a close follow-up program.

5.5.4 Differentiating Primary from Secondary ED and Organic from Psychogenic ED

ED is classified in two major subtypes (Porst et al. 2013): (1) primary (lifelong) ED, defined as ED that occurs from the beginning of sexual activities, and (2) secondary (acquired) ED, defined as ED that occurs after a period of normal sexual life in which erectile function used to be intact.

For clinical purposes, sexual dysfunctions are classified into three types according to their etiology (Hatzichristou et al. 2010): type I, psychogenic; type II, organic; and type III, mixed (Table 2). Types II and III differ as for the absence or presence of significant mental (cognitive) or emotional (affect) distress; in type II, resolution of the main symptom will adequately diminish mental and/or emotional distress, while in type III complementary psychotherapy is indicated. It should be emphasized, however, that in most patients with organic ED, the negative psychological impact significantly contributes to exacerbating the severity of ED.

Sexual history is the most helpful tool in order to differentiate psychogenic from organic ED. Table 3 provides an overview of such specific aspects that may be useful.

5.5.5 Defining the Severity of ED

ED is defined as the persistent inability to attain and maintain an erection sufficient to permit satisfactory sexual performance (Hatzimouratidis et al. 2010). Two questions to the patients reflect this definition:

(a) *Are you able to get an erection of adequate rigidity for penetration?*

This question reflects the problems initiating the erectile process (e.g., neural or arterial insufficiency). In order to explore further the severity of the problem, the use of manual assistance in order to achieve penetration has to be explored.

(b) *Are you able to maintain the erection till ejaculation?*

This question reflects the problems in maintaining good quality, rigid erection in order to complete sexual performance (e.g., venoocclusive dysfunction). In cases where the erectile maintenance capacity is limited, questions regarding "when and how" erection is lost will follow: "Do you lose your erections before, during, or after penetration?" Typically psychogenic cases lose their erection just in the attempt of vaginal penetration, while patients with venoocclusive dysfunction (excluding severe cases) are able to penetrate, but they lose their erection within a few minutes after penetration.

Clinically, severity distinguished in mild, moderate and severe as follows:

- Mild ED reflects a sexual history where patients report sexual intercourse, but they complain of difficulties in achieving adequate rigidity and occasionally sustaining capability. They are usually able to have sexual intercourse more than half of the times.
- Moderate ED reflects a sexual history where patients report inadequate rigidity and/or sustaining capability and occasional sexual intercourse with manual assistance for penetration.
- Severe ED reflects a sexual history where patients are unable to have sexual intercourse due to the quality of their erections.

5.5.6 Questionnaires and Scales for the Everyday Clinical Practice

In supplementation to the sexual history, the IIEF or Sexual Health Inventory for Men (SHIM) questionnaires can also be used, as well as the Sexual Encounter Profile (SEP), especially in order to compare pre- and posttreatment erectile function. In order to facilitate the detection of men with androgen deficiency, the quantitative Androgen Deficiency in the Aging Male (qADAM) questionnaire is indicated.

5.5.6.1 Brief Sexual Symptom Checklist for Men (BSSC-M) and Women (BSSC-M)

Screening checklists can provide a valuable resource in identifying and assessing sexual problems. To facilitate initial identification of a sexual problem, two brief screening checklists have been developed by the ICSM committee on diagnosis (Hatzichristou et al. 2004). This brief checklist consists of four simple questions, and it is suitable for use in office settings, as it takes 1 min to be completed. It addresses the patient's level of satisfaction with sexual function, the duration of the sexual problem, the type/s of

sexual problems experienced, as well as the willingness of the person to discuss the problem with a healthcare provider. Three of the four questions are common for men and women, while the fourth question (type of problem) is specific for gender. BSSC has been used in the literature, however, validation data are lacking.

5.5.6.2 International Index of Erectile Function (IIEF)

The IIEF is the most widely used self-reported inventory to provide standardized measurement of erectile function in five domains of sexual function in men: erection, orgasm, desire, satisfaction, and overall satisfaction. The IIEF was initially developed for use in the clinical trials for the approval of sildenafil (Rosen et al. 1997). Psychometric validation for IIEF (test-retest reliability, construct validity, and treatment responsiveness) has been well established (Rosen et al. 2002). A systematic review of more than 60 studies found the IIEF scale to be highly robust in different ethnic and geographic populations, as well as sensitive to treatment effects across a variety of treatment agents (Rosen et al. 2002).

IIEF scale allows characterization of the ED severity, using a scoring system from 1 to 30 in the erectile function domain (Rosen et al. 1997):

- Normal erectile function: score 26–30
- Mild ED: score 17–25
- Moderate ED: score 11–16
- Severe ED: score 1–10

Most recently, criteria have been established for defining minimal clinically significant change after treatment in the EF domain of the IIEF (Rosen et al. 2011):

- Mild ED: 2-point improvement
- Moderate ED: 4-point improvement
- Severe ED: 7-point improvement

5.5.6.3 Sexual Health Inventory for Men (SHIM)

A 5-item brief form of the IIEF (IIEF-5), termed also as the Sexual Health Inventory for Men (SHIM), has been developed and validated, along with a diagnostic classification and an ED severity scale (Cappelleri and Rosen 2005; Rosen et al. 1999). The scoring system for SHIM is as follows:

- Normal erectile function: score 17–21
- Mild ED: score 12–16
- Moderate ED: score 8–11
- Severe ED: score 1–7

It should be noted that the IIEF and SHIM are not intended to supplant clinical evaluation and diagnostic tests; they are though particularly useful instruments in the urological office setting for the initial screening, as well as for the follow-up visits.

5.5.6.4 Sexual Encounter Profile (SEP)

SEP has been extensively used in clinical trials, although it has never been validated. Actually, the regulatory agencies use SEP results to evaluate the efficacy of drugs. SEP questions use the dichotomous answer system: "YES" or "NO." Data from clinical trials are presented as the mean percentage of participants who answered "yes." Questions SEP2 and SEP3 have been the primary endpoint in most clinical trials. The complete questionnaire includes the following five questions:

SEP 1: "Were you able to achieve at least some erection (some enlargement of the penis)?"

SEP 2: "Were you able to insert your penis into your partner's vagina?"

SEP 3: "Did your erection last long enough for you to have a successful intercourse?"

SEP 4: "Were you satisfied with the hardness of your erection?"

SEP 5: "Were you satisfied with this sexual experience?"

SEP questions are typically used as a diary of sexual attempts, as patients have to complete SEP after every sexual attempt. Practically, SEP questions reflect the typical questions we ask in our office during sexual history taking that provide us valuable qualitative and quantitative information on the patient's experience with his erectile function.

5.5.6.5 Androgen Deficiency in the Aging Male (ADAM)

Androgen Deficiency in the Aging Male (ADAM) questionnaire has been widely used as a screening tool for detecting men at risk for androgen deficiency. It was shown to have a sensitivity of 88 %, but specificity of 60 % (Morley et al. 2000).

Recently, the quantitative Androgen Deficiency in the Aging Male (qADAM) questionnaire showed statistically significant correlation to the SHIM ($p=0.001$) and serum testosterone ($p=0.046$) (Mohamed et al. 2010). The qADAM questionnaire consisted the 10 questions of the original ADAM, with "yes" and "no" replaced by a Likert scale of 1–5, in which 5 represented the absence of a given symptom and 1 represented maximal symptoms. The scoring scale is between 10 and 50, with 10 being most symptomatic and 50 being least symptomatic (Mohamed et al. 2010).

5.5.7 Organic Causes of ED

In the clinical practice, ED may be categorized according to the underlying pathophysiology in six major categories (Table 4). Lifelong ED usually is due to either anatomical (phimosis, congenital curve) or hormonal abnormalities (primary hypogonadism), while vasculogenic ED is rare and usually associated with penile or perineal trauma. Secondary ED is often accompanied with comorbidities associated with ED, such as BPH, CV risk factors, and prostate and bladder cancer therapies.

5.5.8 The ICSM Sexual Dysfunction Management Algorithm for Men and Women

Three principles for the clinical evaluation and management of sexual problems have been reported (Hatzichristou et al. 2010): (1) adoption of a patient-centered framework, with emphasis on cultural competence in clinical practice; (2) application of evidence-based medicine in diagnostic and treatment planning; and (3) use of a unified management approach in evaluating and treating sexual problems in both men and women.

Based on the above principles, the International Consultation in Sexual Medicine developed a common, stepwise diagnostic and treatment algorithm, for every sexual dysfunction, in both men and women (Fig. 5.5) (Hatzichristou et al. 2010). The main goal of ICSM-5 is to reveal the underlying etiology and/or indicate appropriate treatment options according to men/couple's individual needs (patient-centered medicine), using the best available data from population-based research (evidence-based medicine).

5.5.9 The EAU Treatment Algorithm for ED

The primary goal in the management strategy of a patient with ED is to determine its etiology and treat it when possible, and not to treat the symptom alone. Most men with ED will be treated with therapeutic options that are not cause-specific; therefore, treatment strategy depends on efficacy, safety, invasiveness and cost, as well as patient preference (Hatzichristou et al. 2010). Based on the evidence available, the EAU working group on male sexual dysfunction included a treatment algorithm for ED within the recent guidelines report (Hatzimouratidis et al. 2010) (Fig. 5.6). Urologists use the well-known algorithm extensively in their everyday clinical practice. By using this algorithm, the initial effort is to modify any risk factor for ED, as well as to identify any curable cause of ED. First-line treatment options include PDE5i, intracavernosal injections, intraurethral alprostadil, and vacuum devices. In nonresponders, combination of any of the above treatments may be considered, while penile prosthesis implantation remains a gold standard surgical option.

5.6 Diagnostic Approach

The goal of any diagnostic approach is to: (a) increase certainty about presence/absence of a disease, (b) define severity of the disease, (c) monitor clinical course, (d) assess prognosis/risks, and (e) plan treatment. Given that ED is essentially a self-reported condition, diagnostic tests or procedures should not be recommended without controlled clinical data or research evidence supporting their use. A broad array of

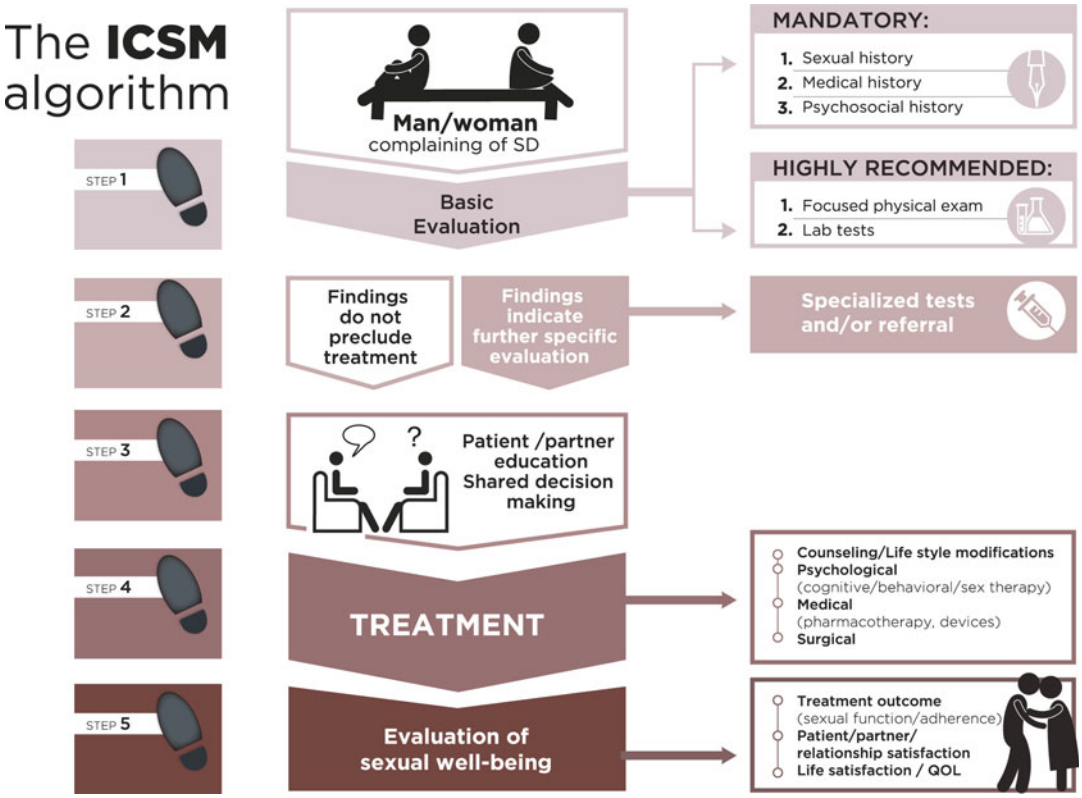

Fig. 5.5 The ICSM algorithm (Hatzichristou et al. (2010); Source: www.impo.gr)

specialized diagnostic tests has been developed, but their clinical utility is limited only to a small minority of men (Meuleman et al. 2010).

5.6.1 Is the Partner's Presence in the Office Substantial or Just Time-Consuming?

Partner involvement is rare in the everyday clinical practice, as urologists typically do not invite partners to be present in the office visits. However, clinical experience has shown that the partner's involvement – even though time-consuming – offers substantial help to easily identify/control potency status, couples' expectations, treatment results, and satisfaction (Hatzichristou et al. 2010). It is not possible to include the partner on the patient's first visit, but an effort should be made to include the partner at the second visit. In conclusion, the partner's presence in the office and further support positively affects the treatment outcome.

5.6.2 What Diagnostic Work-Up Is Mandatory?

Mandatory work-up for ED includes a medical–sexual–psychosocial history, physical examination, and limited laboratory tests (Hatzichristou et al. 2010; Hatzimouratidis et al. 2010). Medical history should also include use of medications. Laboratory tests are recommended only in patients not tested during the last 6 months, while physical examination should not focus exclusively on the genital system.

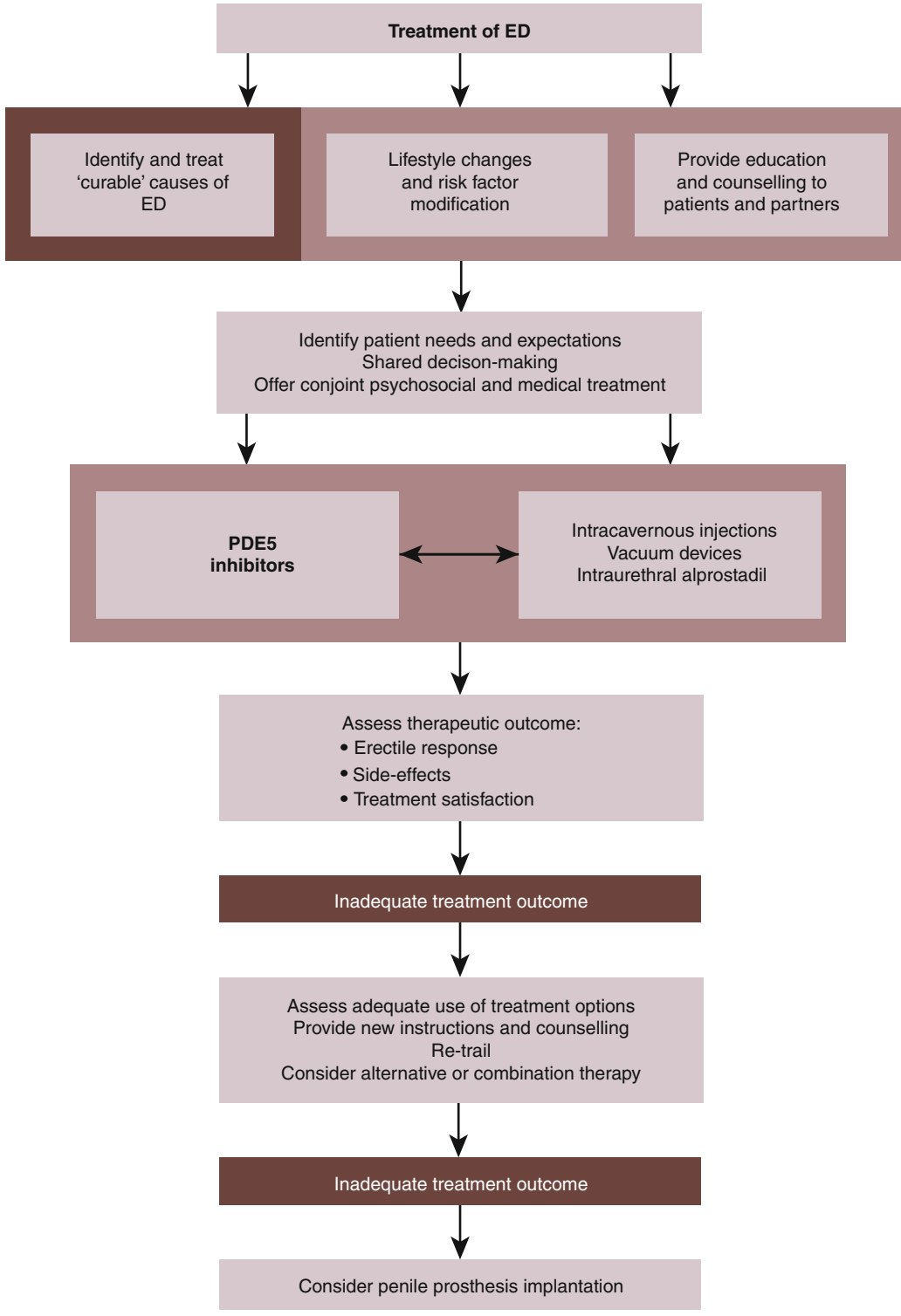

Fig. 5.6 Treatment of ED

5.6.2.1 Medical, Sexual, and Psychosocial History

The first step in evaluating ED is always a detailed medical, sexual, and psychosocial history of patients and partners when available. The sexual history must focus on information about previous and current sexual relationships, current relationship status, onset and duration of the erectile problem, as well as previous consultations and treatments. The partner's sexual health status is also important, as sometimes a sexual problem of the partner may be the cause of ED (e.g., vaginal atrophy and dryness).

Psychological assessment is important in order to identify: (a) potential social problems (e.g., unemployment and its consequences), (b) relationship status and problems (e.g., extramarital relationships), and (c) psychiatric comorbidities. In one study, detectable psychiatric conditions present included depression in 25.2 %, anxiety disorders in 11.7 %, depression-anxiety comorbidity in 6.8 %, and personality disorders in 5.8 % (Mallis et al. 2005). In cases of suspected depression, the use of a 2-question scale for depression is recommended (Whooley et al. 1997):

1. "During the past month have you often been bothered by feeling down, depressed or hopeless?
2. During the past month have you often felt very little or no interest or pleasure in doing things?"

Taking a comprehensive medical history may reveal one of the many common disorders associated with ED. Urologists should screen their patients for symptoms of hypogonadism, LUTS, and prostate cancer. Where indicated, screening questionnaires, such as ADAMS and the IPSS, could very well be utilized.

5.6.2.2 Physical Examination

Physical examination may include basic cardiovascular and neurological assessment, as well as focused detailed examination of the secondary characteristics and genitalia, including DRE. Cardiovascular assessment may include blood pressure, heart rate, peripheral pulses, and waist circumference measurement.

Genital system examination may include penile size, penile plaques and glans lesions, testicular size and consistency, DRE, and bulbocavernosus reflex (glans squeeze results in contraction of anal sphincter), which test the integrity of the sacral spine cord.

A physical examination may reveal unsuspected diagnoses, such as alterations in secondary sexual characteristics, phimosis, Peyronie's disease, and small testes. Given that penile deformities are difficult to be detected in the flaccid state, an intracavernosal injection test could be considered, either alone or in combination with duplex Doppler penile ultrasonography. A positive test, however, clearly demonstrates to the patient that he has already a treatment option: the intracavernosal injection program.

5.6.2.3 Laboratory Testing

Laboratory testing aims at identifying CV risk factors and hormonal status. Patients may need a fasting glucose or HbA1c and lipid profile if not recently assessed. Hormonal tests include a morning sample of total testosterone; when low testosterone levels are detected, prolactin and luteinizing hormone tests are performed. Thyroid function tests may be performed at the discretion of the physician. Regarding PSA, the latest EAU statement is as follows: "A baseline serum PSA should be offered to all men 40–45 years of age to initiate a risk-adapted follow-up approach with the purpose of reducing prostate cancer mortality and the incidence of advanced and metastatic prostate cancer" (Heidenreich et al. 2013).

5.6.2.4 Is the Basic Diagnostic Evaluation Adequate in Most Cases?

Baseline diagnostic evaluation for erectile dysfunction can identify the underlying pathological condition or erectile dysfunction-associated risk factors in most patients. One study included 1,276 consecutive patients who presented at an andrology outpatient clinic (Hatzichristou et al. 2002). Medical history revealed erectile dysfunction-associated comorbidities in 57 %; blood tests identified previously undiagnosed medical conditions in 6.2 %, while physical examination and the

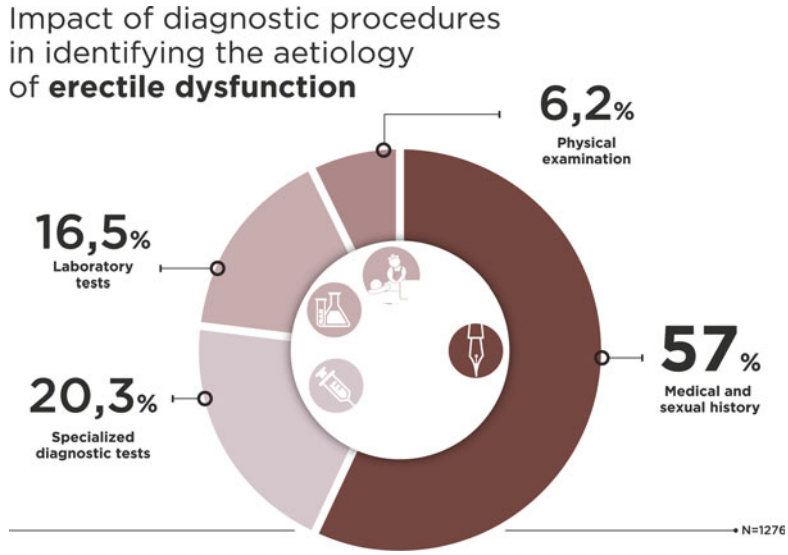

Fig. 5.7 Impact of diagnostic procedures in identifying the etiology of erectile dysfunction (Hatzichristou et al. (2002); Source: www.impo.gr)

intracavernosal injection test were diagnostic in 13.9 and 2.6 %, respectively. Therefore, in 8 out 10 cases the diagnosis can be based on the patient's medical and sexual history, physical exam, and mandatory laboratory tests. In the same study, specialized diagnostic procedures identified an underlying vascular pathology in 12.9 %.

5.6.3 Specialized Tests for ED: Is There Evidence for Their Use?

Specialized tests for the diagnosis of the underlying pathophysiology of ED can be used in the following cases: (a) in patients in whom a reversible form of ED is suspected (b) to differentiate between organic and purely psychogenic cases with nocturnal penile tumescence and rigidity testing and (c) to tailor vascular or penile surgery in patients suspicious for arterial disease or veno-occlusive dysfunction.

According to the report of the International Consultation in Sexual Medicine, the higher level of evidence (2B) indicates vascular testing, e.g., color Duplex Penile Ultrasonography and Dynamic Infusion Cavernosometry and Cavernosography (DICC) (Meuleman et al. 2010). Two non-vascular tests belong to the same evidence-based category: the Nocturnal Penile Tumescence and Rigidity (NPTR) Test by the Rigiscan™ device and the Bulbocavernosus Reflex Latency. Regarding the rest of specialized tests, selective arteriography (loE2B) is considered only for young men with perineal trauma, as well as for the treatment of high-flow priapism; as for MRI, it is a useful tool in cases of penile trauma and prosthesis complications.

5.6.3.1 The Nocturnal Penile Tumescence and Rigidity (NPTR)

NPTR assessment should be done for at least two nights. A functional erectile mechanism is indicated by an erectile event of at least 60 % rigidity recorded on the tip of the penis that lasts for >10 min (Chertin et al. 2013).

5.6.3.2 Intracavernous Injection Test

The intracavernous injection test provides limited information about vascular status. A positive test is a rigid erectile response (unable to bend the penis) that appears within 10 min after the intracavernous injection and lasts for 30 min (Chew and Stuckey 2000). This response indicates a functional, though not necessarily normal, erection, as this erection may coexist with arterial insufficiency and/or venoocclusive dysfunction (Chrysant and Chrysant 2012) (Fig. 5.7).

5.6.3.3 Cavernosometry/ Cavernosography

Cavernosometry is generally applied in young men – who are already diagnosed to have ED that is mainly organic, in order to precisely diagnose a venoocclusive dysfunction. During cavernosometry

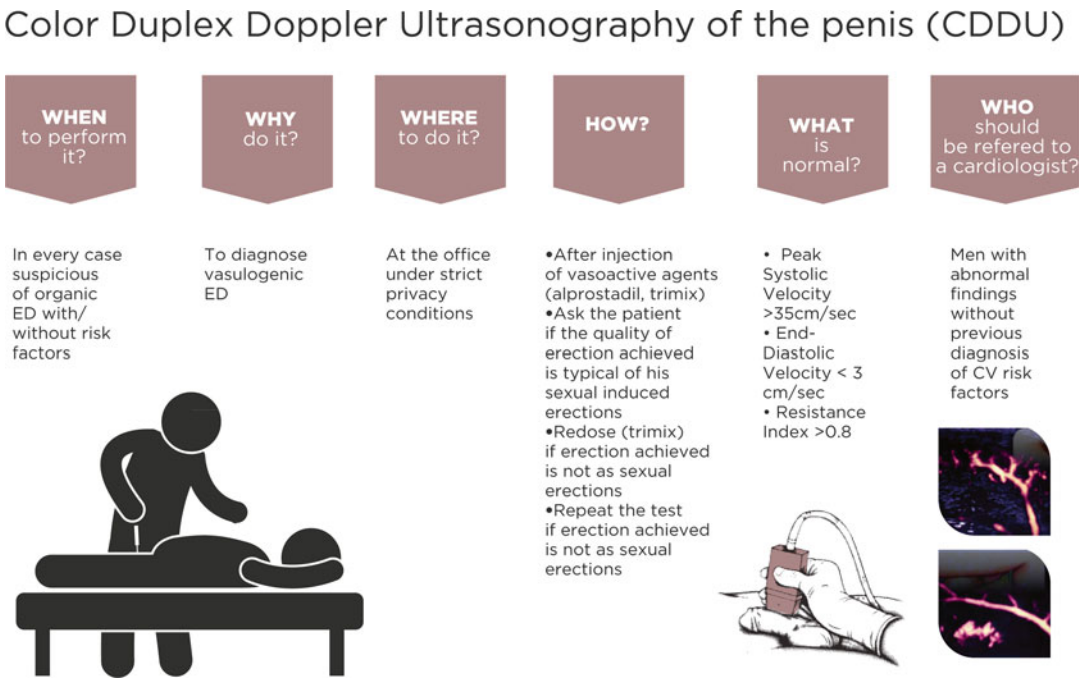

Fig. 5.8 Color Duplex Doppler ultrasonography of the penis (CDDU) (Sikka et al. (2013); Source: www.impo.gr)

arterial inflow to the penis is also assessed. Cavernosography is indicated in those patients who might be candidates for penile vascular surgery to correct a venoocclusive leak and also in men who have Peyronie's disease with poor rigidity before penile reconstructive surgery for identifying the site of the "leakage" (Glina and Ghanem 2013). Cavernosometry/cavernosography should be performed only after the intracavernosal injection of vasoactive drugs, with redosing when necessary in order to achieve complete smooth muscle relaxation (Hatzichristou et al. 1995). Also the use of a tri-mix solution is important (Seyam et al. 2005). There is evidence that 70 % of patients require a second injection and 30 % require a third injection to induce complete relaxation of the smooth muscle (Mulhall et al. 2001).

5.6.4 Color Duplex Doppler Ultrasonography of the Penis (CDDU): Who, How, Why

CDDU is the most useful test for vascular assessment of erectile mechanism (Fig. 5.8). While providing the least invasive and accurate option for documenting penile hemodynamics, CDDU requires skilled personnel and modern equipment (color Doppler U/S with a real-time image scanner and high-resolution solid-state linear array 7.5–12-MHz frequency transducer specific for small parts) that may be cost-prohibitive in certain settings (Sikka et al. 2013). Such relatively objective vascular testing may help direct appropriate therapy, especially in middle age men without history of CVD; in such cases CDDU may diagnose arterial disease in the corpora cavernosa (a warning for silent coronary artery disease) (Meuleman et al. 2010). Other cases in which CDDU of the penis is, or might be, necessary to complete the evaluation are in young men with primary or secondary ED and a history of pelvic trauma or drug abuse, prior to surgical interventions for treating Peyronie's disease, in differentiating psychogenic vs organic ED and in medicolegal cases.

It is crucial during the test to assess the quality of the erectile response after the intracavernosal injection of vasoactive agents; subjective assessment of rigidity is carried out independently both by the patient and physician. This approach minimizes the false diagnosis of venous leak, which is most common with anxiety usually present under such testing environment (Teloken et al. 2011).

5.6.4.1 CDDU: Normal Parameters

Several parameters have been used to infer the integrity of the arterial inflow, such as peak systolic flow velocity (PSV) and acceleration time (AT) (measured in ms from the start of systole to PSV) within the first 5 min following ICI. PSV < 25 cm/s has a 100 and 95 % specificity in selecting patients with abnormal penile angiography. PSV >35 cm/s is associated with normal angiography and defines normal cavernous arterial inflow. Speel et al. have proposed that AT is more powerful than PSV in diagnosing atherosclerotic ED (Speel et al. 2003); the cutoff point for acceleration time to discriminate between atherosclerotic and nonatherosclerotic erectile dysfunction was determined at an acceleration time of 100 ms or greater. Sensitivity was 66 % and specificity 71 %. There has recently been some evidence that PSV measurements in the flaccid state may have value in predicting cavernosal arterial insufficiency, silent coronary disease, and the clinical response to ICI (Corona et al. 2008). With CDDU the cavernous venoocclusive mechanism can be evaluated in the late postinjection phase (over 5 min following ICI). End-diastolic flow velocity (EDV) and resistance index (RI) may be used to estimate the degree of venoocclusive function. Thus, persisting diastolic blood flow or a low RI, 5 min or more following ICI, reflects persistent high flow rates due to impaired venoocclusion.

The consensus however for the everyday clinical practice remains that a peak systolic blood flow >30 cm/s, an end-diastolic velocity of <3 cm/s, and a resistance index >0.8 are generally considered normal (Glina and Ghanem 2013). Further vascular investigation is unnecessary when a Duplex examination is normal.

5.6.4.2 CAUTION: The False Diagnosis of Vasculogenic ED in Young Men

PSV in young men can be falsely low (Shamloul 2006). It is noteworthy that in a series of normal controls, 30 % had venoocclusive dysfunction, indicating the inability of CDDU to differentiate between a pathological and a functional (anxiety induced incomplete smooth muscle relaxation) cause of venoocclusive dysfunction (Meuleman et al. 1992). Such false-positive results (low specificity) could lead to a serious psychological setback if a young man is informed, erroneously, that his ED is primarily organic, thus requiring lifetime therapy or surgery. In order to control smooth muscle relaxation, in every case with abnormal results, redosing of tri-mix is required (Hatzichristou et al. 1995). After redosing, all parameters are re-recorded (Glina and Ghanem 2013). This protocol is repeated until a maximum of three doses of tri-mix solution. There is evidence that 70 % of patients require a second injection and 30 % require a third injection to induce a complete relaxation of the smooth muscle. In cases of doubt, DICC under the controlled condition of complete smooth muscle relaxation may be utilized to differentiate between these two entities (Haynes et al. 1996).

5.6.5 Referrals

After the availability of PDE5i, general practitioners manage the majority of ED cases. The urologist is typically the referral physician in cases of (a) life-long ED, (b) nonresponders to PDE5i, or (c) penile disorders (anatomical and trauma) (Hatzichristou et al. 2010). In a minority of patients, however, urologists may refer patients for specialized consultation or testing. Reasons for referral either for further consultation or for a specialized test are the following (Hatzimouratidis et al. 2010):

- Primary/lifelong sexual dysfunction
- Complicated anatomical deformities (congenital/acquired)
- Trauma (pelvic, perineal, genital)
- Endocrinopathies
- Complex medical problems (comorbidities)
- Treatment failure
- Medicolegal cases
- Patient's request

It is worth mentioning that sometimes the patient and/or his partner may wish to obtain further diagnostic evaluation for several reasons; most often patients request referral in order to learn the precise etiology of ED ("need to know" referral).

5.6.6 The Seven Steps of the Difficult First Visit

Every effort should be made by the physician to ensure the patient's privacy, confidentiality, and personal comfort during the patients' visits. The first visit is crucial in order to establish a physician–patient relationship; offering the patient the opportunity to discuss sexual matters in a nonthreatening manner and making a statement about the confidentiality of the information being discussed are therefore necessary. Independently of our personal opinion and ethics, direct acknowledgment that any sexual problem is a relevant clinical issue and that the physician's role is not to judge but to help solving it, may substantially help the patient feel comfortable. Lastly, it is also essential to evaluate the patient's and partner's values and preferences, especially when the patient comes from a different ethnic/religious background.

In order to be even more practical, the first visit is described step-by-step:

Step 1. Identify the sexual problem. Every consultation begins with the typical question of "What brings you here?" As ignorance and knowledge gaps about sexual function and dysfunction are common, very often sexual myths or Internet-based misinformation may easily lead to the development of a sexual concern. The first step therefore is for physicians to discriminate between sexual concerns (e.g., size of the penis) and difficulties (e.g., differences between the couple's sexual desire) versus dysfunctions (erectile dysfunction) and/or disorders (e.g., congenital penile deviation).

Step 2. Duration and severity of ED. By asking about the duration of ED, we indirectly differentiate lifelong from secondary cases. For evaluating severity of ED, a typical question that we may ask is: "Out of the last ten attempts for sexual intercourse, in how many were you able to achieve penetration and ejaculation?" Patients who are able to have intercourse at least sometimes are the ones who can easily get successful treatment. Patients who are seldom or never able to complete sexual intercourse are difficult cases and usually have long-lasting ED (with the exception of occasional failures). Alternatively, the use of IIEF ED domain or SHIM will lead to accurate classification with regard to ED severity.

Step 3. Coexistence of other sexual problems. It is well known that ED provokes or coexists with other sexual problems, such as low sexual desire and premature ejaculation. Also, ED may occur due to a sexual problem of the partner (e.g., dry vagina, orgasmic disorders). Of great value at this point is the use of the 3 first questions of the Brief Sexual symptom Checklist for Men (BSSC-M) and Women (BSSC-M). They both consist of four simple questions, with the only difference being the content of question 3a that has to do with men and women reporting different sexual problems according to gender. Question 4 has to do with screening purposes and may be omitted when the screener is used during the interview. However, it is a critical question when the tool is used to assess sexual problems in patients coming to the office complaining about other urological conditions, such as BPH.

Step 4. Defining quality of erectile response. Erectile dysfunction is defined as the persistent inability to attain and maintain an erection sufficient to permit satisfactory sexual performance. Therefore, two are the main characteristics of erection: rigidity and maintenance capacity. Rigidity is a key parameter of erectile response. Asking questions such as "Are your erections hard enough to penetrate without any manual assistance?" give you the first piece of information. It should be noticed that there are men, e.g., with arteriogenic ED, who have adequate rigidity for penetration, but complain that their rigidity is "not like it used to be in the past" or that "it takes effort and time to achieve a good/rigid erection." Both answers are typically seen in patients with arteriogenic ED. On the contrary, excellent rigidity, but losing the erection before or after penetration, is characteristic of venoocclusive dysfunction. Checking the circumstances under which lost of the erection occurs, it may differentiate between structural (neurogenic or arteriogenic) and functional (anxiety-induced) etiology of venoocclusive dysfunction.

Step 5. Medical history. Potentially modifiable risk factors, such as cigarette smoking, alcohol abuse, obesity, uncontrolled hypertension, or diabetes, should be addressed at this stage in the process. The potential role of prescription or nonprescription drugs, including psychotropic agents (e.g., SSRIs), cardiovascular drugs, or other iatrogenic causes of sexual dysfunction, should also be addressed. Patients with specific endocrine deficiencies, such as hypogonadism, should be placed on hormone replacement therapy (in the absence of medical contraindications, such as prostate cancer) prior to initiation of direct therapies for sexual dysfunction. A specialist referral is generally indicated in these cases. Additionally, sexual problems in the partner such as a lack of lubrication, hypoactive sexual desire, or pain disorders (e.g., dyspareunia) should be addressed whenever possible.

Step 6. Physical examination. Physical exam should include general screening for medical risk factors or comorbidities that are associated with ED, including secondary sexual characteristics, assessment of blood pressure, central and peripheral pulses, basic neurological exam, and particular focus on the genitalia. Never forget that the physical examination is a great opportunity to inform the patient about aspects of their sexual anatomy or physiology, as well as provide reassurance about his body appearance and function (e.g., size of the penis).

Step 7. Laboratory test. At the end of the initial assessment, laboratory tests will be asked. Most of ED patients suffer from several comorbidities and usually have adequate lab test results with them. In case of men without medical history and suspicious for organic ED etiology, laboratory testing may be of value in order to unmask undiagnosed comorbidities, such as diabetes mellitus and hyperlipidemia.

Step 8. Review results/education. Results of the initial evaluation should be reviewed with the patient and his partner whenever possible, prior to initiating therapy. This review should be used as an opportunity to educate patients on the anatomy and physiology of sexual function and provide appropriate understanding of "what is wrong." Furthermore, presentation of the available treatment options will allow to identify patient's preferences and partner's endorsement of the proposed solution; such discussion is critical, as together with a close follow-up schedule (usually in 3–4 weeks) minimize dropout rate.

5.7 Is It Possible to Cure ED?

Typically, ED is curable in most psychogenic cases; in organic ED, cure is possible in cases of endocrinological etiology and in mild cases through lifestyle modifications and better management of comorbidities. Lastly, urologists pay high attention to a novel treatment the shockwave therapy for vasculogenic ED. Finally, in rare cases of trauma-associated ED, vascular surgery may offer cure potential. The treatment options that offer not symptom relief, but cure, are briefly discussed.

5.7.1 Lifestyle Changes: What Should We Expect?

5.7.1.1 Sex Is a Healthy Habit for Erections ("Use It or Lose It")

Sexual activity is inversely related to mortality; in one cohort study, mortality risk was 50 % lower in men with high frequency of orgasm than in men with low frequency of orgasm (Davey Smith et al. 1997). In a survey conducted in Finland in men aged 55–75 years, Koskimäki et al. observed that men reporting intercourse less than once per week at baseline had twice the incidence of ED compared to those reporting intercourse once per week (79 vs 33/1,000). The risk of ED was inversely related to the frequency of intercourse and the authors concluded that regular intercourse protects against the development of ED among men aged 55–75 years (Koskimaki et al. 2008). The well-known quote "use it or lose it" has a scientific basis as frequency of intercourse offers – together with nocturnal erections – better oxygenation in the corpora cavernosa.

5.7.1.2 Physical Activity and Weight Loss May Restore ED

Meta-analysis data of randomized controlled studies using the IIEF for measuring the treatment outcome have shown that the exercise and weight loss are improving erectile function (Esposito et al. 2010; Hsiao et al. 2012; Lamina and Agbanusi 2013). Data from five studies indicated significant effect of aerobic training on erectile dysfunction (Lamina and Agbanusi 2013). Even in young men (18–40 years), exercise –defined as ≤1,400 cal/week – is associated with better sexual function (Hsiao et al. 2012).

Overall, especially in men with the aspects of the metabolic syndrome, both clinical and experimental studies have confirmed that combining the exercise with weight loss provides additional benefit to erectile function, likely via reduced metabolic disturbances (e.g., inflammatory markers, insulin resistance), decreased visceral adipose tissue, and improvement in vascular function (e.g., increased endothelial function) (Hannan et al. 2009).

5.7.1.3 Pharmacotherapy for CV Risk Factors May Improve ED

According to a meta-analysis of six randomized controlled clinical trials with a follow-up of at least 6 weeks of lifestyle modification interventions or pharmacotherapy for CV risk factor reduction, it was found that lifestyle modifications and pharmacotherapy for CV risk factors were associated with statistically significant improvement in IIEF-5 score (mean difference, 2.66 with 95 % CI, 1.86–3.47) (Gupta et al. 2011).

5.7.1.4 The Mediterranean Secret: "Beware What You Eat!"

Going through a systematic literature search, one realizes that a dietary pattern which is high in fruit, vegetables, nuts, whole grains, and fish, but low in red and processed meat and refined grains, is more common in subjects without ED. The Mediterranean diet has been proposed as a healthy dietary pattern based on the evidence that greater adherence to this diet is associated with lower all-cause and disease-specific survival (Esposito et al. 2010). In men with type two diabetes, those with the highest adherence to the Mediterranean diet had the lowest prevalence of ED and were more likely to be sexually active. In clinical trials, the Mediterranean diet has been found to be more effective than a control diet in ameliorating or restoring ED in people with obesity or metabolic syndrome (Esposito et al. 2010).

The above data show us the aspects of a prevention strategy for ED (Fig. 5.6).

5.7.2 Low-Intensity Shockwave Therapy: Is It Really "the Cure Therapy"?

Available treatment options for organic ED may help men reduce or control symptoms, but are unable to cure the disease. Low-intensity extracorporeal shockwave therapy (LI-ESWT) has been used in the management of chronic wounds, peripheral neuropathy, and cardiac neovascularization for many years (Gruenwald et al. 2013). Application of the method to the penis has emerged during the last 5 years as a new and promising modality in the treatment of vasculogenic erectile dysfunction (ED). Basic science has provided evidence that LI-ESWT induces cellular microtrauma, which in turn stimulates the release of angiogenic factors and the subsequent neovascularization of the treated tissue (Gruenwald et al. 2013). In a diabetic rat model, low-intensity extracorporeal shockwave therapy ameliorated ED associated with diabetes mellitus by promoting regeneration of nNOS-positive nerves, endothelium, and smooth muscle in the penis (Qiu et al. 2013). These beneficial effects appear to be mediated by recruitment of endogenous mesenchymal stem cells.

In randomized, double-blind, sham-controlled studies in men with ED, the LI-ESWT eliminated the dependence on PDE5i in patients who responded to oral therapy (PDE5i), and 60–75 % were thus able to successfully achieve erections and vaginal penetration (Vardi et al. 2012). Furthermore, 72 % of the nonresponders to oral pharmacotherapy became responders to PDE5i and capable of vaginal penetration after shockwave treatment. Additionally, LI-ESWT resulted

in long-term improvement of the erectile mechanism. The feasibility and tolerability of this treatment, coupled with its potential rehabilitative characteristics, make it an attractive new therapeutic option for men with ED.

Multicentered studies with longer follow-up are underway to confirm that LI-ESWT has the potential to improve and permanently restore erectile function by reinstating penile blood flow (Gruenwald et al. 2013).

5.7.3 Vascular Surgery

5.7.3.1 Penile Revascularization: Only for Young Patients with Pure Arteriogenic ED

Penile revascularization procedures concern a highly selected young patient group with circumscribed acquired or congenital vascular abnormalities. The procedure is performed in centers of excellence to young men, who are nonsmokers and nondiabetic and demonstrate perineal trauma-associated isolated arterial stenoses in the absence of generalized vascular disease (Sohn et al. 2013). All types of the described procedures use the internal pudendal artery (which becomes the common penile artery) as the arterial source to penile blood supply:

- Anastomosis of the IEA to dorsal penile arteries end-to-end or end-to-side (true revascularization)
- Anastomosis of the IEA to the deep dorsal vein with additional proximal and/or distal vein ligation (venous arterialization)
- Anastomosis of the IEA to the deep dorsal vein and artery (arterial-venous shunt)

In one study, a ≥5 point increase in the IIEF-5 score was defined as success threshold; at 5 years after surgery, the success rate in this study was 63.6 % (Kayigil et al. 2012). In another study with 70.8 months and definition of success the satisfactory intercourse without additional therapy, patients under 28 years showed a 73 % success rate vs 23 % in the older ones, while nonsmokers had a 57 % success compared to 29 % in smokers (Vardi et al. 2004). A systematic review and meta-analysis of the 25 published studies showed that the results in men younger than 30 years old are better than older ones (odds ratio, 3.7; 95 % confidence interval, 2.2–6.4; $p = .001$). Venous leak and history of smoking negative influenced success rate (Babaei et al. 2009). Finally, the evaluation of the long-term results in a Center of Excellence with the use of validated instruments showed that in patients with no vascular risk factors and pure cavernous arterial insufficiency, the microvascular arterial bypass surgery provides long-term improvement in erectile function, depression, and overall satisfaction (Munarriz et al. 2009).

5.7.3.2 Surgery for Venoocclusive Dysfunction: Only for Site-Specific Leak

The results of venous ligation surgery for diffuse venous leak have been disappointing; in one study with a follow-up of at least 3 years, only 21.87 % sustained potency without adjunctive therapy (Da Ros et al. 2000). Young patients, however, with site-specific congenital posttraumatic or post-inflammatory leaks may be considered candidates for vein ligation, as crural ligation surgery improves erectile function in most men treated 1 year postoperatively (Flores et al. 2011). New technologies, such as 3D-CT cavernosography, can provide high-resolution images of venous drainage for precise identification the leaking veins (Kawanishi et al. 2011).

5.8 Vacuum Erection Devices

Despite the fact that VED is considered a first-line therapy option for ED of any etiology, erections with these devices are not normal because they provide passive engorgement of the corpora cavernosa. A constrictor ring is placed at the base of the penis to retain blood within the corpora, which has to be removed within 30 min in order to avoid skin necrosis. Also, VEDs are contraindicated in patients with bleeding disorders or on anticoagulant therapy.

Satisfaction rates range between 27 and 94 % (Levine and Dimitriou 2001). Older men with a motivated, interested, and understanding partner

report the high satisfaction rates. Most men who discontinue use of VEDs do so within 3 months. The commonest adverse events include pain, inability to ejaculate, petechiae, bruising, and numbness, which occur in <30 % of patients (Lewis and Witherington 1997). VEDs may be the treatment of choice for well-informed older patients who are in long-term partnerships with occasional intercourse attempts or in patients where comorbidity requires noninvasive, drug-free management of ED.

5.9 Phosphodiesterase Type 5 Inhibitors (PDE5i)

Phosphodiesterase 5 (PDE 5) inhibitors are selective inhibitors of the enzyme PDE-5, which catalyze the hydrolysis of cyclic guanosine monophosphate (cGMP), a potent vasodilator and nitric oxide (NO) donor, into its corresponding metabolites (monophosphates) (Andersson 2011). PDE5-Is exert their beneficial effect by producing vasodilation and increased blood flow to the corpora cavernosa of the penis, which facilitate penile erection.

Currently, three PDE5-Is are in clinical use worldwide for on-demand use with indication for ED: sildenafil (25, 50, 100 mg), vardenafil (5, 10, 20 mg), and tadalafil (10, 20 mg). Vardenafil 10 mg is available also in the form of orodispersible tablet (ODT) in a discreet packaging; it is applied on the tongue without the need of water or any other fluid and provides a rapid disintegration within the mouth before swallowing. Tadalafil has been approved for daily application (OAD) in doses of 2.5 and 5 mg as an alternative treatment regimen to on-demand dosing. Recently, this form of treatment has been approved also for the treatment of BPH-associated lower urinary tract symptoms. Two of the PDE5-Is (sildenafil and tadalafil) are also approved with indication pulmonary arterial hypertension.

Four new PDE5 inhibitors (avanafil, udenafil, lodenafil, and mirodenafil) have been investigated in randomized controlled trials (RCTs) and have shown similar efficacy and safety profiles to sildenafil, tadalafil, and vardenafil. Two of them are marketed in European countries; avanafil has been recently approved in the EU (and the USA), and udenafil is marketed in Russia (and Korea); lodenafil is approved only in Brazil and mirodenafil in South Korea.

5.9.1 Pharmacological Characteristics

The pharmacologic profile of the 5 PDE5i available in Europe is briefly summarized in Table 6.

5.9.1.1 Onset of Action

Although some patients respond to PDE5i even in 15 min, at least 30 min are necessary for response of 50 % of the patients (Porst 2012). Therefore, patients are advised to use the pills the earliest possible: sildenafil and vardenafil about 60 min before sexual attempts and tadalafil 60–120 min in order to get a peak efficacy. Based on the pharmacological profile, avanafil has the distinctly shorter T_{max} compared to the others. Tadalafil OAD results in significant efficacy from day 2 that increases over the next 5 days (Seftel et al. 2011).

5.9.1.2 Duration of Action

Sildenafil and vardenafil efficacy may be maintained between 6 and 12 h (Moncada et al. 2004). Avanafil efficacy sustains >6 h after dosing (Goldstein et al. 2012). Efficacy of tadalafil is maintained for up to 36 h (Porst et al. 2003). Udenafil is the only long-acting drug among the new PDE5 inhibitors with a half-life of 11–13 h and therefore expected efficacy of 24 h.

5.9.1.3 Food and Alcohol Interactions

The efficacy of sildenafil and vardenafil depends on food intake, as after intake of a high-fat (59 % fat) meal, a delay in T_{Max} and a reduction in C_{Max} is observed. The t(max) of udenafil is delayed and the C(max) is reduced by approximately 21 % in the low fat-fed state; however, overall bioavailability is not affected (Kim et al. 2009). Tadalafil and avanafil are not affected by food (Porst 2012). Vardenafil ODT absorption is also unrelated to food intake and exhibit better bioavailability compared to film-coated tablets (Heinig et al. 2011).

5.9.2 Efficacy

5.9.2.1 PDE5i Are Highly Efficacious Drugs

All three PDE5 inhibitors extensively studied in large-scale clinical and postmarketing trials worldwide (sildenafil, tadalafil, vardenafil) have demonstrated impressive efficacy data with SEP3 "yes" response in about 75 % of the attempts (Porst 2012). In the real life PDE5i, between 30 and 40 % of a mixed ED population of patients do not sufficiently respond to the maximum dose of the PDE5i (Porst et al. 2013).

Two-year studies have not shown any tachyphylaxis effect and efficacy has been maintained. Besides providing sexual satisfaction for both men and their partners and therefore improving their relationships, PDE5i treatment is also effective in improving the depressive symptoms of ED patients (Porst et al. 2013).

Efficacy is clearly dose dependent. Improvement of erectile function was reported with the use of sildenafil by 56, 77, and 84 % of a general ED population taking 25, 50, and 100 mg sildenafil, respectively, compared to 25 % of men receiving placebo (Goldstein et al. 2002). As for tadalafil, erection improvement was reported by 67 and 81 % of a general ED population taking 10 and 20 mg tadalafil, respectively, compared to 35 % of men in the control placebo group (Montorsi et al. 2004b). Improved erections with vardenafil were reported by 66, 76,, and 80 % of a general ED population taking 5, 10, and 20 mg vardenafil, respectively, compared to 30 % of men taking placebo (Porst et al. 2001). Finally, the efficacy of vardenafil ODT has been demonstrated in randomized controlled trials and did not seem to differ from the regular formulation (Sperling et al. 2011).

According to a recent systematic review and network meta-analysis, the absolute effects and rank tests indicated that tadalafil and vardenafil are the most effective agents with regard to all aspects of efficacy, even after adjusting for dosage (Yuan et al. 2013).

In a large multicenter trial, the newly approved PDE5i, avanafil, in doses of 50, 100, or 200 mg, showed significantly improved SEP 2, SEP 3, and IIEF-EF domain score compared to placebo (Goldstein et al. 2012).

A recent meta-analysis of the five randomized clinical trials with udenafil in a sample of 1,109 patients has suggested that udenafil is an effective and well-tolerated therapy for erectile dysfunction. The authors highlight the need for long-term, randomized controlled trials to verify the efficacy and safety of udenafil (Ding et al. 2012).

Patients with long-standing diabetes mellitus, post-radical prostatectomy, and neurological disorders are considered to be difficult-to-treat subpopulations and will be reported separately.

5.9.2.2 On-Demand or Chronic Use of PDE5i

A randomized study ($n=145$) has shown that daily tadalafil led to a significantly higher IIEF-EF score and higher completion of successful intercourse attempts compared to on-demand tadalafil (McMahon 2005). Two major randomized double-blind studies, using 5 and 10 mg/day tadalafil for 12 weeks ($n=268$) (Porst et al. 2006) and 2.5 and 5 mg/day tadalafil for 24 weeks ($n=286$) (Rajfer et al. 2007), have shown that daily dosing was well tolerated and significantly improved erectile function. However, these studies lacked a comparative on-demand treatment arm. An open-label extension was carried out for both studies in 234 patients for 1 year and 238 patients for 2 years. Tadalafil, 5 mg once daily, was shown to be well tolerated and effective (Porst et al. 2008). Tadalafil, 5 mg once daily, therefore provides an alternative to on-demand dosing of tadalafil for couples who prefer spontaneous rather than scheduled sexual activities or who anticipate frequent sexual activity, with the advantage that dosing and sexual activity no longer need to be temporally linked. The first trial of daily dosing of udenafil 75 mg trial showed a 73 % SEP 3 success rate (Zhao et al. 2011).

Other studies (open-label, randomized, crossover studies with limited patient numbers) have shown that chronic, but not on-demand, tadalafil treatment improves endothelial function with a sustained effect after its discontinuation (Aversa et al. 2008; Rosano et al. 2005). This has been confirmed in another study of chronic sildenafil in men with type two diabetes (Aversa et al.

2008). Despite preclinical evidence, once-daily dosing does not offer any sustainable erectile effect after discontinuation of treatment compared to on-demand administration in patients with mild-to-moderate ED (Zumbe et al. 2008).

5.9.2.3 PDE5i in Patients with Diabetes Mellitus

PDE5-Is have shown moderate efficacy in patients with DM without disturbing blood glucose control. In patients with diabetes, sildenafil demonstrated 63 % successful intercourse attempts compared to 33 % of placebo (Stuckey et al. 2003). Tadalafil successful intercourse rates increased from 21.8 % with placebo to 45.4 and 49.9 % with 10 and 20 mg of tadalafil on demand, respectively (Fonseca et al. 2004). In a double-blind, placebo-controlled study of 298 men with diabetes and ED, 2.5 and 5 mg tadalafil once daily for 12 weeks was moderately efficacious and well tolerated. This regimen provides an alternative to on-demand treatment for some men with diabetes (Hatzichristou et al. 2008). Vardenafil increased successful intercourse rates from 23 % with placebo to 49 and 54 % with 10 and 20 mg of vardenafil on demand, respectively. In a review of randomized clinical trials of PDE5i in diabetic patients (Vardi and Nini 2007), the weighted mean difference for the IIEF-EF and the percentage of successful attempts in the PDE-5 inhibitors and in the control arm were 26.7 (95 % CI 23.1–30.3) and 6.6 (95 % CI 5.2–7.9), respectively, in favor of the PDE-5 inhibitors arm. The overall risk ratio for developing any adverse reaction was 4.8 (CI 95 % 3.74–6.16) in the PDE-5 inhibitors arm as compared to the control.

ED due to diabetes mellitus remains difficult to treat. This is mainly because the pathophysiology of diabetes-induced ED is multifactorial, including elevated advanced glycation end-products, high levels of oxygen free radicals, impaired nitric oxide synthesis, increased endothelin B receptor binding sites and upregulated RhoA/rho-kinase pathway, neuropathic damage, and impaired cyclic guanosine monophosphate (cGMP)-dependent protein kinase-1 (Thorve et al. 2011). The only existing strategy to improve response rates includes initially management of the underlying hyperglycemia and comorbidities (also to prevent or halt the progression of disease). Future strategies in the evolution of the treatment of diabetic ED are aimed at treating the underlying mechanisms. A new hypothesis proposed that a microvascular deficit in the vasa nervorum of nerve trunks and ganglia is a major trigger for a cascade of events that eventually lead to diabetic neuropathy, autonomic neuropathy, and ED (Cellek et al. 2013). Restoring diminished blood flow to the vasa nervorum as early as possible – before irreversible changes such as fibrosis and neuronal degeneration occur – should be the primary target in medical management of diabetic neuropathy and ED. According to preclinical and clinical studies, PDE5 inhibitors, statins, and alpha-1 adrenoceptor antagonists are among the drugs that, when used on a chronic basis, are beneficial in correcting nerve blood flow and function in diabetes (Cellek et al. 2013).

5.9.2.4 PDE5 Inhibitors in Post-radical Prostatectomy Patients

Post-radical prostatectomy ED is multifactorial. Cavernosal nerve injury induces loss of smooth muscle and an increase in collagen within the corpora cavernosa, while cavernosal changes may also be attributed to hemodynamic changes (Hatzimouratidis et al. 2009). In general, PDE5-Is are efficacious in young patients with normal preoperative erectile function who have undergone bilateral nerve-sparing radical prostatectomy and on-demand use of a PDE5-I may be at least as efficacious as daily use. PDE5i use in penile rehabilitation programs is under question, as well-designed studies to date found no long-term effect of either daily or on-demand PDE5I administration compared to placebo (Montorsi et al. 2008; Pavlovich et al. 2013).

A careful analysis of the results of the largest well-designed study available today offer answers to the most difficult questions regarding post-radical prostatectomy potency (Montorsi et al. 2008). This randomized, double-blind, double-dummy, multicenter, parallel group study conducted at 87 centers worldwide included 628 patients scheduled to undergo bilateral NSRP within 1 month of screening and having a normal

IIEF-EF score of >26 at screening. Patients were randomized to placebo, nightly vardenafil, or on-demand vardenafil. This phase was followed by a 9-month double-blind treatment period, a 2-month single-blind washout period and an optional 2-month open-label period. In the double-blind period of the study, the proportions of patients with IIEF–EF scores >26 at double-blind LOCF were 16.8, 20.1, and 36.2 % for the placebo, vardenafil nightly, and vardenafil on demand groups, respectively. Mean SEP3 success rates at open-label were 57.1, 59.8, and 62.6 % for patients who had previously taken placebo, vardenafil nightly, and vardenafil on demand (during the double-blind treatment period), respectively. Three significant observations are of particular interest:

- In 87 centers of excellence worldwide, 9 months postoperatively, only 16.8 % of the patients in the placebo group had normal erectile function, as they had preoperatively; such an observation questions the high rates of early potency reported in literature from uncontrolled clinical studies.
- Statistically significant difference compared to placebo was noticed only at the vardenafil on-demand group ($p=0.0003$); penile rehabilitation program and nightly PDE5i treatment therefore are at least under question.
- On-demand administration of PDE5i 1 year postoperatively reached mean SEP3 success rates of approximately 60 %, regardless of treatment group during the double-blind period; such data clearly favor nerve-sparing surgery and prove the efficacy of on-demand PDE5i in this difficult-to-treat population.

Overall, candidates for nerve-sparing radical prostatectomy should be aware that they most probably need PD-Is postoperatively in order to restore their erectile function. Moreover, they have to be informed that the rehabilitation program is not supported by rigorous level of evidence (Fode et al. 2013; Hatzimouratidis et al. 2009).

5.9.2.5 PDE5i in Patients with Neurological Disorders

Despite the fact that ED is reported in a high percentage of patients with central neurological disorders (CND), there are only limited data concerning efficacy and safety of PDE5i (Lombardi et al. 2012). In a review of 28 articles, significant statistical improvement was reported only in patients with spinal cord injury for up to 10 years. The most frequent predictable factor for PDE5 success was the presence of upper motoneuron lesion. Three sildenafil studies documented statistically significant improvement on erectile function in Parkinson's patients, while two studies reported discordant results about sildenafil's effectiveness on multiple sclerosis (MS) patients; one on tadalafil showed significant statistical efficacy on erection versus baseline ($p<0.01$; $p<0.05$). The only spina bifida article determined that sildenafil remarkably improved erectile function. Adverse events were well tolerated in most neurological patients, except in subjects with multiple system atrophy where sildenafil caused severe hypotension.

5.9.2.6 Which PDE5i Should We Prescribe?

Although the question is relevant for clinicians, patients, and their partners, there are no significant differences in PDE5i safety and efficacy, a fact that has led to the initiation of studies aiming to evaluate them regarding patient preference (Al-Shaiji and Brock 2009). In addition, more than 50 % of ED patients discontinue therapy (Hatzimouratidis and Hatzichristou 2009).

The availability of short- and long-acting PDE5 inhibitors created the tendency for younger men to choose tadalafil because it gives them a broader window of opportunity, while older men tend to prefer vardenafil or sildenafil. Choice of drug, however, will depend on the frequency of intercourse (occasional use or regular therapy, 3–4 times weekly) and the patient's personal experience. Numerous studies, aiming to evaluate them regarding patient preference, have been published with most studies showing a consistency in patients' preference for tadalafil (52–65 % of patients prefer tadalafil versus 12–20 % vardenafil or 8–30 % sildenafil), mainly because of the longer duration of action that increases patients' freedom in sexual life (Morales et al. 2011). However, most patient preference studies of PDE5-Is have serious

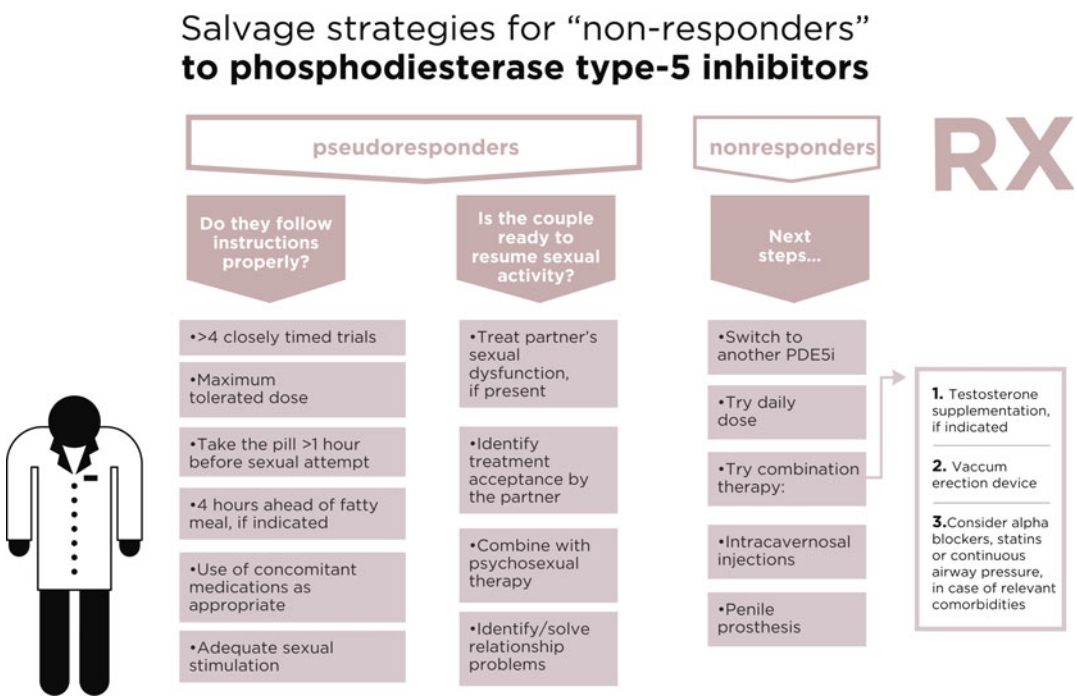

Fig. 5.9 Salvage strategies for "nonresponders" to phosphodiesterase type-5 inhibitors (Porst et al. (2013); Source: www.impo.gr)

design flaws that hinder the proper interpretation of the data and thus limit the utility of the result (Mulhall and Montorsi 2006).

The aim of ED treatment is to restore an erection satisfactory for the sexual needs of the patient. Thus, the patient-reported outcome is the gold standard in treatment evaluation; an option is to let the patient try all three available agents and make his own choice (Hedelin and Stroberg 2005). In one study with more than 2-year follow-up, 25 % of the patients switched between a short- and long-acting drug depending on the situation (Ljunggren et al. 2008). What is highly interesting in this study is that, allowing the patient to try all 3 PDE5i, an impressive 86 % of 3 years of PDE5 inhibitor continuous use was observed.

5.9.2.7 Is It Possible to Salvage "Nonresponders" to PDE5-Is?

Several salvage strategies have been developed for nonresponders to PDE5i (Fig. 5.9). Nonresponders to PDE5i may be classified in the following groups:

1. *Inappropriate instructions/use of the PDE5i.* Nonresponders have been defined as follows (Carson et al. 2004): "Any patient who, after four successive or closely timed trials of the maximum tolerated dose of the medication, in accordance with the regulatory agency's guidelines with respect to timing relative to meals, alcohol ingestion, use of concomitant medications and adequate sexual stimulation, is unable to achieve or sustain adequate penile rigidity until completion of sexual performance." Therefore adequate re-instructions are always the first step when a patient reports that "the drug didn't work".
2. *Psychological/relationship problems.* Salvage strategy for such cases includes referrals for psychosexual counselling and therapy of the patient and his partner in combination with pharmacotherapy. Without the partners' support, ED treatment in such cases becomes problematic.
3. *Partners' sexual dysfunction.* Female sexual dysfunctions are at least as common as male

sexual problems. If the partner has a sexual dysfunction, her treatment is indicated.

4. *Severe organic ED.* This category reflects the truly nonresponders, otherwise patients with severe nerve damage and/or severe venoocclusive dysfunction. These patients represent the difficult-to-treat subpopulations; salvage strategies include other treatment modalities with or without PDE5i.

Clinically, in order to apply salvage strategies, the following ten *steps* should be considered:

1. *Identify if the drug was used according to the instructions.* In one study, inappropriate use of sildenafil was recognized in 56 % of the patients (Hatzichristou et al. 2005); 45 % had never used the highest recommended dose, 32 % had taken the pill with a full stomach right after a meal, 22 % had taken the pill just before the initiation of sexual activity, 12 % were not aware that sexual stimulation was mandatory to achieve an erection, while 8 % had tried the 100 mg dose despite the presence of factors associated with sildenafil clearance reduction. Following adequate dose titration and time adjustment, 31 % patients responded to sildenafil.
2. *Spend time for patients' counselling.* In one study on nonresponders, a short video with sexual counselling content was added in one office visit, and as a result 23.6 % of the study patients achieved normal erectile function at the end of the study (Hatzichristou et al. 2005).
3. *Advise patients to take the pill in advance.* PDE5-Is are taken different times to reach maximum plasma concentrations (Forgue et al. 2006; Nichols et al. 2002). Even though all three drugs have an onset of action within 15 min in some patients, most patients require 60 min in order to get full benefit of the drug efficacy (Montorsi et al. 2004a; Padma-Nathan et al. 2003; Rosen et al. 2004). So, ask the patients to try again the PDE5i earlier than the recommended period in order to exclude late metabolism of the drug; for example, patients taking tadalafil should be advised to wait at least 2 h between oral ingestion and intercourse attempt (Hatzimouratidis et al. 2006).
4. *Ask patients to try any PDE5i at least four times in the maximum recommended dose.* Although more than 80 % of ED patients have successful intercourse with the very first dose of a PDE5i (Schulman et al. 2004), it has also been shown that sometimes it takes 3–8 attempts to reach the maximum efficacy (Porst et al. 2001, 2013). Titration to the maximum tolerated dose has also shown to increase the efficacy and satisfaction, with no increase in the number or severity of adverse events (Buvat et al. 2008). Finally, adequate trial of a PDE5i involves at least six sexual attempts (McCullough et al. 2002).
5. *Switch patient into another PDE5i.* According to a randomized, open-label, crossover trial comparing sildenafil and tadalafil, some patients might respond better to one PDE5i than to another (Eardley et al. 2007); 17 % of patients had a better response (>5 points on IIEF score) to tadalafil than to sildenafil, while 14 % had a better response to sildenafil than tadalafil.
6. *Try daily dosing.* According to two nonrandomized trials, daily dosing with a PDE5i might salvage some nonresponders to intermittent dosing. In one trial (McMahon 2004), some men benefited from regular dosing with either vardenafil or tadalafil, while in the other trial (Hatzimouratidis et al. 2012) daily dosing with tadalafil salvaged some men who had failed to respond to intermittent dosing with a PDE5I.
7. *Offer counselling to the patient and her partner.* Counselling and dose adjustment were directly influential in achieving an excellent response to a second trial of the drug in patients with ED who had previously failed treatment with the drug and obviated their need to seek more invasive measures (Gruenwald et al. 2006).
8. *Discuss with patients the common reasons for treatment discontinuation.*

The most common reasons for discontinuation, other than efficacy and side effects, are the partners' reluctance to pharmacotherapy,

lack of spontaneity/drug interference with sexual attempt, fear for drug dependency, unrealistic expectations, and cost. Such issues have to be addressed by the physician in an effort to overcome, if possible.

9. *Ask discreetly the partner about her sexual health.* In one study, 55 % female partners of men with ED attending a sexual dysfunction clinic reported at least one complaint concerning sexual dysfunction including arousal and pain disorders (Greenstein et al. 2006). It should be noticed that it is not uncommon that women do not tell their partners about their own sexual dysfunctions. In a large epidemiological study (Nappi et al. 2013), 28 % of women did not tell their partners when they first encountered vaginal discomfort, mainly because they felt "it was just a natural part of growing older" or because "they felt embarrassed."
10. *Offer combination treatment or second-line treatment options.*

    Combination treatment may salvage part of the nonresponders; if such strategy has no results, the efficacy of intracavernosal injections and penile prosthesis implantation are well established.

5.9.3 Adverse Events

Adverse events are generally mild to moderate, and the dropout rate due to adverse events is similar to that with placebo with all PDE5i. Table 7 summarizes adverse events for the PDE5i available in the European market.

5.9.4 Safety

Clinical trial results and post-marketing data regarding sildenafil, tadalafil (OAD and on-demand), and vardenafil have demonstrated no increase in myocardial infarction rates in patients receiving PDE5i, as part of either double-blind, placebo-controlled trials or open-label studies, or compared to expected rates in age-matched male populations. None of the PDE5i had an adverse effect on total exercise time or time-to-ischemia during exercise testing in men with stable angina (Kloner 2004; Thadani et al. 2002).

A non-industry-sponsored analysis of FDA reports on sildenafil, tadalafil, and vardenafil has been recently published, evaluating the reported cardiovascular and mortality events over the past 10 years (Lowe and Costabile 2012). Overall, 14,818 adverse events were reported for sildenafil; there were 1,824 (12.3 %) reported deaths and 2,406 (16.2 %) reports of cardiovascular adverse events. Tadalafil was associated with 5,548 adverse events and 236 deaths were reported. Vardenafil was associated with 6,085 adverse events and 121 reports of deaths. The percentage of reported severe cardiovascular disorders has stabilized at 10–15 % in all adverse events reports for sildenafil and tadalafil and 5–10 % for vardenafil. A recent systematic review and network meta-analysis showed no major difference in terms of safety among the 3 PDe5-Is (Yuan et al. 2013).

5.9.4.1 Nitrates Contraindication

Since nitrates are also NO donors, their coadministration with PDE5i could cause severe vasodilation and severe decrease of blood pressure. Organic nitrates, such as nitroglycerine, isosorbide mononitrate, isosorbide dinitrate, as well as amyl nitrite or amyl nitrate ("poppers" used for recreation), are absolute contraindications for the use of PDE5i. However, nitrates can be safely administered 24 h after the administration of sildenafil or vardenafil and 48 h after the administration of tadalafil.

5.9.4.2 Antihypertensives and Alpha-Blockers Coadministration

Coadministration of PDE5i with antihypertensive agents or alpha-blockers may result in additive decreases in blood pressure, which are usually minor. In the clinical practice, for such patients the following strategies are valuable:

(a) A 4-h window between the administration of any drug lowering blood pressure and PDE5i.
(b) Starting with the lower available PDE5i dose.

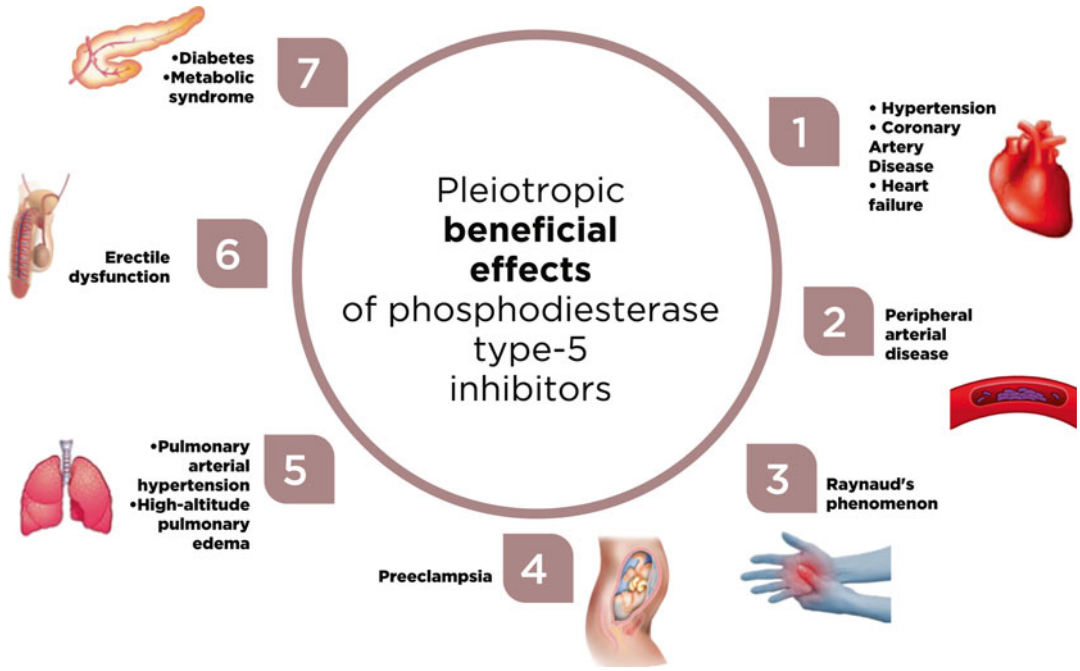

Fig. 5.10 Pleiotropic beneficial effects of phosphodiesterase type-5 inhibitors (Schwartz et al. (2013), Chrysant and Chrysant (2012); Source: www.impo.gr)

(c) Concomitant treatment with PDE5i should only be initiated if the patient has been stabilized on his alpha-blocker and/or antihypertensive therapy.
(d) Patients treated for BPH with either doxazosin or terazosin may first switch to tamsulosin or alfuzosin before PDE5i administration.

In treating patients with such comorbidities and treatments, caution should be exercised with respect to baseline BP levels and whether some of the medications they are taking are metabolized through the cytochrome P450 3A4 pathway because they might increase the blood levels of PDE-5 inhibitors, since these drugs are also metabolized through the same pathway. With respect to baseline BP, this should be >90⁄50 mmHg, because in most studies with PDE5i, patients with a baseline BP >90⁄50 mmHg were excluded from participating (Chrysant and Chrysant 2012).

5.9.4.3 Dose Adjustment: The CYP34A Pathway

Drugs that inhibit the CYP34A pathway (ketoconazole, itraconazole, erythromycin, clarithromycin, HIV protease inhibitors) will inhibit the metabolic breakdown of PDE5i; therefore the lower doses of PDE5i are recommended. On the other hand, in patients using drugs that induce CYP3A4 and enhance the breakdown of PDE5i (rifampin, phenobarbital, phenytoin, carbamazepine), higher doses of PDE5i are required. Finally, in patients with renal and hepatic insufficiency, the use of the lowest dose is recommended.

5.9.5 Pleiotropic Beneficial Effects of PDE5i

Recent studies have shown several pleiotropic beneficial effects of PDE5i in patients with CAD, hypertension, heart failure, diabetes mellitus, pulmonary arterial hypertension, high-altitude pulmonary edema, Raynaud's phenomenon, resistant hypertension, preeclampsia, and peripheral arterial disease (Fig. 5.10) (Chrysant and Chrysant 2012; Schwartz et al. 2012, 2013).

PDE5i also benefit the endothelial function, including normalization of serum biomarkers, increased levels of endothelial progenitor cells, ischemia–reperfusion protection mechanisms,

and other actions specific to patients with diabetes (Schwartz et al. 2013).

Besides enhancing vasodilation, PDE5i seem to protect the myocardium through complex pathways that involve nitric oxide, cyclic guanosine monophosphate, protein kinase G, extracellular-signal-regulated kinase, B-cell lymphoma protein-2, and rho-kinase inhibition (Schwartz et al. 2012).

5.9.6 Counterfeit PDE5i

Counterfeit PDE5i constitute a growing and inherently dangerous problem; out of those men who purchase without a prescription, 67 % do so using the Internet (Jackson et al. 2010). In one study monitoring 22 top search results for the query "buy Viagra," none required a prescription for purchase, all of them lacked product information leaflets, and 90 % offered illegal "generic Viagra" (Campbell et al. 2012). Out of 22 sample tablets examined, 77 % were counterfeit and sildenafil citrate contents varied between 30 and 50 % of the label claim. Such data becomes even more important, as abuse of PDE5i has been commonly documented in combination with illicit drugs among men and women of all ages. Counterfeit PDE5i use has linked with increased rates of high-risk sexual behavior and HIV transmission in some individuals (Rosen et al. 2006). Several studies have shown independent associations between use of PDE5i and sexual risk behavior, as well as an increased risk for STDs, including incident HIV infection, particularly among men who have sex with men (Swearingen and Klausner 2005).

5.9.7 Are PDE5i "Lifestyle Drugs"?

Lifestyle drugs are generally defined as drugs taken to satisfy a nonmedical or non-health-related goal (Flower 2004). The major media exposure of the "magic pill" – fuelled initially by the launching of sildenafil and afterwards of the other PDE5i – is the main reason why PDE5i are regarded as "lifestyle drugs." On the other hand, the direct-to-consumer advertising in the USA has created the impression that the industry promoted these marketed drugs for enhancing sexual performance rather than its licensed indication to treat erectile dysfunction (Dinsmore et al. 2007).

Theoretically, as these drugs can be used to alter our physical capabilities (sexual performance), PDE5i can be considered to be lifestyle drugs when used by men with normal erectile function (Flower 2004). Several reports support PDE5i misuse (Swearingen and Klausner 2005). Furthermore, it has been estimated that up to 2.5 million men in Europe are exposed to illicit sildenafil (Jackson et al. 2010), further supporting the extensive lifestyle use of PDE5i. Many men, on the other hand, with real problem, order PDE5i through the Internet or buy them through the pharmacies without prescriptions (Martin Morales et al. 2013).

It is clear that PDE5i can benefit healthy men; one randomized placebo-controlled double-blind study in healthy sexually active males without erectile complaints (Gruenwald et al. 2009) found significant differences between the sildenafil vs placebo groups in the IIEF-EF domain score (25.1 ± 4.8 vs 23 ± 5.3, $p = 0.013$), and mostly in the EDITS (70.8 ± 18 vs 60.3 ± 19, $p = 0.013$) and SEAR (57.6 ± 1 vs 51 ± 1. $p < 0.0001$) questionnaires. As EDITS reflects sexual satisfaction and SEARS self-esteem and sexual relationship, the results of the study pose a difficult challenge to the medical community: as there is no available mechanism to stop self-diagnosis and self-medication, the risk for medicalization of sexuality does exist (Salonia 2009). Physicians can guard against unnecessary requests for the drug; office visits for such requests offer the opportunity to physicians for the appropriate check-up in order to unmask medical conditions that are undiagnosed and may lead to ED in the future. Furthermore, it is an excellent opportunity for education on prevention strategies for ED.

5.10 Intracavernosal Injection Program (ICI): The Most Efficacious Pharmacotherapy

ICI used to be the gold standard treatment for ED patients for several years (Porst 1996). The availability of PDE5i has dramatically changed their use, as most long-term injection users can switch to sildenafil despite the underlying

pathophysiology. In the first real-life, preference study in patients using different solution and doses of ICI, 74.8 % of the patients in ICI responded to sildenafil (Hatzichristou et al. 2000); regarding preference, only 26.7 % preferred ICI, while 12.1 % decided to use both treatments alternately. The main advantages of ICI include fast onset of action within 5–15 min, duration according to the dose injected and no need for sexual stimulation.

The office-training program usually is completed in two visits, in order for the patient to learn the correct injection technique; in some cases of needle-phobia or of limited manual dexterity, the technique may be taught to their partners. The use of an automatic injection pen simplifies the technique (Wespes et al. 2013). Follow-up visits are important for dose adjustment and further patients' education and counselling.

ICI therapy continues to play a significant role in ED treatment. Despite its invasiveness, complications, and high discontinuation rate especially at the initial phase of treatment, the patients' satisfaction is greater with ICI compared to PDE5i in patients who have tried both forms of treatment (Porst et al. 2013). Thirty years of clinical experience have shown that a small percentage of patients are extremely satisfied with this form of treatment and use it for many years successfully with practically no priapistic episodes and minor side effects.

Although only alprostadil has been approved for ED treatment, papaverine and phentolamine (bi-mix), as well as papaverine-phentolamine-PGE1 (tri-mix) mixtures, have been in clinical use for three decades. Combination mixtures enable a patient to take advantage of the different modes of action of the drugs being used and also alleviate side effects by using lower doses of each drug. Today, most experts start the ICI with alprostadil monotherapy, and in case of failure the tri-mix solution is the most popular. The typical tri-mix solution ingredients are papaverine 300 mg, phentolamine 10 mg, and PGE1 100 μg. Starting dose is 0.1 ml, which gradually can reach 1 ml in patients with significant venoocclusive dysfunction and corporal fibrosis.

5.10.1 Alprostadil

The main action of PGE1 is to increase the intracellular concentrations of cAMP in the corporal smooth muscle cells through binding at E-prostaglandin receptors (Andersson 2011). Little is known about its pharmacokinetics, but it has a short duration of action and is extensively metabolized, which may partly explain why it seldom causes circulatory side effects when injected intracavernosaly (Andersson 2011).

Intracavernous alprostadil is more efficacious as monotherapy at a dose of 5–40 μg, although the 40 μg dose is not registered in every European country (Hatzimouratidis et al. 2012). Efficacy rates for intracavernous alprostadil of >70 % have been demonstrated in general ED populations, as well as in patient subgroups (e.g., diabetes or cardiovascular disease), with reported sexual activity after 94 % of the injections and satisfaction rates of 87–93.5 % in patients and 86–90.3 % in partners (Porst 1996; Wespes et al. 2013).

Complications of intracavernous alprostadil include penile pain (after 11 % of total injections), prolonged erections (5 %), priapism (1 %), and fibrosis (2 %) (Lakin et al. 1990). Pain is usually self-limited after prolonged use; otherwise, addition of lidocaine 1 % 1 cc may solve the problem in many patients (Kattan 1995). Long-term use is associated with cavernosal fibrosis, especially in those patients who frequently inject at the same site; temporary discontinuation for a couple of months may resolve the fibrotic nodules. However, tunical fibrosis suggests early onset of Peyronie's disease and may indicate stopping intracavernosal injections indefinitely (Hatzimouratidis et al. 2012). Systemic side effects are rare and hypotension is uncommon with alprostadil. Contraindications include men with a history of hypersensitivity to alprostadil, men at risk for priapism, and men with bleeding disorders.

Compliance is the main problem in ICI program. Dropout rates of 41–68 % have been reported, with most dropouts occurring within the first 2–3 months. In a comparative study, alprostadil monotherapy had the lowest discontinuation rate (27.5 %) compared to drug

combinations (37.6 %), with an attrition rate after the first few months of therapy of 10 % per year. Reasons for discontinuation included desire for a permanent modality of therapy (29 %), lack of a suitable partner (26 %), poor response (23 %) (especially among early dropout patients), fear of needles (23 %), fear of complications (22 %), and lack of spontaneity (21 %). Careful counselling of patients during the office-training phase, as well as close follow-up, is important in addressing patient withdrawal from an intracavernous injection program (Vardi et al. 2000).

5.10.2 Vasoactive Mixtures Used in ICI Program

5.10.2.1 Papaverine/Phentolamine Solution (Bi-Mix)

Although papaverine is considered as a phosphodiesterase inhibitor, it has a very complex mode of action and may be regarded as a "multilevel acting drug" (Hedlund 1994). It has been demonstrated that papaverine has a dual hemodynamic effect, decreasing the resistance to arterial inflow and increasing the resistance to venous outflow. Given that papaverine as monotherapy is associated with high rates of fibrosis and priapism, it is used in combination with phentolamine and/or alprostadil. Phentolamine is an alpha-adrenergic antagonist with similar affinity to alpha1- and alpha2 receptors, without systemic side effects. The combination of papaverine and phentolamine has been widely used (Porst 2012). The mixture is commercially available and approved in several European countries. It is marketed in 2 ml ampules, containing 15 mg of papaverine and 0.5 mg of phentolamine per 1 ml, i.e., a total content of 30 mg of papaverine + 1 mg of phentolamine per ampule (Porst et al. 2013).

5.10.2.2 Papaverine/Phentolamine/PGE1 Solution (Tri-Mix)

It is the most popular combination among urologists. As it has three different modes of action, it is the most efficacious pharmacotherapy available today. Also, it induces limited side effects, such as pain due to the limited amount of PGE1. A disadvantage of the tri-mix is that pharmacists need to reconstitute this combination on an individual basis. Initial dose of tri-mix should be 0.1 ml of the solution (300 mg papaverine + 10 mg phentolamine + 100 μg PGE1). In cases of no response to PDE5i, the initial dose may be 0.2 ml; if only tumescence occurs, the second dose may be 0.5 ml and in case of inadequate rigidity the highest dose of 1 ml may be used. In severe cases with partial response to 1 ml tri-mix, it is possible to double the dose of phentolamine and PGE1 in the mixture (300 mg papaverine + 20 mg phentolamine + 200 μg PGE1) and again use up to 1 ml of the mixture. It should be mentioned that responders to the highest dose of tri-mix never present with priapism due to existing severe venoocclusive dysfunction. However, this group is prone to clinical symptoms of hypotension, as the vasoactive agents produce systemic vasodilation. In a recent study of 1,412 patients following ICI (Coombs et al. 2012), 89 % of tri-mix users were capable of having sexual intercourse with limited complications and priapism rate of 0.5 %.

5.10.2.3 Other Mixtures

Several other mixtures have been reported for clinical use, such as vasoactive intestinal peptide (VIP), forskolin, linsidomine, moxisylyte, *chlorpromazine*, and calcitonin gene-related peptide (CGRP); yet, there are only limited data in the literature supporting the use of these drugs. The combination of vasoactive intestinal polypeptide (VIP) and phentolamine, in doses of 25 mg/1 mg or 25 mg/2 mg, is the only commercially available mixture approved in some European countries. A comparative study of alprostadil and VIP/phentolamine showed that over 80 % of the patients preferred VIP/phentolamine (Porst et al. 2013).

5.10.3 How to Store Intracavernosal Agents?

Alprostadil is the least stable of the drug components at room temperature and under refrigeration. About 8 % alprostadil loss occurred in 5 days at room temperature; under refrigeration losses of about 6 and 11 % occurred after 1 and 2 months,

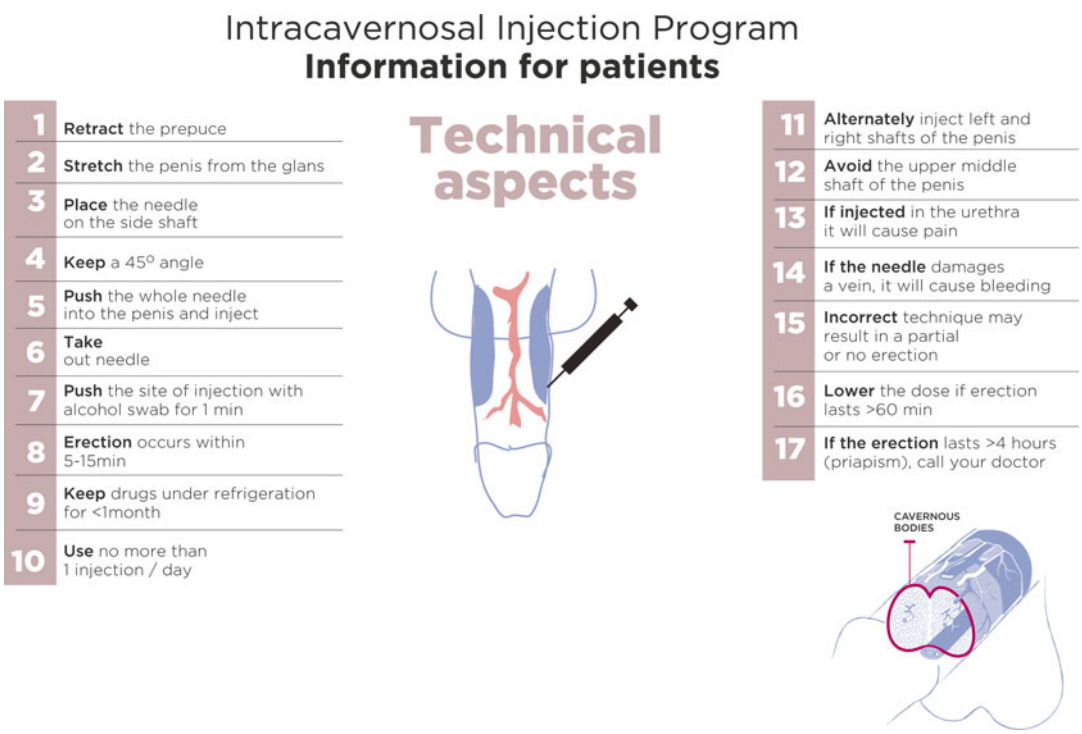

Fig. 5.11 Intracavernosal injection program information for patients (Source: www.impo.gr)

respectively. Bi-mix and tri-mix remain stable for 1 month when stored refrigerated at 4 °C. Room temperature exposure should be limited, and the vial should be returned to refrigeration as soon as possible (Trissel and Zhang 2004).

5.10.4 Information for the Patients

Typically instruction on the technique includes retracting the prepuce and stretching the penis from the glans with left hand (for right-handed), till it reaches its maximum length. Placement of the needle on the side shaft of the penis follows, keeping a 45° angle. Finally, the whole needle is pushed into the corpora and the medicine is slowly injected. After retraction of the syringe, an alcohol swab is kept for 1 min at the injection site (Fig. 5.11).

The patients who will follow the intracavernosal injection program should be informed about the following:

1. Medication must be kept refrigerated in order to maintain its effectiveness.
2. ICI may be used no more than once per day.
3. ICI may be given along the left and right shafts of the penis, avoiding the upper middle shaft, as nerves and vessels run to the pubis.
4. Frequent ICI use prones to fibrosis; therefore alternate sides of injection each time is recommended.
5. Incorrect technique may result in partial or no erection; if injected in the urethra, it will cause pain; if the needle damages a vein, it will cause bleeding, but no harm anyway.
6. Adjustment of the dose is necessary, in order to induce an erection lasting up to 60 min.
7. If the erection lasts more than 4 h (priapism), it is an emergency and detumescence should be achieved as early as possible.

For patients with manual dexterity or needle phobia, different types of automatic injectors are commercially available. Autoinjectors are also useful during the evaluation in the office in order

to minimize the patients' anxiety, which interferes with the results of specialized tests, such as duplex ultrasonography.

5.10.5 Dealing with Priapism

Even though ischemic priapism has an overall incidence of 1.5 cases per 100,000 person-years (Eland et al. 2001), the most common etiological factor is the intracavernosal injections used to treat erectile dysfunction (Huang et al. 2009). Following overdose of intracavernosal injection of vasoactive drugs, persistent cavernous smooth muscle relaxation and failure of contraction occurs, leading to intracavernosal anoxia, pCO_2 rising, and acidosis. An erection lasting >4 h should be considered as a medical emergency, as 90 % of patients with priapism >24 h develop complete erectile dysfunction (Pryor et al. 2004). Diagnosis is based on the patient's history; therefore, immediate action should follow; if priapism lasts for less than 4 h, intracavernosal injection of diluted phenylephrine can produce flaccidity. In cases with longer-lasting priapism, intracavernosal blood aspiration should be the first step, followed by phenylephrine injection. Repeated injections of phenylephrine and saline irrigation further deferred definitive management. In the rare cases that both strategies do not result in detumescence, urologists should precede with surgical shunting (Kovac et al. 2013). In late presenting cases, immediate implantation of a penile prosthesis is indicated, despite the fact that such cases are associated with increased complication rates. However, implantation in acute priapism allows the painful priapic episode to settle and to preserve penile length, while implantation in chronic priapism is technically much more challenging and often requires the use of downsized shorter cylinders (Zacharakis et al. 2013).

5.11 Intraurethral Alprostadil

Intraurethral pharmacotherapy provides an alternative to intracavernous injections in patients who prefer a less-invasive treatment option. As intracavernosal alprostadil, intraurethral alprostadil contains a synthetic vasodilator chemically identical to the naturally occurring prostaglandin E1. The specific formulation of alprostadil (125, 250, 500, 1,000 μg) is delivered by the Medicated System for Erection (MUSE™); it is a single-use pellet containing alprostadil suspended in polyethylene glycol administered using an applicator (Costa and Potempa 2012). The application of a constriction ring (ACTIS™) at the root of the penis may improve efficacy. It is recommended that intraurethral alprostadil should be initiated at a dose of 500 μg, as it has a higher efficacy than the 250 μg dose, demonstrating minimal differences with regard to adverse events.

Data from key clinical studies of intraurethral alprostadil show that it has a fast onset of action. Its efficacy however is limited, especially in direct comparative trials with intracavernously injected alprostadil (Porst et al. 2013). This is mainly due to the limited vascular supply between the urethra and the corpora cavernosa, enabling limited drug transfer between these structures. In clinical practice, only the higher doses (500 and 1,000 μg) have been used with low consistency response rates (Fulgham et al. 1998). The most common adverse events are local pain (29–41 %), dizziness with possible hypotension (1.9–14 %), and urethral bleeding (5 %), while penile fibrosis and priapism are very rare (<1 %) (Hatzimouratidis et al. 2010).

Nowadays intraurethral alprostadil is useful in selected cases of patients, e.g., in young spinal cord injury patients who, even with the lowest dose of intracavernosal alprostadil, suffer from priapistic episodes. Also, intraurethral alprostadil has a role in treating the "cold glans" syndrome after penile prosthesis implantation.

5.12 The Gold Surgical Solution: Prosthesis Implantation

Prosthesis implantation has one of the highest satisfaction rates (92–100 % in patients and 91–95 % in partners) among the treatment options for ED based on appropriate consultation (Hatzimouratidis et al. 2010). The surgical

implantation of a penile prosthesis should be considered in patients who do not respond to pharmacotherapy or who prefer a permanent solution to their problem. The two currently available classes of penile implants include inflatable (2- and 3-piece) and malleable devices.

The main advantage of the three-piece inflatable devices is that patients obtain close to natural erections with excellent rigidity and relatively good flaccidity. The two-piece inflatable prosthesis provides comparable rigidity, but partial flaccidity. Finally, malleable prostheses result in a firm penis, which may be manually placed in an erect or flaccid state at a much lower cost. Personal issues, such as expectations and cost, remain important, and psychosexual counselling is indicated, in order to limit the postoperative misuse or dissatisfaction.

Regarding surgical approaches for penile prosthesis implantation, the penoscrotal approach provides an excellent exposure, even in the proximal crural exposure if necessary, avoids dorsal nerve injury, and permits direct visualization of pump placement. The only disadvantage is the blindly placement of the reservoir into the retropubic space, which can be a problem in patients with a history of major pelvic surgery. In such cases the infrapubic approach offers direct vision reservoir placement. Revision surgery is always more challenging.

In patients with favorable prognosis after radical prostatectomy, but presence of urinary incontinence and ED, combination surgery with implantation of penile prosthesis, and male sling or artificial urinary sphincter at the same time seems effective and durable (Lee et al. 2011).

The two main complications of penile prosthesis implantation are mechanical failure and infection. Several technical modifications of the most commonly used three-piece prosthesis (AMS 700CX/CXRTM and Coloplast Alpha ITM) resulted in mechanical failure rates of <5 % after a 5-year follow-up (Carson et al. 2011; Serefoglu et al. 2012). Infection requires removal of the prosthesis and antibiotic administration. Alternatively, removal of the infected device with immediate replacement by a new prosthesis has been described using a washout protocol with successful salvages achieved in >80 % of cases (Henry et al. 2012). The majority of revisions are secondary to mechanical failure and/or combined erosion, as well as infection. Overall, 93 % of cases are successfully revised, providing functioning penile prosthesis. Careful surgical technique with proper antibiotic prophylaxis against Gram-positive and Gram-negative bacteria reduces infection rates to 2–3 % with primary implantation in low-risk patients. The infection rate may be further reduced to 1–2 % by implanting an antibiotic-impregnated prosthesis (AMS InhibizoneTM) or hydrophilic-coated prosthesis (Coloplast TitanTM).

In retrospectively reviewed patient information forms of AMS inflatable penile prostheses within a 7.7 year follow-up, it was found that 1.1 % vs 2.5 % of 3,268 men with impregnated vs nonimpregnated implants underwent initial revision due to infection. In the longest post-marketing registry report, including review of 36,391 patient information form of Coloplast Corporation (Minneapolis, MN, USA), during an 11-year follow-up, 4.6 % of non-coated IPPs were removed or replaced due to infections, whereas 1.4 % of hydrophilic-coated implants reported replacements due to device infections. The hydrophilic coating of the IPP components makes the device slippery and prevents bacterial attachment. The revision rate due to device infection was reduced by 69.56 % in patients with hydrophilic-coated IPPs (Serefoglu et al. 2012).

The most challenging cases are those with penile corporal fibrosis, even for a skillful surgeon. Traditional approaches include scar tissue resection, performing extensive corporotomies and the eventual use of grafts to cover the corporal gap. Surgical strategies, like upsizing prosthesis, suspensory ligament release, or scrotoplasty, must be kept in mind to utilize in this special scenario. According to a recent review, the outcome can be improved by combining the use of techniques for scar incision (extensive wide excision, multiple incisions minimizing excision, corporal counter incisions, corporal excavation technique, or Shaeer's technique), cavernotomes, and downsized prosthesis (Martinez-Salamanca et al. 2011).

Despite the ease of achieving a strong erection, disadvantages to IPPs include lack of mechanical glans engorgement and the "cold penis" syndrome. PDE5i (Mulhall et al. 2004),

intraurethral alprostadil (Chew and Stuckey 2000), or VED (Soderdahl et al. 1997) seems to have partial effect on glans engorgement; a high dropout rate due to penile pain was noticed in the intraurethral alprostadil study. All these studies had a small sample and short follow-up.

5.13 Psychosexual Counselling and Therapy

Most ED will benefit from an integrated psychosexual approach, in which cognitive underpinnings of poor sexual performance, diminished self-esteem, lack of confidence, and perceived failures in the male role are included in the therapeutic goals (Simopoulos and Trinidad 2013). Men receiving psychosexual therapy in addition to PDE5i have shown significant improvement in successful intercourse (Melnik et al. 2008).

5.14 Combination Treatment Options

Treatment of erectile dysfunction included combinations from the very beginning, as difficult-to-treat ED populations not responding properly to a certain treatment option are looking for ways to improve the quality of erection; secondly, in cases with noticeable side effects, combination treatment allows the use of lower doses of erectogenic drugs, which theorically will disappear or at least minimize the intensity of certain side effect. In a recent review on combination treatment, the authors identified numerous limitations including study biases and small subject size (Dhir et al. 2011). Limitations to therapeutic combination include lack of randomized controlled trials as well as overall treatment cost. A brief report of the published combination follows.

5.14.1 PDE5i Combinations

5.14.1.1 PDE5i Plus VED

VED has been shown to have synergistic effects when used in conjunction with sildenafil with significantly increased scores in all five domains of the IIEF questionnaire (Chen et al. 2004). The method seems to be attractive in younger men who are more open to pursuing combinations to achieve a strong erection and less likely to compromise on the quality and efficacy of their ED treatment. Other studies showed similar results in nonresponders to PDE5i and in post-radical prostatectomy patients (Canguven et al. 2009; Raina et al. 2005a).

5.14.1.2 PDE5i Plus Intraurethral Alprostadil

This combination is efficacious in men who failed both PDE5i and intraurethral alprostadil monotherapy (Mydlo 2000), as well as in post-prostatectomy patients (Raina et al. 2005b). The adverse effects associated with this combination therapy are about the same as those seen with PDE5i or MUSE monotherapy.

5.14.1.3 PDE5i Plus Intracavernosal Injection Program

This combination has been tested successfully in patients nonresponding to ICI (McMahon et al. 1999), as well as in post-radical prostatectomy patients (Nandipati et al. 2006). The combination of sildenafil with intracavernosal injection of the triple combination regimen may salvage as many as 31 % of patients who do not respond to the triple combination alone (McMahon et al. 1999). However, the combination is associated with an incidence of adverse effects in 33 % of patients, including dizziness in 20 % of patients.

5.14.1.4 PDE5i Plus Testosterone Supplementation

Late-onset hypogonadism is common in men with ED. Many studies have shown that the subset of patients with low to low-normal levels of testosterone (*T* value below <300 ng/dl) who do not respond to PDE5i monotherapy may benefit from testosterone supplementation (Buvat et al. 2013). Low-onset hypogonadism has been shown to be associated with reduced longevity, risk of fatal cardiovascular events, obesity, sarcopenia, mobility limitations, osteoporosis, frailty, cognitive impairment, depression, sleep apnea syndrome, and other chronic diseases. There is limited evidence suggesting that such

treatment may not pose an undue risk of prostate cancer recurrence or progression (Morgentaler 2013). Before initiating testosterone replacement, digital rectal examination, serum PSA test, hematocrit, liver function tests, and lipid profile should be performed (Hatzimouratidis et al. 2010). Patients given androgen therapy should be monitored for clinical response, elevated hematocrit, and development of hepatic or prostatic disease. Testosterone therapy is contraindicated in patients with untreated prostate cancer or unstable cardiac disease. Caution should also be taken regarding potential infertility caused by long-term exogenous androgen replacement in young men.

5.14.1.5 PDE5i Plus Alpha-Adrenoreceptor Antagonists

Several combinations have been studied, including sildenafil plus doxazosin or alfuzosin (Kaplan et al. 2007), tadalafil plus alfuzosin (Liguori et al. 2009). All studies suggest a synergistic effect of PDE5i with alpha-blockers. However, some degree of caution is recommended when using PDE5i in conjunction with alpha-adrenergic receptor antagonists to avoid any adverse hemodynamic effect (Hatzimouratidis et al. 2010).

5.14.1.6 PDE5i Plus Statins

Combination therapy of sildenafil and atorvastatin in ED patients with concurrent coronary artery disease yielded significantly higher IIEF scores in comparison with the placebo arm (Herrmann et al. 2006).

5.14.1.7 PDE5i Plus Continuous Positive Airway Pressure

In obstructive sleep apnea patients, the use of continuous airway pressure in combination with sildenafil had a significantly higher successful intercourse rate compared to monotherapy (Perimenis et al. 2007).

5.14.1.8 PDE5-Is Plus Psychosexual Therapy

Combination of sildenafil with cognitive-behavior sex therapy or brief couple sex therapy showed beneficial results (Banner and Anderson 2007).

5.15 VED Plus Intraurethral or Intracavernosal Treatment

VED has been used with either intraurethral alprostadil or intracavernosal injection in order to augment erectile response (Chen et al. 1995; John et al. 1996).

5.16 Prosthesis Combinations

PDE5-Isi (Mulhall et al. 2004), intraurethral alprostadil (Chew and Stuckey 2000), and VED (Soderdahl et al. 1997) have all been used for the management of the "cold penis" syndrome in patients with implanted prosthesis.

5.17 Follow-Up: FAST

ED should be managed in a similar way to other chronic diseases. Follow-up visits are of outstanding significance. The following "FAST" acronym is a useful reminder of the key aspects for follow-up visits (Hatzichristou 2002).

- *Follow-Up Patients*
  Follow-up is essential in order to address treatment issues or problems that may potentially occur (e.g., treatment administration, efficacy, adverse effects, partner's acceptance), to identify changes in sexual function status or new medical conditions, and to offer continuing education and support to patients and their partners.
- *Dose Adjustment*
  Careful attention to prescribing instructions is necessary. Adjust either to a higher dose if the patient reports inadequate efficacy or lower the dose in cases of adverse events.
- *Sexual Stimulation*
  Adequate sexual stimuli are key elements for the success of any treatment method, including all psychosexual and medical treatments available; therefore, sexual stimulation is essential and it may be also necessary to consider educating the patient and partner on suitable methods of stimulation.

- *Titration to the Maximal Tolerated Dose*
  As all treatments for sexual problems are stepwise, it is important to follow closely the steps made by the patient or the couple.

5.18 Assessing Treatment Outcome

Treatment outcomes can be regarded as having three major components (Evangelia et al. 2010; Kirana et al. 2009): (a) relief of symptoms and/or restoration of sexual function, (b) reduction of bother/distress, and (c) improvement of patient/partner sexual well-being. Although the consequences of the problem and associated distress in most cases will be diminished or abolished due to the restoration of erectile function, the man's and/or couples' sexual well-being are considered to be the most important treatment outcome.

References

Al Ansari A, Talib RA, Shamsodini A et al (2013) Which is guilty in self-induced penile fractures: marital status, culture or geographic region? A case series and literature review. Int J Impot Res. doi:10.1038/ijir.2013.16

Al-Shaiji TF, Brock GB (2009) Phosphodiesterase type 5 inhibitors for the management of erectile dysfunction: preference and adherence to treatment. Curr Pharm Des 15:3486–3495

Andersson KE (2011) Mechanisms of penile erection and basis for pharmacological treatment of erectile dysfunction. Pharmacol Rev 63:811–859

Athanasiadis L, Papaharitou S, Salpiggidis G et al (2006) Educating physicians to treat erectile dysfunction patients: development and evaluation of a course on communication and management strategies. J Sex Med 3:47–55

Aversa A, Vitale C, Volterrani M et al (2008) Chronic administration of Sildenafil improves markers of endothelial function in men with Type 2 diabetes. Diabet Med 25:37–44

Babaei AR, Safarinejad MR, Kolahi AA (2009) Penile revascularization for erectile dysfunction: a systematic review and meta-analysis of effectiveness and complications. Urol J 6:1–7

Banner LL, Anderson RU (2007) Integrated sildenafil and cognitive-behavior sex therapy for psychogenic erectile dysfunction: a pilot study. J Sex Med 4:1117–1125

Bar-Yosef Y, Greenstein A, Beri A et al (2007) Dorsal vein injuries observed during penile exploration for suspected penile fracture. J Sex Med 4:1142–1146

Buvat J, Hatzichristou D, Maggi M et al (2008) Efficacy, tolerability and satisfaction with sildenafil citrate 100-mg titration compared with continued 50-mg dose treatment in men with erectile dysfunction. BJU Int 102:1645–1650

Buvat J, Maggi M, Guay A et al (2013) Testosterone deficiency in men: systematic review and standard operating procedures for diagnosis and treatment. J Sex Med 10:245–284

Campbell N, Clark JP, Stecher VJ et al (2012) Internet-ordered viagra (sildenafil citrate) is rarely genuine. J Sex Med 9:2943–2951

Canguven O, Bailen J, Fredriksson W et al (2009) Combination of vacuum erection device and PDE5 inhibitors as salvage therapy in PDE5 inhibitor nonresponders with erectile dysfunction. J Sex Med 6:2561–2567

Cappelleri JC, Rosen RC (2005) The Sexual Health Inventory for Men (SHIM): a 5-year review of research and clinical experience. Int J Impot Res 17:307–319

Carson C, Giuliano F, Goldstein I et al (2004) The 'effectiveness' scale–therapeutic outcome of pharmacologic therapies for ED: an international consensus panel report. Int J Impot Res 16:207–213

Carson CC 3rd, Mulcahy JJ, Harsch MR (2011) Long-term infection outcomes after original antibiotic impregnated inflatable penile prosthesis implants: up to 7.7 years of followup. J Urol 185:614–618

Cellek S, Cameron NE, Cotter MA et al (2013) Pathophysiology of diabetic erectile dysfunction: potential contribution of vasa nervorum and advanced glycation endproducts. Int J Impot Res 25:1–6

Chang S, Hypolite JA, Zderic SA et al (2005) Increased corpus cavernosum smooth muscle tone associated with partial bladder outlet obstruction is mediated via Rho-kinase. Am J Physiol Regul Integr Comp Physiol 289:R1124–R1130

Chen J, Godschalk MF, Katz PG et al (1995) Combining intracavernous injection and external vacuum as treatment for erectile dysfunction. J Urol 153:1476–1477

Chen J, Sofer M, Kaver I et al (2004) Concomitant use of sildenafil and a vacuum entrapment device for the treatment of erectile dysfunction. J Urol 171:292–295

Chertin B, Natsheh A, Ben-Zion I et al (2013) Objective and subjective sexual outcomes in adult patients after hypospadias repair performed in childhood. J Urol. doi:10.1016/j.juro.2012.12.104

Chew KK, Stuckey BG (2000) Use of transurethral alprostadil (MUSE) (prostaglandin E1) for glans tumescence in a patient with penile prosthesis. Int J Impot Res 12:195–196

Chrysant SG, Chrysant GS (2012) The pleiotropic effects of phosphodiesterase 5 inhibitors on function and safety in patients with cardiovascular disease and hypertension. J Clin Hypertens (Greenwich) 14:644–649

Chung E, Clendinning E, Lessard L et al (2011) Five-year follow-up of Peyronie's graft surgery: outcomes and patient satisfaction. J Sex Med 8:594–600

Coombs PG, Heck M, Guhring P et al (2012) A review of outcomes of an intracavernosal injection therapy programme. BJU Int 110:1787–1791

Corona G, Fagioli G, Mannucci E et al (2008) Penile doppler ultrasound in patients with erectile dysfunction (ED): role of peak systolic velocity measured in the flaccid state in predicting arteriogenic ED and silent coronary artery disease. J Sex Med 5:2623–2634

Costa P, Potempa AJ (2012) Intraurethral alprostadil for erectile dysfunction: a review of the literature. Drugs 72:2243–2254

Da Ros CT, Teloken C, Antonini CC et al (2000) Long-term results of penile vein ligation for erectile dysfunction due to cavernovenous disease. Tech Urol 6:172–174

Davey Smith G, Frankel S, Yarnell J (1997) Sex and death: are they related? Findings from the Caerphilly cohort study. BMJ 315:1641–1644

DeBusk R, Drory Y, Goldstein I et al (2000) Management of sexual dysfunction in patients with cardiovascular disease: recommendations of The Princeton Consensus Panel. Am J Cardiol 86:175–181

Derby CA, Mohr BA, Goldstein I et al (2000) Modifiable risk factors and erectile dysfunction: can lifestyle changes modify risk? Urology 56:302–306

Dhir RR, Lin HC, Canfield SE et al (2011) Combination therapy for erectile dysfunction: an update review. Asian J Androl 13:382–390

Ding H, Du W, Wang H et al (2012) Efficacy and safety of udenafil for erectile dysfunction: a meta-analysis of randomized controlled trials. Urology 80:134–139

Dinsmore WW, Hackett G, Goldmeier D et al (2007) Topical eutectic mixture for premature ejaculation (TEMPE): a novel aerosol-delivery form of lidocaine-prilocaine for treating premature ejaculation. BJU Int 99:369–375

Dong JY, Zhang YH, Qin LQ (2011) Erectile dysfunction and risk of cardiovascular disease: meta-analysis of prospective cohort studies. J Am Coll Cardiol 58:1378–1385

Eardley I (2013) The incidence, prevalence, and natural history of erectile dysfunction. Sex Med Rev 1:3–16

Eardley I, Montorsi F, Jackson G et al (2007) Factors associated with preference for sildenafil citrate and tadalafil for treating erectile dysfunction in men naive to phosphodiesterase 5 inhibitor therapy: post hoc analysis of data from a multicentre, randomized, open-label, crossover study. BJU Int 100:122–129

Eland IA, van der Lei J, Stricker BH et al (2001) Incidence of priapism in the general population. Urology 57:970–972

Esposito K, Giugliano F, Maiorino MI et al (2010) Dietary factors, Mediterranean diet and erectile dysfunction. J Sex Med 7:2338–2345

Evangelia N, Kirana PS, Chiu G et al (2010) Level of bother and treatment-seeking predictors among male and female in-patients with sexual problems: a hospital-based study. J Sex Med 7:700–711

Flores S, Tal R, O'Brien K et al (2011) Outcomes of crural ligation surgery for isolated crural venous leak. J Sex Med 8:3495–3499

Flower R (2004) Lifestyle drugs: pharmacology and the social agenda. Trends Pharmacol Sci 25:182–185

Fode M, Ohl DA, Ralph D et al (2013) Penile rehabilitation after radical prostatectomy: what the evidence really says. BJU Int. doi:10.1111/bju.12228

Fonseca V, Seftel A, Denne J et al (2004) Impact of diabetes mellitus on the severity of erectile dysfunction and response to treatment: analysis of data from tadalafil clinical trials. Diabetologia 47:1914–1923

Forgue ST, Patterson BE, Bedding AW et al (2006) Tadalafil pharmacokinetics in healthy subjects. Br J Clin Pharmacol 61:280–288

Foster SA, Annunziata K, Shortridge E et al (2013) Erectile dysfunction with or without coexisting benign prostatic hyperplasia in the general US population: analysis of US national health and wellness survey. Curr Med Res Opin. doi:10.1185/03007995.2013.837385

Frieben RW, Lin HC, Hinh PP et al (2010) The impact of minimally invasive surgeries for the treatment of symptomatic benign prostatic hyperplasia on male sexual function: a systematic review. Asian J Androl 12:500–508

Fu Q, Zhang J, Sa YL et al (2013) Recurrence and complications after transperineal bulboprostatic anastomosis for posterior urethral strictures resulting from pelvic fracture: a retrospective study from a urethral referral centre. BJU Int 112:E358–E363

Fulgham PF, Cochran JS, Denman JL et al (1998) Disappointing initial results with transurethral alprostadil for erectile dysfunction in a urology practice setting. J Urol 160:2041–2046

Gacci M, Eardley I, Giuliano F et al (2011) Critical analysis of the relationship between sexual dysfunctions and lower urinary tract symptoms due to benign prostatic hyperplasia. Eur Urol 60:809–825

Gacci M, Corona G, Salvi M et al (2012) A systematic review and meta-analysis on the use of phosphodiesterase 5 inhibitors alone or in combination with alpha-blockers for lower urinary tract symptoms due to benign prostatic hyperplasia. Eur Urol 61:994–1003

Gamal WM, Osman MM, Hammady A et al (2011) Penile fracture: long-term results of surgical and conservative management. J Trauma 71:491–493

Gandaglia G, Briganti A, Jackson G et al (2013) A systematic review of the association between erectile dysfunction and cardiovascular disease. Eur Urol. doi:10.1016/j.eururo.2013.08.023

Garcia-Cruz E, Leibar-Tamayo A, Romero J et al (2013) Metabolic syndrome in men with low testosterone levels: relationship with cardiovascular risk factors and comorbidities and with erectile dysfunction. J Sex Med. doi:10.1111/jsm.12265

Giuliano F, Uckert S, Maggi M et al (2013) The mechanism of action of phosphodiesterase type 5 inhibitors in the treatment of lower urinary tract symptoms related to benign prostatic hyperplasia. Eur Urol 63:506–516

Glina S, Ghanem H (2013) SOP: corpus cavernosum assessment (cavernosography/cavernosometry). J Sex Med 10:111–114

Glina S, Sharlip ID, Hellstrom WJ (2013) Modifying risk factors to prevent and treat erectile dysfunction. J Sex Med 10:115–119

Goel A, Sharma K, Sharma P (2013) De novo erectile dysfunction after anterior urethroplasty: a systematic review and meta-analysis. BJU Int 112:E425

Goldstein I (2000) The mutually reinforcing triad of depressive symptoms, cardiovascular disease, and erectile dysfunction. Am J Cardiol 86:41F–45F

Goldstein I, Lue TF, Padma-Nathan H et al (2002) Oral sildenafil in the treatment of erectile dysfunction. 1998. J Urol 167:1197–1203; discussion 1204

Goldstein I, McCullough AR, Jones LA et al (2012) A randomized, double-blind, placebo-controlled evaluation of the safety and efficacy of avanafil in subjects with erectile dysfunction. J Sex Med 9:1122–1133

Greenstein A, Abramov L, Matzkin H et al (2006) Sexual dysfunction in women partners of men with erectile dysfunction. Int J Impot Res 18:44–46

Gruenwald I, Shenfeld O, Chen J et al (2006) Positive effect of counseling and dose adjustment in patients with erectile dysfunction who failed treatment with sildenafil. Eur Urol 50:134–140

Gruenwald I, Leiba R, Vardi Y (2009) Effect of sildenafil on middle-aged sexually active males with no erectile complaints: a randomized placebo-controlled double-blind study. Eur Urol 55:969–976

Gruenwald I, Appel B, Kitrey ND et al (2013) Shockwave treatment of erectile dysfunction. Ther Adv Urol 5:95–99

Gupta BP, Murad MH, Clifton MM et al (2011) The effect of lifestyle modification and cardiovascular risk factor reduction on erectile dysfunction: a systematic review and meta-analysis. Arch Intern Med 171:1797–1803

Gur S, Kadowitz PJ, Hellstrom WJ (2013) Effects of 5-alpha reductase inhibitors on erectile function, sexual desire and ejaculation. Expert Opin Drug Saf 12:81–90

Han TS, Tajar A, O'Neill TW et al (2011) Impaired quality of life and sexual function in overweight and obese men: the European Male Ageing Study. Eur J Endocrinol 164:1003–1011

Hannan JL, Maio MT, Komolova M et al (2009) Beneficial impact of exercise and obesity interventions on erectile function and its risk factors. J Sex Med 6(Suppl 3):254–261

Hatzichristou DG (2002) Sildenafil citrate: lessons learned from 3 years of clinical experience. Int J Impot Res 14(Suppl 1):S43–S52

Hatzichristou D (2008) Understanding individuals' response to erectile dysfunction. Int J Impot Res 20(Suppl 2):S15–S20

Hatzichristou D (2012) Post-radical prostatectomy erectile function: the five Ws and the H. Eur Urol 62:287–289

Hatzichristou D, Tsimtsiou Z (2005) Prevention and management of cardiovascular disease and erectile dysfunction: toward a common patient-centered, care model. Am J Cardiol 96:80M–84M

Hatzichristou DG, Saenz de Tejada I, Kupferman S et al (1995) In vivo assessment of trabecular smooth muscle tone, its application in pharmaco-cavernosometry and analysis of intracavernous pressure determinants. J Urol 153:1126–1135

Hatzichristou DG, Apostolidis A, Tzortzis V et al (2000) Sildenafil versus intracavernous injection therapy: efficacy and preference in patients on intracavernous injection for more than 1 year. J Urol 164:1197–1200

Hatzichristou D, Hatzimouratidis K, Bekas M et al (2002) Diagnostic steps in the evaluation of patients with erectile dysfunction. J Urol 168:615–620

Hatzichristou D, Rosen RC, Broderick G et al (2004) Clinical evaluation and management strategy for sexual dysfunction in men and women. J Sex Med 1:49–57

Hatzichristou D, Moysidis K, Apostolidis A et al (2005) Sildenafil failures may be due to inadequate patient instructions and follow-up: a study on 100 non-responders. Eur Urol 47:518–522; discussion 522–513

Hatzichristou D, Gambla M, Rubio-Aurioles E et al (2008) Efficacy of tadalafil once daily in men with diabetes mellitus and erectile dysfunction. Diabet Med 25:138–146

Hatzichristou D, Rosen RC, Derogatis LR et al (2010) Recommendations for the clinical evaluation of men and women with sexual dysfunction. J Sex Med 7:337–348

Hatzimouratidis K, Hatzichristou DG (2009) Phosphodiesterase type 5 inhibitors: unmet needs. Curr Pharm Des 15:3476–3485

Hatzimouratidis K, Moysidis K, Bekos A et al (2006) Treatment strategy for "non-responders" to tadalafil and vardenafil: a real-life study. Eur Urol 50:126–132; discussion 132–123

Hatzimouratidis K, Burnett AL, Hatzichristou D et al (2009) Phosphodiesterase type 5 inhibitors in post-prostatectomy erectile dysfunction: a critical analysis of the basic science rationale and clinical application. Eur Urol 55:334–347

Hatzimouratidis K, Amar E, Eardley I et al (2010) Guidelines on male sexual dysfunction: erectile dysfunction and premature ejaculation. Eur Urol 57:804–814

Hatzimouratidis K, Eardley I, Giuliano F et al (2012) EAU guidelines on penile curvature. Eur Urol 62:543–552

Haynes RB, Sackett DL, Gray JM et al (1996) Transferring evidence from research into practice: 1. The role of clinical care research evidence in clinical decisions. ACP J Club 125:A14–A16

Hedelin H, Stroberg P (2005) Treatment for erectile dysfunction based on patient-reported outcomes: to every man the PDE5 inhibitor that he finds superior. Drugs 65:2245–2251

Hedlund P, Holmquist F, Hedlund H, Andersson KE. Effects of nicorandil on human isolated corpus cavernosum and cavernous artery. J Urol 1994;151:1107–1113

Heidenreich A, Abrahamsson PA, Artibani W et al (2013) Early detection of prostate cancer: European association of urology recommendation. Eur Urol 64:347–354

Heinig R, Weimann B, Dietrich H et al (2011) Pharmacokinetics of a new orodispersible tablet formulation of vardenafil: results of three clinical trials. Clin Drug Investig 31:27–41

Hekal IA, El-Bahnasawy MS, Mosbah A et al (2009) Recoverability of erectile function in post-radical cystectomy patients: subjective and objective evaluations. Eur Urol 55:275–283

Hekal IA, Mosbah A, El-Bahnasawy MS et al (2011) Penile haemodynamic changes in post-radical cystectomy patients. Int J Androl 34:27–32

Henry GD, Donatucci CF, Conners W et al (2012) An outcomes analysis of over 200 revision surgeries for penile prosthesis implantation: a multicenter study. J Sex Med 9:309–315

Herrmann HC, Levine LA, Macaluso J Jr et al (2006) Can atorvastatin improve the response to sildenafil in men with erectile dysfunction not initially responsive to sildenafil? Hypothesis and pilot trial results. J Sex Med 3:303–308

Hsiao W, Shrewsberry AB, Moses KA et al (2012) Exercise is associated with better erectile function in men under 40 as evaluated by the International Index of Erectile Function. J Sex Med 9:524–530

Huang YC, Harraz AM, Shindel AW et al (2009) Evaluation and management of priapism: 2009 update. Nat Rev Urol 6:262–271

Jackson G, Arver S, Banks I et al (2010) Counterfeit phosphodiesterase type 5 inhibitors pose significant safety risks. Int J Clin Pract 64:497–504

John H, Lehmann K, Hauri D (1996) Intraurethral prostaglandin improves quality of vacuum erection therapy. Eur Urol 29:224–226

Kadioglu A, Sanli O, Akman T et al (2011) Factors affecting the degree of penile deformity in Peyronie disease: an analysis of 1001 patients. J Androl 32:502–508

Kaplan SA, Gonzalez RR, Te AE (2007) Combination of alfuzosin and sildenafil is superior to monotherapy in treating lower urinary tract symptoms and erectile dysfunction. Eur Urol 51:1717–1723

Karatas OF, Bayrak O, Cimentepe E et al (2010) An insidious risk factor for cardiovascular disease: benign prostatic hyperplasia. Int J Cardiol 144:452

Karavitakis M, Komninos C, Theodorakis PN et al (2011) Evaluation of sexual function in hypertensive men receiving treatment: a review of current guidelines recommendation. J Sex Med 8:2405–2414

Kattan S (1995) Double-blind randomized crossover study comparing intracorporeal prostaglandin E1 with combination of prostaglandin E1 and lidocaine in the treatment of organic impotence. Urology 45:1032–1036

Kawanishi T, Shiraishi T, Okano Y et al (2011) New detection systems of bacteria using highly selective media designed by SMART: selective medium-design algorithm restricted by two constraints. PLoS One 6:e16512

Kayigil O, Okulu E, Aldemir M et al (2012) Penile revascularization in vasculogenic erectile dysfunction (ED): long-term follow-up. BJU Int 109:109–115

Kim TE, Kim BH, Kim JR et al (2009) Effect of food on the pharmacokinetics of the oral phosphodiesterase 5 inhibitor udenafil for the treatment of erectile dysfunction. Br J Clin Pharmacol 68:43–46

Kirana PS, Rosen R, Hatzichristou D (2009) Subjective well-being as a determinant of individuals' responses to symptoms: a biopsychosocial perspective. Int J Clin Pract 63:1435–1445

Kirby M, Chapple C, Jackson G et al (2013) Erectile dysfunction and lower urinary tract symptoms: a consensus on the importance of co-diagnosis. Int J Clin Pract 67:606–618

Kloner RA (2004) Novel phosphodiesterase type 5 inhibitors: assessing hemodynamic effects and safety parameters. Clin Cardiol 27:I20–I25

Koraitim MM (2013) Predictors of erectile dysfunction post pelvic fracture urethral injuries: a multivariate analysis. Urology 81:1081–1085

Koskimaki J, Shiri R, Tammela T et al (2008) Regular intercourse protects against erectile dysfunction: tampere aging male urologic study. Am J Med 121:592–596

Kostis JB, Jackson G, Rosen R et al (2005) Sexual dysfunction and cardiac risk (the Second Princeton Consensus Conference). Am J Cardiol 96:85M–93M

Kovac JR, Mak SK, Garcia MM et al (2013) A pathophysiology-based approach to the management of early priapism. Asian J Androl 15:20–26

Kwon H, Kang HC, Lee JH (2013) Relationship between predictors of the risk of clinical progression of benign prostatic hyperplasia and metabolic syndrome in men with moderate to severe lower urinary tract symptoms. Urology 81:1325–1329

La Vignera S, Condorelli RA, Vicari E et al (2012) Statins and erectile dysfunction: a critical summary of current evidence. J Androl 33:552–558

Lakin MM, Montague DK, VanderBrug Medendorp S et al (1990) Intracavernous injection therapy: analysis of results and complications. J Urol 143:1138–1141

Lamina S, Agbanusi E (2013) Effect of aerobic exercise training on maternal weight gain in pregnancy: a meta-analysis of randomized controlled trials. Ethiop J Health Sci 23:59–64

Lee D, Westney OL, Wang R (2011) Combination surgery for erectile dysfunction and male incontinence. Curr Urol Rep 12:461–469

Lee RK, Chung D, Chughtai B et al (2012) Central obesity as measured by waist circumference is predictive of severity of lower urinary tract symptoms. BJU Int 110:540–545

Levine LA (2013) The clinical and psychosocial impact of Peyronie's disease. Am J Manag Care 19:S55–S61

Levine LA, Burnett AL (2013) Standard operating procedures for Peyronie's disease. J Sex Med 10:230–244

Levine LA, Dimitriou RJ (2001) Vacuum constriction and external erection devices in erectile dysfunction. Urol Clin North Am 28:335–341, ix–x

Lewis RW, Witherington R (1997) External vacuum therapy for erectile dysfunction: use and results. World J Urol 15:78–82

Lewis RW, Fugl-Meyer KS, Corona G et al (2010) Definitions/epidemiology/risk factors for sexual dysfunction. J Sex Med 7:1598–1607

Liguori G, Trombetta C, De Giorgi G et al (2009) Efficacy and safety of combined oral therapy with tadalafil and

alfuzosin: an integrated approach to the management of patients with lower urinary tract symptoms and erectile dysfunction. Preliminary report. J Sex Med 6:544–552

Lindau ST, Gavrilova N (2010) Sex, health, and years of sexually active life gained due to good health: evidence from two US population based cross sectional surveys of ageing. BMJ 340:c810

Lindau ST, Schumm LP, Laumann EO et al (2007) A study of sexuality and health among older adults in the United States. N Engl J Med 357:762–774

Ljunggren C, Hedelin H, Salomonsson K et al (2008) Giving patients with erectile dysfunction the opportunity to try all three available phosphodiesterase type 5 inhibitors contributes to better long-term treatment compliance. J Sex Med 5:469–475

Lombardi G, Nelli F, Celso M et al (2012) Treating erectile dysfunction and central neurological diseases with oral phosphodiesterase type 5 inhibitors. Review of the literature. J Sex Med 9:970–985

Lowe G, Costabile RA (2012) 10-Year analysis of adverse event reports to the Food and Drug Administration for phosphodiesterase type-5 inhibitors. J Sex Med 9:265–270

Mallis D, Moysidis K, Nakopoulou E et al (2005) Psychiatric morbidity is frequently undetected in patients with erectile dysfunction. J Urol 174:1913–1916

Mamoulakis C, Skolarikos A, Schulze M et al (2013) Bipolar vs monopolar transurethral resection of the prostate: evaluation of the impact on overall sexual function in an international randomized controlled trial setting. BJU Int 112:109–120

Martin Morales A, Hatzichristou D, Ramon Llados J et al (2013) Community pharmacy detection of erectile dysfunction in men with risk factors or who seek treatment or advice but lack a valid prescription. J Sex Med. doi:10.1111/jsm.12238

Martin AL, Huelin R, Wilson D et al (2013) A systematic review assessing the economic impact of sildenafil citrate (Viagra) in the treatment of erectile dysfunction. J Sex Med 10:1389–1400

Martinez-Salamanca JI, Mueller A, Moncada I et al (2011) Penile prosthesis surgery in patients with corporal fibrosis: a state of the art review. J Sex Med 8:1880–1889

McCullough AR, Barada JH, Fawzy A et al (2002) Achieving treatment optimization with sildenafil citrate (Viagra) in patients with erectile dysfunction. Urology 60:28–38

McMahon C (2004) Efficacy and safety of daily tadalafil in men with erectile dysfunction previously unresponsive to on-demand tadalafil. J Sex Med 1:292–300

McMahon C (2005) Comparison of efficacy, safety, and tolerability of on-demand tadalafil and daily dosed tadalafil for the treatment of erectile dysfunction. J Sex Med 2:415–425; discussion 425–417

McMahon CG, Samali R, Johnson H (1999) Treatment of intracorporeal injection nonresponse with sildenafil alone or in combination with triple agent intracorporeal injection therapy. J Urol 162:1992–1997; discussion 1997–1998

McVary KT, Rademaker A, Lloyd GL et al (2005) Autonomic nervous system overactivity in men with lower urinary tract symptoms secondary to benign prostatic hyperplasia. J Urol 174:1327–1433

Melnik T, Soares BG, Nasello AG (2008) The effectiveness of psychological interventions for the treatment of erectile dysfunction: systematic review and meta-analysis, including comparisons to sildenafil treatment, intracavernosal injection, and vacuum devices. J Sex Med 5:2562–2574

Meuleman EJ, Bemelmans BL, van Asten WN et al (1992) Assessment of penile blood flow by duplex ultrasonography in 44 men with normal erectile potency in different phases of erection. J Urol 147:51–56

Meuleman EJ, Hatzichristou D, Rosen RC et al (2010) Diagnostic tests for male erectile dysfunction revisited. Committee Consensus Report of the International Consultation in Sexual Medicine. J Sex Med 7:2375–2381

Miner M, Seftel AD, Nehra A et al (2012) Prognostic utility of erectile dysfunction for cardiovascular disease in younger men and those with diabetes. Am Heart J 164:21–28

Mohamed O, Freundlich RE, Dakik HK et al (2010) The quantitative ADAM questionnaire: a new tool in quantifying the severity of hypogonadism. Int J Impot Res 22:20–24

Moncada I, Jara J, Subira D et al (2004) Efficacy of sildenafil citrate at 12 hours after dosing: re-exploring the therapeutic window. Eur Urol 46:357–360; discussion 360–351

Montorsi F, Padma-Nathan H, Buvat J et al (2004a) Earliest time to onset of action leading to successful intercourse with vardenafil determined in an at-home setting: a randomized, double-blind, placebo-controlled trial. J Sex Med 1:168–178

Montorsi F, Verheyden B, Meuleman E et al (2004b) Long-term safety and tolerability of tadalafil in the treatment of erectile dysfunction. Eur Urol 45:339–344; discussion 344–335

Montorsi P, Ravagnani PM, Galli S et al (2005) The artery size hypothesis: a macrovascular link between erectile dysfunction and coronary artery disease. Am J Cardiol 96:19M–23M

Montorsi P, Ravagnani PM, Galli S et al (2006) Association between erectile dysfunction and coronary artery disease. Role of coronary clinical presentation and extent of coronary vessels involvement: the COBRA trial. Eur Heart J 27:2632–2639

Montorsi F, Brock G, Lee J et al (2008) Effect of nightly versus on-demand vardenafil on recovery of erectile function in men following bilateral nerve-sparing radical prostatectomy. Eur Urol 54:924–931

Montorsi F, Basson R, Adaikan G et al (2010a) Sexual medicine. In: Sexual dysfunctions in men and women. Health Publications, Paris, 2010 edn

Montorsi F, Adaikan G, Becher E et al (2010b) Summary of the recommendations on sexual dysfunctions in men. J Sex Med 7:3572–3588

Morales AM, Casillas M, Turbi C (2011) Patients' preference in the treatment of erectile dysfunction: a critical review of the literature. Int J Impot Res 23:1–8

Morgentaler A (2013) Testosterone therapy in men with prostate cancer: scientific and ethical considerations. J Urol 189:S26–S33

Morley JE, Charlton E, Patrick P et al (2000) Validation of a screening questionnaire for androgen deficiency in aging males. Metabolism 49:1239–1242

Mulat B, Arbel Y, Mashav N et al (2010) Depressive symptoms and erectile dysfunction in men with coronary artery disease. Urology 75:104–107

Mulhall JP, Montorsi F (2006) Evaluating preference trials of oral phosphodiesterase 5 inhibitors for erectile dysfunction. Eur Urol 49:30–37

Mulhall JP, Abdel-Moneim A, Abobakr R et al (2001) Improving the accuracy of vascular testing in impotent men: correcting hemodynamic alterations using a vasoactive medication re-dosing schedule. J Urol 166:923–926

Mulhall JP, Jahoda A, Aviv N et al (2004) The impact of sildenafil citrate on sexual satisfaction profiles in men with a penile prosthesis in situ. BJU Int 93:97–99

Mulhall J, Anderson M, Parker M (2005) A surgical algorithm for men with combined Peyronie's disease and erectile dysfunction: functional and satisfaction outcomes. J Sex Med 2:132–138

Mulhall JP, Bella AJ, Briganti A et al (2010) Erectile function rehabilitation in the radical prostatectomy patient. J Sex Med 7:1687–1698

Munarriz R, Uberoi J, Fantini G et al (2009) Microvascular arterial bypass surgery: long-term outcomes using validated instruments. J Urol 182:643–648

Mydlo JH, Volpe MA, MacChia RJ (2000) Results from different patient populations using combined therapy with alprostadil and sildenafil: predictors of satisfaction. BJU Int 86:469–473

Nandipati K, Raina R, Agarwal A et al (2006) Early combination therapy: intracavernosal injections and sildenafil following radical prostatectomy increases sexual activity and the return of natural erections. Int J Impot Res 18:446–451

Nappi RE, Kingsberg S, Maamari R et al (2013) The CLOSER (CLarifying vaginal Atrophy's Impact On SEx and Relationships) survey: implications of vaginal discomfort in postmenopausal women and in male partners. J Sex Med. doi:10.1111/jsm.12235

Nehra A, Jackson G, Miner M et al (2012) The Princeton III Consensus recommendations for the management of erectile dysfunction and cardiovascular disease. Mayo Clin Proc 87:766–778

Nichols DJ, Muirhead GJ, Harness JA (2002) Pharmacokinetics of sildenafil after single oral doses in healthy male subjects: absolute bioavailability, food effects and dose proportionality. Br J Clin Pharmacol 53(Suppl 1):5S–12S

Padma-Nathan H, Stecher VJ, Sweeney M et al (2003) Minimal time to successful intercourse after sildenafil citrate: results of a randomized, double-blind, placebo-controlled trial. Urology 62:400–403

Papaharitou S, Athanasiadis L, Nakopoulou E et al (2006) Erectile dysfunction and premature ejaculation are the most frequently self-reported sexual concerns: profiles of 9,536 men calling a helpline. Eur Urol 49:557–563

Parish SJ, Rubio-Aurioles E (2010) Education in sexual medicine: proceedings from the international consultation in sexual medicine, 2009. J Sex Med 7:3305–3314

Parsons JK (2007) Modifiable risk factors for benign prostatic hyperplasia and lower urinary tract symptoms: new approaches to old problems. J Urol 178:395–401

Pavlovich CP, Levinson AW, Su LM et al (2013) Nightly vs on-demand sildenafil for penile rehabilitation after minimally invasive nerve-sparing radical prostatectomy: results of a randomized double-blind trial with placebo. BJU Int. doi:10.1111/bju.12253

Perimenis P, Konstantinopoulos A, Karkoulias K et al (2007) Sildenafil combined with continuous positive airway pressure for treatment of erectile dysfunction in men with obstructive sleep apnea. Int Urol Nephrol 39:547–552

Porst H (1996) The rationale for prostaglandin E1 in erectile failure: a survey of worldwide experience. J Urol 155:802–815

Porst H (2012) Erectile dysfunction. In: Porst H, Reisman C (eds) The ESSM syllabus of sexual medicine. Medix, Amsterdam

Porst H, Rosen R, Padma-Nathan H et al (2001) The efficacy and tolerability of vardenafil, a new, oral, selective phosphodiesterase type 5 inhibitor, in patients with erectile dysfunction: the first at-home clinical trial. Int J Impot Res 13:192–199

Porst H, Padma-Nathan H, Giuliano F et al (2003) Efficacy of tadalafil for the treatment of erectile dysfunction at 24 and 36 hours after dosing: a randomized controlled trial. Urology 62:121–125; discussion 125–126

Porst H, Giuliano F, Glina S et al (2006) Evaluation of the efficacy and safety of once-a-day dosing of tadalafil 5 mg and 10 mg in the treatment of erectile dysfunction: results of a multicenter, randomized, double-blind, placebo-controlled trial. Eur Urol 50:351–359

Porst H, Rajfer J, Casabe A et al (2008) Long-term safety and efficacy of tadalafil 5 mg dosed once daily in men with erectile dysfunction. J Sex Med 5:2160–2169

Porst H, Burnett A, Brock G et al (2013) SOP conservative (medical and mechanical) treatment of erectile dysfunction. J Sex Med 10:130–171

Pryor J, Akkus E, Alter G et al (2004) Priapism. J Sex Med 1:116–120

Qiu X, Lin G, Xin Z et al (2013) Effects of low-energy shockwave therapy on the erectile function and tissue of a diabetic rat model. J Sex Med 10:738–746

Raina R, Agarwal A, Allamaneni SS et al (2005a) Sildenafil citrate and vacuum constriction device combination enhances sexual satisfaction in erectile dysfunction after radical prostatectomy. Urology 65:360–364

Raina R, Nandipati KC, Agarwal A et al (2005b) Combination therapy: medicated urethral system for erection enhances sexual satisfaction in sildenafil citrate failure following nerve-sparing radical prostatectomy. J Androl 26:757–760

Rajfer J, Aliotta PJ, Steidle CP et al (2007) Tadalafil dosed once a day in men with erectile dysfunction: a randomized, double-blind, placebo-controlled study in the US. Int J Impot Res 19:95–103

Reisman Y, Eardley I, Porst H et al (2013) New developments in education and training in sexual medicine. J Sex Med 10:918–923

Rosano GM, Aversa A, Vitale C et al (2005) Chronic treatment with tadalafil improves endothelial function in men with increased cardiovascular risk. Eur Urol 47:214–220; discussion 220–212

Rosen RC, Riley A, Wagner G et al (1997) The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. Urology 49:822–830

Rosen RC, Cappelleri JC, Smith MD et al (1999) Development and evaluation of an abridged, 5-item version of the International Index of Erectile Function (IIEF-5) as a diagnostic tool for erectile dysfunction. Int J Impot Res 11:319–326

Rosen RC, Cappelleri JC, Gendrano N 3rd (2002) The International Index of Erectile Function (IIEF): a state-of-the-science review. Int J Impot Res 14:226–244

Rosen R, Altwein J, Boyle P et al (2003) Lower urinary tract symptoms and male sexual dysfunction: the multinational survey of the aging male (MSAM-7). Eur Urol 44:637–649

Rosen RC, Padma-Nathan H, Shabsigh R et al (2004) Determining the earliest time within 30 minutes to erectogenic effect after tadalafil 10 and 20 mg: a multicenter, randomized, double-blind, placebo-controlled, at-home study. J Sex Med 1:193–200

Rosen RC, Catania JA, Ehrhardt AA et al (2006) The Bolger conference on PDE-5 inhibition and HIV risk: implications for health policy and prevention. J Sex Med 3:960–975; discussion 973–965

Rosen RC, Allen KR, Ni X et al (2011) Minimal clinically important differences in the erectile function domain of the International Index of Erectile Function scale. Eur Urol 60:1010–1016

Salonia A (2009) Editorial comment on: effect of sildenafil on middle-aged sexually active males with no erectile complaints: a randomized placebo-controlled double-blind study. Eur Urol 55:976–977

Salonia A, Burnett AL, Graefen M et al (2012a) Prevention and management of postprostatectomy sexual dysfunctions part 2: recovery and preservation of erectile function, sexual desire, and orgasmic function. Eur Urol 62:273–286

Salonia A, Burnett AL, Graefen M et al (2012b) Prevention and management of postprostatectomy sexual dysfunctions. Part 1: choosing the right patient at the right time for the right surgery. Eur Urol 62:261–272

Sanda MG, Dunn RL, Michalski J et al (2008) Quality of life and satisfaction with outcome among prostate-cancer survivors. N Engl J Med 358:1250–1261

Schulman CC, Shen W, Stothard DR et al (2004) Integrated analysis examining first-dose success, success by dose, and maintenance of success among men taking tadalafil for erectile dysfunction. Urology 64:783–788

Schwartz BG, Levine LA, Comstock G et al (2012) Cardiac uses of phosphodiesterase-5 inhibitors. J Am Coll Cardiol 59:9–15

Schwartz BG, Jackson G, Stecher VJ et al (2013) Phosphodiesterase type 5 inhibitors improve endothelial function and may benefit cardiovascular conditions. Am J Med 126:192–199

Seftel A, Goldfischer E, Kim ED et al (2011) Onset of efficacy of tadalafil once daily in men with erectile dysfunction: a randomized, double-blind, placebo controlled trial. J Urol 185:243–248

Selvin E, Burnett AL, Platz EA (2007) Prevalence and risk factors for erectile dysfunction in the US. Am J Med 120:151–157

Serefoglu EC, Mandava SH, Gokce A et al (2012) Long-term revision rate due to infection in hydrophilic-coated inflatable penile prostheses: 11-year follow-up. J Sex Med 9:2182–2186

Seyam R, Mohamed K, Akhras AA et al (2005) A prospective randomized study to optimize the dosage of trimix ingredients and compare its efficacy and safety with prostaglandin E1. Int J Impot Res 17:346–353

Shabsigh R, Sadovsky R, Rosen RC et al (2009) Impact of an educational initiative on applied knowledge and attitudes of physicians who treat sexual dysfunction. Int J Impot Res 21:74–81

Shamloul R (2006) Peak systolic velocities may be falsely low in young patients with erectile dysfunction. J Sex Med 3:138–143

Sikka SC, Hellstrom WJ, Brock G et al (2013) Standardization of vascular assessment of erectile dysfunction: standard operating procedures for duplex ultrasound. J Sex Med 10:120–129

Simopoulos EF, Trinidad AC (2013) Male erectile dysfunction: integrating psychopharmacology and psychotherapy. Gen Hosp Psychiatry 35:33–38

Soderdahl DW, Petroski RA, Mode D et al (1997) The use of an external vacuum device to augment a penile prosthesis. Tech Urol 3:100–102

Sohn M, Hatzinger M, Goldstein I et al (2013) Standard operating procedures for vascular surgery in erectile dysfunction: revascularization and venous procedures. J Sex Med 10:172–179

Speel TG, van Langen H, Wijkstra H et al (2003) Penile duplex pharmaco-ultrasonography revisited: revalidation of the parameters of the cavernous arterial response. J Urol 169:216–220

Sperling H, Gittelman M, Norenberg C et al (2011) Efficacy and safety of an orodispersible vardenafil formulation for the treatment of erectile dysfunction in elderly men and those with underlying conditions: an integrated analysis of two pivotal trials. J Sex Med 8:261–271

St Sauver JL, Jacobsen SJ, Jacobson DJ et al (2011) Statin use and decreased risk of benign prostatic enlargement and lower urinary tract symptoms. BJU Int 107:443–450

Steinke EE, Jaarsma T, Barnason SA et al (2013) Sexual counseling for individuals with cardiovascular disease and their partners: a consensus document from the American Heart Association and the ESC Council on Cardiovascular Nursing and Allied Professions

(CCNAP). Circulation. doi:10.1161/CIR.0b013e31829c2e53
Stuckey BG, Jadzinsky MN, Murphy LJ et al (2003) Sildenafil citrate for treatment of erectile dysfunction in men with type 1 diabetes: results of a randomized controlled trial. Diabetes Care 26:279–284
Swearingen SG, Klausner JD (2005) Sildenafil use, sexual risk behavior, and risk for sexually transmitted diseases, including HIV infection. Am J Med 118:571–577
Taylor MJ, Rudkin L, Bullemor-Day P et al (2013) Strategies for managing sexual dysfunction induced by antidepressant medication. Cochrane Database Syst Rev (5):CD003382
Teloken PE, Park K, Parker M et al (2011) The false diagnosis of venous leak: prevalence and predictors. J Sex Med 8:2344–2349
Thadani U, Smith W, Nash S et al (2002) The effect of vardenafil, a potent and highly selective phosphodiesterase-5 inhibitor for the treatment of erectile dysfunction, on the cardiovascular response to exercise in patients with coronary artery disease. J Am Coll Cardiol 40:2006–2012
Thorstenson A, O'Connor RC, Ahonen R et al (2009) Clinical outcome following prostatic capsule- and seminal-sparing cystectomy for bladder cancer in 25 men. Scand J Urol Nephrol 43:127–132
Thorve VS, Kshirsagar AD, Vyawahare NS et al (2011) Diabetes-induced erectile dysfunction: epidemiology, pathophysiology and management. J Diabetes Complications 25:129–136
Traish AM, Hassani J, Guay AT et al (2011) Adverse side effects of 5alpha-reductase inhibitors therapy: persistent diminished libido and erectile dysfunction and depression in a subset of patients. J Sex Med 8:872–884
Trissel LABRF, Zhang YB (2004) Long-term stability of trimix: a three-drug injection used to treat erectile dysfunction. Int J Pharm Compd 8:231–235
Tsimtsiou Z, Hatzimouratidis K, Nakopoulou E et al (2006) Predictors of physicians' involvement in addressing sexual health issues. J Sex Med 3:583–588
U.S. (2010) Drugs causing ED. Lue TF, Basson R, Rosen R, Giuliano F, Khoury S, Montorsi F (eds) exual medicine: Sexual dysfunctions in men and women Paris, Health Publications, Paris. 2010 edn
Vardi M, Nini A (2007) Phosphodiesterase inhibitors for erectile dysfunction in patients with diabetes mellitus. Cochrane Database Syst Rev. doi:10.1002/14651858.CD002187.pub3:CD002187
Vardi Y, Sprecher E, Gruenwald I (2000) Logistic regression and survival analysis of 450 impotent patients treated with injection therapy: long-term dropout parameters. J Urol 163:467–470
Vardi Y, Gruenwald I, Gedalia U et al (2004) Evaluation of penile revascularization for erectile dysfunction: a 10-year follow-up. Int J Impot Res 16:181–186
Vardi Y, Appel B, Kilchevsky A et al (2012) Does low intensity extracorporeal shock wave therapy have a physiological effect on erectile function? Short-term results of a randomized, double-blind, sham controlled study. J Urol 187:1769–1775
Vlachopoulos CV, Terentes-Printzios DG, Ioakeimidis NK et al (2013) Prediction of cardiovascular events and all-cause mortality with erectile dysfunction: a systematic review and meta-analysis of cohort studies. Circ Cardiovasc Qual Outcomes 6:99–109
Weber MF, Smith DP, O'Connell DL et al (2013) Risk factors for erectile dysfunction in a cohort of 108 477 Australian men. Med J Aust 199:107–111
Wein AJ, Coyne KS, Tubaro A et al (2009) The impact of lower urinary tract symptoms on male sexual health: EpiLUTS. BJU Int 103(Suppl 3):33–41
Wespes E, Eardley I, Giuliano F et al (2013) Guidelines on male sexual dysfunction: Erectile dysfunction and premature ejaculation. in EAU Guidelines. EAU
Whooley MA, Avins AL, Miranda J et al (1997) Case-finding instruments for depression. Two questions are as good as many. J Gen Intern Med 12:439–445
Yuan J, Zhang R, Yang Z et al (2013) Comparative effectiveness and safety of oral phosphodiesterase type 5 inhibitors for erectile dysfunction: a systematic review and network meta-analysis. Eur Urol 63:902–912
Zacharakis E, Raheem AA, Freeman A et al (2013) The efficacy of the T shunt procedure and Intracavernous Tunnelling (snake maneuver) for the management of refractory ischaemic priapism. J Urol. doi:10.1016/j.juro.2013.07.034
Zargooshi J (2009) Sexual function and tunica albuginea wound healing following penile fracture: An 18-year follow-up study of 352 patients from Kermanshah, Iran. J Sex Med 6:1141–1150
Zhao C, Kim SW, Yang DY et al (2011) Efficacy and safety of once-daily dosing of udenafil in the treatment of erectile dysfunction: results of a multicenter, randomized, double-blind, placebo-controlled trial. Eur Urol 60:380–387
Zumbe J, Porst H, Sommer F et al (2008) Comparable efficacy of once-daily versus on-demand vardenafil in men with mild-to-moderate erectile dysfunction: findings of the RESTORE study. Eur Urol 54:204–210

Editorial on Erectile Dysfunction as Sentinel for Cardiovascular Disease

6

Thierry Roumeguère

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Erectile dysfunction (ED) affects millions of men worldwide with implications that go far beyond sexual activity. ED is predominantly a vascular disease, frequently coexists with cardiovascular diseases (CVD), and shares common risk factors such as metabolic syndrome, hyperlipidemia, smoking, excessive alcohol consumption, and sedentary behavior (Feldman et al. 2000). ED is now recognized as an early marker of cardiovascular disease, diabetes mellitus, and depression (Tan et al. 2012). It is an important component of the quality of life, but it also confers an independent risk for future cardiovascular events (Araujo et al. 2010; Dong et al. 2011). A usual 2–5-year time period is reported between the onset of ED in men with no known CVD and a cardiovascular event (Gazzaruso et al. 2004; Vlachopoulos et al. 2005; Montorsi et al. 2006). Furthermore, evidence suggests that ED is predictive of peripheral arterial disease and stroke (Polonsky et al. 2009; Ponholzer et al. 2005). It offers to physicians an opportunity for risk assessment (Jackson et al. 2010). Incident ED has a similar or greater predictive value for cardiovascular events as traditional risk factors, such as family history of myocardial infarction, smoking, and hyperlipidemia (Thompson et al. 2005; Araujo et al. 2009). Coronary heart disease is often more severe in patients with ED compared to patients without ED (Montorsi et al. 2003a). For that reason, patients who seek treatment for sexual dysfunction have a high prevalence of CVD that can be live threatening (Salonia et al. 2012).

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V. Mirone (ed.), *Clinical Uro-Andrology*,
DOI 10.1007/978-3-662-45018-5_6, © Springer-Verlag Berlin Heidelberg 2015

Management of patient with erectile dysfunction according to the risk for sexual activity and future cardiovascular events is then to be proposed (Gazzaruso et al. 2008; Vlachopoulos et al. 2013).

Vascular problems due to atherosclerosis are a process that begins during childhood and becomes clinically evident from middle age. Endothelial dysfunction has been shown to be a precursor of atherosclerosis lesions (Azadzoi et al. 1996). The main link between ED, CVD, and the risk factors is the vascular endothelium, which plays a fundamental role in the regulation of the circulation. This association is likely to be caused by impairment in the endothelium-dependent relaxation of smooth muscle cells in the corpus cavernosum, which impairs cavernosal perfusion of the penis (Solomon et al. 2003). Endothelial dysfunction can be demonstrated in patients with cardiovascular risk factors and has been found in men with ED and no CVD (Kaiser et al. 2004).

As the endothelial cells recover the sinusoid spaces in the cavernous tissue, it is logical that vascular impotence presents the same pathophysiology than other vascular diseases. This is further substantiated by a similar pathogenic involvement of nitric oxide (NO) pathway (Li et al. 2002). In the oxygen enhancement environment, autonomic dilator nerves and the endothelium are able to stimulate NO formation, mediating trabecular smooth muscle relaxation. Decreased endothelin receptor sites in the corpus cavernosum could reduce NO production and could be one of the explanations for the development of ED. At low oxygen concentrations, measured at the flaccid state of the penis, the synthesis of NO is inhibited (Kim et al. 1993). However, the penis is the only organ which changes from venous to arterial oxygen tensions during the course of its normal function. Lower critical oxygen tension could alter endothelial cells activity but also reduce smooth muscle content and decrease the penile elasticity with higher ratio of penile collagen (Sattar et al. 1995; Raviv et al. 1997).

The link between ED and subsequent cardiac events includes also the artery-size hypothesis. Clinical manifestations of vascular diseases rarely appear simultaneously, because arteries supplying various districts have different sizes. A lumen obstruction of the penile artery would represent a minor abnormality to cause significant obstruction to blood flow in coronary or peripheral arteries due to their larger size (Montorsi et al. 2003b, 2005).

Of particular importance is the increased risk of a cardiac event in men with ED aged 50 years or less with an incidence of atherosclerotic cardiovascular events in men younger than 40 years with ED more than seven times the incidence in a reference population (Chew et al. 2010). Data from the Olmsted County Study also suggested that ED is far more predictive of CVD in men 40–49 years of age than in older men (Inman et al. 2009).

The link is strong enough to justify the statement that men with ED should be considered cardiovascular patients unless proved otherwise. The presence of ED, especially in men aged 30–60 years, should alert the physician to the possibility of increased CVD risk and the workup recommended should, therefore, be used to modify risk. Assessment of ED must include ED severity because more severe ED has been associated with greater risk of major cardiovascular events and extent of CVD (Hall et al. 2010; Salem et al. 2009; Greenstein et al. 1997).

Prevention for arteriosclerosis should be a prime therapeutic target, especially in age-related ED patients, as they are often involved in ischemic heart disease. The interval between the onsets of symptoms is one of the most important factors as it provides an opportunity for early diagnosis, treatment, and prevention.

6.1 Assessment of Endothelial Function

Inflammation is of importance in early atherosclerosis. Several inflammatory markers, such as interleukin-6, tumor necrosis factor-α, or C-reactive protein (CRP), have all been associated with impaired endothelial function, cardiovascular events, and ED. Elevated CRP levels have also been found to significantly correlate

with vascular ED as measured by penile Doppler (Billups et al. 2003). But with the exception of CRP, most markers are not commonly run in commercial laboratories, and they can also be elevated in a multitude of other inflammatory processes. Endothelin-1 (ET-1) is a potent vasoconstrictor and proinflammatory peptide associated with endothelial dysfunction, inflammation, and vasoconstriction and of the serum markers studied, ET-1 is probably the one that is closest to achieve clinical relevance (Bohm and Pernow 2007). This underlines the importance of inflammation in early atherosclerosis (Vlachopoulos et al. 2006).

When the endothelium is damaged, circulating endothelial progenitor cells (cEPCs) from the bone marrow are activated in the bloodstream and mature into endothelial cells that help repair the site of injury (Hill et al. 2003). This process, called vasculogenesis, is impaired as documented by low levels of cEPCs in ED and CAD. Circulating markers of endothelial cell damage have been reported in patients with erectile dysfunction, while they have not yet presented any other vascular pathology (Foresta et al. 2005; Baumhakel et al. 2006). Determination of cEPC levels with flow cytometry is not a test that is widely commercially available.

Intima-media thickness (IMT) of the common carotid artery is measured after visualization by ultrasonography. IMT has been found to correlate with other measures of endothelial function and is firmly correlated with ED, but interpretation is hampered by discordant measurements hailing from operator variability (Bocchio et al. 2005).

Flow-mediated dilation of the brachial artery (FMD)

FMD of the brachial artery with ultrasonographic assessment has become the most widely published standard in the assessment of endothelial dysfunction. Briefly, arterial occlusion with a blood pressure cuff for 5 min and subsequent release leads to reactive hyperemia and local endothelial activation. When this is performed on the patient's arm, increased shear stress leads to endothelium-dependent dilation of the brachial artery, which can be measured and quantified by ultrasound. The results can then be contrasted to endothelium-independent dilation provoked by administration of nitroglycerin. Endothelial function of the brachial artery as measured by FMD has long been firmly linked to coronary endothelial function (Wu et al. 2005). Numerous studies have solidly connected impaired FMD with ED even without manifest CVD (Chiurlia et al. 2005; Yavuzgil et al. 2005; Kaya et al. 2006). Although FMD is noninvasive and the most widely published method to evaluate endothelial function, problems with reproducibility persist. Results are highly operator dependent and can be confounded by changes in baseline diameter of the brachial artery. A more recent method of assessing endothelial function is peripheral arterial tonometry measuring reactive hyperemia (RH-PAT). This office-based technique uses a finger probe to assess digital volume changes accompanying pulse waves after inducing reactive hyperemia with a blood pressure cuff on the upper arm (Kuvin et al. 2007). Nevertheless, assessment of endothelial dysfunction may be used in the future to replace the more invasive penile Doppler to help determine ED etiology.

Modifications of reversible causes or risk factors at the base of the pathogenesis of atherosclerosis remain the first approach toward improving endothelial function and associated with chronic exposure to PDE5-I; they could improve or even cure ED and could avoid fatal cardiovascular attacks in the future (Gupta et al. 2011). As the first point of medical contact for men with erectile dysfunction symptoms, the primary care physician or urologist has a unique opportunity to identify those who require early intervention to prevent cardiovascular disease (Nehra et al. 2013).

The Princeton Consensus expert panel focused on the evaluation and management of cardiovascular risk in men with erectile dysfunction (ED) and no known cardiovascular disease (CVD), with particular emphasis on identification of men with ED who may require additional cardiologic workup (Nehra et al. 2012).

It is of interest to consider the whole patient management in men presenting ED. Patients with ED have a higher risk to develop cardiovascular diseases. ED is often of vascular origin and

should be considered as a sentinel symptom of a cardiovascular pathology. An appropriate clinical and biological evaluation for cardiovascular risk factors should be considered. The dietary reduction of serum lipids and physical activity are probably the first-line treatment. An early adoption of a healthy life style may be the best approach to reduce the burden of erectile dysfunction on the health and well-being of men. As endothelial dysfunction is one important feature of both ED and cardiovascular disease, inhibition of PDE5 as first-line therapy of ED may enhance endothelial function by amplifying the response of vascular smooth muscles to NO.

This may encourage men with erection problems to consult and help practitioners to identify patients with ED with the opportunity for the diagnosis of other serious conditions clearly named cardiovascular disease of which ED could be a symptom. This would allow earlier intervention and improve treatment outcomes, reducing morbidity and mortality of cardiovascular disease. ED is a window of opportunities for cardiac diseases.

References

Araujo A, Travison T, Ganz P et al (2009) Erectile dysfunction and mortality. J Sex Med 6(9):2445–2454

Araujo A, Hall S, Ganz P et al (2010) Does erectile dysfunction contribute to cardiovascular disease risk prediction beyond the Framingham risk score? J Am Coll Cardiol 55(4):350–356

Azadzoi K, Siroki M, Goldstein I (1996) Study of etiologic relationship of arterial atherosclerosis to corporeal veno-occlusive dysfunction in the rabbit. J Urol 155:1795–1800

Baumhakel M, Werner N, Bohm M et al (2006) Circulating endothelial progenitor cells correlate with erectile function in patients with coronary heart disease. Eur Heart J 27:2184–2188

Billups K, Kaiser D, Kelly A et al (2003) Relation of C-reactive protein and other cardiovascular risk factors to penile vascular disease in men with erectile dysfunction. Int J Impot Res 15:231–236

Bocchio M, Scarpelli P, Necozione S et al (2005) Intima-media thickening of common carotid arteries is a risk factor for severe erectile dysfunction in men with vascular risk factors but no clinical evidence of atherosclerosis. J Urol 173:526–529

Bohm F, Pernow J (2007) The importance of endothelin-1 for vascular dysfunction in cardiovascular disease. Cardiovasc Res 76:8–18

Chew KK, Finn J, Stuckey B et al (2010) Erectile dysfunction as a predictor for subsequent atherosclerotic cardiovascular events: findings from a linked-data study. J Sex Med 7:192–202

Chiurlia E, D'Amico R, Ratti C et al (2005) Subclinical coronary artery atherosclerosis in patients with erectile dysfunction. J Am Coll Cardiol 46:1503–1506

Dong J, Zhang Y, Qin L (2011) Erectile dysfunction and risk of cardiovascular disease: meta-analysis of prospective cohort studies. J Am Coll Cardiol 58:1378–1385

Feldman H, Johannes C, Derby C et al (2000) Erectile dysfunction and coronary risk factors: prospective results from the Massachusetts male aging study. Prev Med 30:328–338

Foresta C, Caretta N, Lana A et al (2005) Circulating endothelial progenitor cells in subjects with erectile dysfunction. Int J Impot Res 17:288–290

Gazzaruso C, Giordanetti S, De Amici E et al (2004) Relationship between erectile dysfunction and silent myocardial ischemia in apparently uncomplicated type 2 diabetic patients. Circulation 110(1):22–26

Gazzaruso C, Solerte S, Pujia A et al (2008) Erectile dysfunction as a predictor of cardiovascular events and death in diabetic patients with angiographically proven asymptomatic coronary artery disease: a potential protective role for statins and 5-phosphodiesterase inhibitors. J Am Coll Cardiol 51(21):2040–2044

Greenstein A, Chen J, Miller H et al (1997) Does severity of ischemic coronary disease correlate with erectile function? Int J Impot Res 9(3):123–126

Gupta B, Murad M, Clifton M et al (2011) The effects of lifestyle modification and cardiovascular risk factor reduction on erectile dysfunction : a systematic review and meta-analysis. Arch Intern Med 171:1797–1803

Hall S, Shackelton R, Rosen R et al (2010) Sexual activity, erectile dysfunction, and incident cardiovascular events. Am J Cardiol 105(2):192–197

Hill J, Zalos G, Halcox J et al (2003) Circulating endothelial progenitor cells, vascular function, and cardiovascular risk. N Engl J Med 348:593–600

Inman B, Sauver J, Jacobson D et al (2009) A population-based, longitudinal study of erectile dysfunction and future coronary artery disease. Mayo Clin Proc 84(2): 108–113

Jackson G, Boon N, Eardley I et al (2010) Erectile dysfunction and coronary artery disease prediction: evidence-based guidance and consensus. Int J Clin Pract 64(7):848–857

Kaiser DR, Billups K, Mason C, Wetterling R, Lundberg JL, Bank AJ (2004) Impaired brachial artery endothelium-dependent and -independent vasodilation in men with erectile dysfunction and no other clinical cardiovascular disease. J Am Coll Cardiol 43:179–184

Kaya C, Uslu Z, Karaman I (2006) Is endothelial function impaired in erectile dysfunction patients? Int J Impot Res 18:55–60

Kim N, Vardy Y, Padma-Nathan H, Daley J et al (1993) Oxygen tension regulates the nitric oxyde pathway. Physiological role in penile erection. J Clin Invest 91:437–442

Kuvin J, Mammen A, Mooney P et al (2007) Assessment of peripheral vascular endothelial function in the ambulatory setting. Vasc Med 12:13–16

Li H, Wallerath T, Förstermann U (2002) Physiological mechanisms regulating the expression of endothelial-type NO synthase. Nitric Oxide 7:132–147

Montorsi F, Briganti A, Salonia A et al (2003a) Erectile dysfunction prevalence, time of onset and association with risk factors in 300 consecutive patients with acute chest pain and angiographically documented coronary artery disease. Eur Urol 44:360–364

Montorsi P, Montorsi F, Schulman C (2003b) Is erectile dysfunction the "tip of the iceberg" of a systemic vascular disorder? Eur Urol 44:352–354

Montorsi P, Ravagnani P, Galli S et al (2005) The artery size hypothesis: a macrovascular link between erectile dysfunction and coronary artery disease. Am J Cardiol 96(Suppl):19M–23M

Montorsi P, Ravagnani P, Galli S et al (2006) Association between erectile dysfunction and coronary artery disease: role of coronary clinical presentation and extent of coronary vessels involvement: the COBRA trial. Eur Heart J 27(22):2632–2639

Nehra A, Jackson G, Miner M (2012) The Princeton III Consensus recommendations for the management of erectile dysfunction and cardiovascular disease. Mayo Clin Proc 87(8):766–778

Nehra A, Jackson G, Miner M et al (2013) Diagnosis and treatment of erectile dysfunction for reduction of cardiovascular risk. J Urol 189(6):2031–2038

Polonsky T, Taillon L, Sheth H et al (2009) The association between erectile dysfunction and peripheral arterial disease as determined by screening ankle-brachial index testing. Atherosclerosis 207(2):440–444

Ponholzer A, Temml C, Obermayr R et al (2005) Is erectile dysfunction an indicator for increased risk of coronary heart disease and stroke? Eur Urol 48(3): 512–518

Raviv G, Kiss R, Vanegas J et al (1997) Objective measurement of the different collagen types in the corpus cavernosum of potent and impotent men: an immunohistochemical staining with computerized image analysis. World J Urol 15:50–55

Salem S, Abdi S, Mehrsai A et al (2009) Erectile dysfunction severity as a risk predictor for coronary artery disease. J Sex Med 6(12):3425–3432

Salonia A, Castagna C, Sacca A et al (2012) Is erectile dysfunction a reliable proxy of general male health status? The case for the International Index of Erectile Function-Erectile function domain. J Sex Med 9: 2708–2715

Sattar A, Schulman C, Wespes E (1995) Objective quantification of cavernous endothelium in potent and impotent men. J Urol 153:1136–1138

Solomon H, Man J, Jackson G (2003) Erectile dysfunction and the cardiovascular patient: endothelial dysfunction is the common denominator. Heart 89:251–253

Tan H, Tong S, Ho C (2012) Men's health: sexual dysfunction, physical and psychological health; Is there a link? J Sex Med 9:663–671

Thompson I, Tangen C, Goodman P et al (2005) Erectile dysfunction and subsequent cardiovascular disease. JAMA 294(23):2996–3002

Vlachopoulos C, Rokkas K, Ioakeimidis N et al (2005) Prevalence of asymptomatic coronary artery disease in men with vasculogenic erectile dysfunction: a prospective angiographic study. Eur Urol 48(6):996–1003

Vlachopoulos C, Aznaouridis K, Ioakeimidis N et al (2006) Unfavourable endothelial and inflammatory state in erectile dysfunction patients with or without coronary artery disease. Eur Heart J 27:2640–2648

Vlachopoulos C, Jackson G, Stefanadis C, Montorsi P (2013) Erectile dysfunction in the cardiovascular patient. Eur Heart J 34(27):2034–2046. doi:10.1093/eurheartj/eht112

Wu WC, Sharma SC, Choudhary G et al (2005) Flow-mediated vasodilation predicts the presence and extent of coronary artery disease assessed by stress thallium imaging. J Nucl Cardiol 12:538–544

Yavuzgil O, Altay B, Zoghi M et al (2005) Endothelial function in patients with vasculogenic erectile dysfunction. Int J Cardiol 103:19–26

Premature Ejaculation

7

Vincenzo Mirone and Ferdinando Fusco

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Premature ejaculation (PE) is recognized as the most common male sexual dysfunction; however, despite its prevalence—about 30 % in the general population—the pathophysiology of this condition still remains unclear.

PE tends to be a problem of developed countries and is known to cause distress in sexual relationships. An occasional instance of premature ejaculation might not be cause for concern, but if the problem occurs with more than 50 % of attempted sexual relations, a dysfunctional pattern usually exists for which treatment may be appropriate.

PE is a self-defined condition and there is no established diagnostic test for this condition, although many different definitions exist. These definitions have been imprecise, subjective and lacking an evidence base that causes confusion as to what truly constitutes PE.

Intravaginal ejaculatory latency time (IELT) is an objective (timed) measure of the time from vaginal penetration until ejaculation. It is one of the standard primary outcome measures in clinical trials of PE. Criteria have been published that define any ejaculation occurring in 1, 2, 3 min or even 7 min from penetration, or 8–15 penile thrusts, as premature. Alternatively, the European Association of Urology's disorders of ejaculation guidelines, published in 2004, defined PE as the inability to control ejaculation for a "sufficient" length of time before vaginal penetration. A population-based multicentre study with 500 couples from

V. Mirone (ed.), *Clinical Uro-Andrology*,
DOI 10.1007/978-3-662-45018-5_7, © Springer-Verlag Berlin Heidelberg 2015

five countries (the Netherlands, the United Kingdom, Spain, Turkey and the United States), using a stopwatch during intercourse, showed a median IELT of 5.4 min (0.55–44.1 min). This multicentre study was conducted with a "normal" general male population, with no complaints of PE.

Recently the International Society for Sexual Medicine (ISSM) has proposed the following evidence-based definition: "Premature ejaculation is a male sexual dysfunction characterized by ejaculation that always or nearly always occurs prior to or within about 1 minute of vaginal penetration; inability to delay ejaculation on all or nearly all vaginal penetrations; and negative personal consequences, such as distress, bother, frustration and/or the avoidance of sexual intimacy".

Subtypes of PE are defined according to their characteristics and include lifelong versus acquired, global (occurring in all sexual encounters), situational (occurring in some situations, with some partners) and subtypes based on the co-occurrence of other sexual problems, particularly erectile dysfunction.

Premature ejaculation may be lifelong or acquired. Lifelong premature ejaculation applies to individuals who have had the condition since they became capable of functioning sexually.

Acquired premature ejaculation means that the condition began in an individual who previously experienced an acceptable level of ejaculatory control and, for unknown reasons, began experiencing premature ejaculation later in life. Acquired premature ejaculation is not related to a general medical disorder and usually is not related to substance inducement, though in rare cases, hyperexcitability might be associated with a psychotropic drug and resolves when the drug is withdrawn.

Ejaculate time is important, but PE solely based on IELT does not accurately characterize the condition. Other important aspects to consider in the diagnosis include the patient's subjective feeling of lack of control and the negative psychosocial consequences of the condition (distress) and the well-being of individuals and on their sexual relationships. Men with PE have reported decreased sexual self-confidence, difficulty in establishing relationships and distress at not satisfying their partners because of PE.

7.1 Physiology of Ejaculation and Pathophysiology of Premature Ejaculation

Ejaculation is a reflex comprised of sensory receptors and areas, afferent pathways, cerebral sensory areas, cerebral motor centres, spinal motor centres and efferent pathways. There are three basic mechanisms involved in normal antegrade ejaculation—emission, ejection and orgasm. Emission is the result of a sympathetic spinal cord reflex initiated by genital and/or cerebral erotic stimuli and involves the sequential contraction of accessory sexual organs. Considerable initial voluntary control of emission progressively decreases until the point of ejaculatory inevitability. Ejection also involves a sympathetic spinal cord reflex upon which there is little or no voluntary control. Ejection involves bladder neck closure, rhythmic contractions of bulbocavernous, bulbospongiosus and other pelvic floor muscles and relaxation of the external urinary sphincter. Orgasm is the result of cerebral processing of pudendal nerve sensory stimuli resulting from increased pressure in the posterior urethra, sensory stimuli arising from the verumontanum and contraction of the urethral bulb and accessory sexual organs.

The ejaculatory reflex is predominantly controlled by a complex interplay between central serotonergic and dopaminergic neurons with secondary involvement of cholinergic, adrenergic, nitrergic, oxytocinergic, galanergic and GABAergic neurons. The cerebral events which occur during ejaculation and the abnormalities present in men with PE have not been clearly defined with positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) techniques. Seminal emission and ejection are integrated into the complex pattern of copulatory behaviour by several forebrain structures including the medial preoptic area (MPOA) and the nucleus paragigantocellularis (nPGi).

Descending serotonergic pathways from the nPGI to the lumbosacral motor nuclei tonically inhibit ejaculation. Disinhibition of the nPGI by the MPOA facilitates ejaculation. A population of lumbar spinothalamic neurons has been identified in male rats (LSt cells) that constitute an integral part of the generation of ejaculation. LSt cells send projections to the autonomic nuclei and motoneurons involved in the emission and expulsion phase and receive sensory projections from the pelvis. Several brain areas are activated after ejaculation by ascending fibres from the spinal cord and may have a possible role in satiety and the postejaculatory refractory time.

Central nervous system areas are involved before, during and after ejaculation. Somatosensory tactile input from the penis/genitals ascends to the cerebral cortex. Efferent pathways project from the hypothalamus to the sacral spinal cord and genitals.

Animal and human sexual psychopharmacological studies have attributed a serotonergic basis and possible genetic aetiology to premature ejaculation. Male rat studies demonstrate that serotonin and 5-HT receptors are involved in the ejaculatory process. The speed of ejaculation appears to be determined by 5-HT2C and 5-HT1A receptors. Stimulation of 5-HT2C receptors with non-selective 5-HT2C agonists delays ejaculation in male rats, whereas stimulation of postsynaptic 5-HT1A receptors resulted in shorter ejaculation latency. Administration of SSRIs results in active blockade of presynaptic membrane 5-HT transporters, and the resultant higher synaptic cleft levels of 5-HT activate postsynaptic 5-HT2C and 5-HT1A receptors to delay ejaculation.

Ejaculatory latency time is probably a biological variable, which is genetically determined and may differ between populations and cultures, ranging from extremely rapid to average to slow ejaculation.

Biogenic theories of PE are multivariate at best, ranging from psychosomatic manifestations of anxiety or imprinting from early sexual experience to biologic explanations, such as a hyperexcitable ejaculatory reflex or dysfunction of 5-hydroxytryptamine (5-HT) receptor (Waldinger 2008).

Serotonin is the most studied neurotransmitter in the control of ejaculation, but only a small percentage (2–5 %) of cases are explained by its genetic dysregulation. Indeed, SSRIs (selective serotonin reuptake inhibitors), which modulate 5-HT signalling, have demonstrated efficacy in this setting and may be prescribed off label to men with PE.

Hyposensitivity of the 5-HT2C and/or hypersensitivity of the 5-HT1A receptors have been suggested as a possible explanation of lifelong PE. Men with low 5-HT neurotransmission and probable 5-HT2C receptor hyposensitivity may have their ejaculatory threshold genetically "set" at a lower point and ejaculate quickly and with minimal stimulation. On the other hand, men with a higher set-point can sustain more prolonged and higher levels of sexual stimulation and can exert more control over ejaculation. Men with a very high set-point may experience delayed or absent ejaculation despite achieving a full erection and prolonged sexual stimulation.

Other questions have been raised regarding possible biochemical components of premature ejaculation. Testosterone could play a role in the ejaculatory reflex. Higher free and total testosterone levels have been demonstrated in men with premature ejaculation than in men without premature ejaculation.

A Chinese andrology group of researchers showed that semen from men with premature ejaculation contained significantly less alpha-glucosidase and phosphates than did the semen of control group. The researchers concluded that these biochemical parameters may reflect dysfunction of the prostate and epididymis, possibly contributing to premature ejaculation; however, further studies are needed.

A study by Corona et al. found that many men with premature ejaculation have low serum prolactin levels.

However, this same study found that men in the lowest quartile of serum prolactin levels who had premature ejaculation also demonstrated associated metabolic syndrome, ED and anxiety.

Psychological factors have been found to contribute greatly to premature ejaculation, beyond merely reducing the time to ejaculation. Whereas patients with premature ejaculation show significantly lower intravaginal ejaculatory latency time

(IELT) overall, IELT in those who fit DSM-5 criteria for premature ejaculation overlaps with IELT in patients who do not fit the criteria.

Although premature ejaculation probably is not a purely psychological disorder, such associations demonstrate that psychological factors play a significant role in its pathogenesis.

7.2 Diagnosis of Premature Ejaculation

7.2.1 Diagnostic Criteria (DSM-5)

The *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5), classifies premature ejaculation as belonging to a group of sexual dysfunction disorders that are typically characterized by a clinically significant inability to respond sexually or to experience sexual pleasure.

Sexual functioning involves a complex interaction among biologic, sociocultural and psychological factors, and the complexity of this interaction makes it difficult to ascertain the clinical aetiology of sexual dysfunction. Before any diagnosis of sexual dysfunction is made, problems that are explained by a nonsexual mental disorder or other stressors must first be addressed. Thus, in addition to the criteria for premature (early) ejaculation, the following must be considered:

- Partner factors
- Relationship factors
- Individual vulnerability factors
- Cultural or religious factors
- Medical factors

The specific DSM-5 criteria for premature (early) ejaculation are as follows:

- In almost all or all (75–100 %) sexual activities, the experience of a pattern of ejaculation occurring during partnered sexual activity within 1 min after vaginal penetration and before the individual wishes it.
- The symptoms above have persisted for at least 6 months.
- The symptoms above cause significant distress to the individual.
- The dysfunction cannot be better explained by nonsexual mental disorder, a medical condition, the effects of a drug or medication or severe relationship distress or other significant stressors.

The severity of premature (early) ejaculation is specified as follows:

- Mild (occurring within approximately 30 s to 1 min of vaginal penetration)
- Moderate (occurring within approximately 15–30 s of vaginal penetration)
- Severe (occurring before sexual activity, at the start of sexual activity or within approximately 15 s of vaginal penetration)

The duration of the dysfunction is specified as follows:

- Lifelong (present since first sexual experience)
- Acquired (developing after a period of relative normal sexual functioning)

In addition, the context in which the dysfunction occurs is specified as follows:

- Generalized (not limited to certain types of stimulation, situations or partners)
- Situational (limited to specific types of stimulation, situations or partners)

Operationalization of PE using the length of time between penetration and ejaculation—the IELT—forms the basis of most current clinical studies on PE. There is considerable variance of the latencies used to identify men with PE with IELTs ranging from 1 to 7 min, and none of the definitions is based on normative data or offers any supportive rationale for their proposed cut-off time for IELT. An average duration of intercourse of 4–7 min was reported by Gebhard, suggesting that ejaculation before 4 min after intromission should be considered premature.

Waldinger et al. reported IELTs of less than 30 s and less than 60 s in 77 and 90 % of 110 men with PE, respectively. McMahon et al. reported similar results in 1,346 consecutive men with PE and a mean IELT of 43.4 s. Predominant anteportal ejaculation (during foreplay) occurred in 5.6 % of men. Although normative data is lacking, it is reasonable for clinicians to regard men who ejaculate within 2 min of penetration as suffering from PE. Anteportal ejaculation or ejaculation within 1 min should be regarded as severe PE.

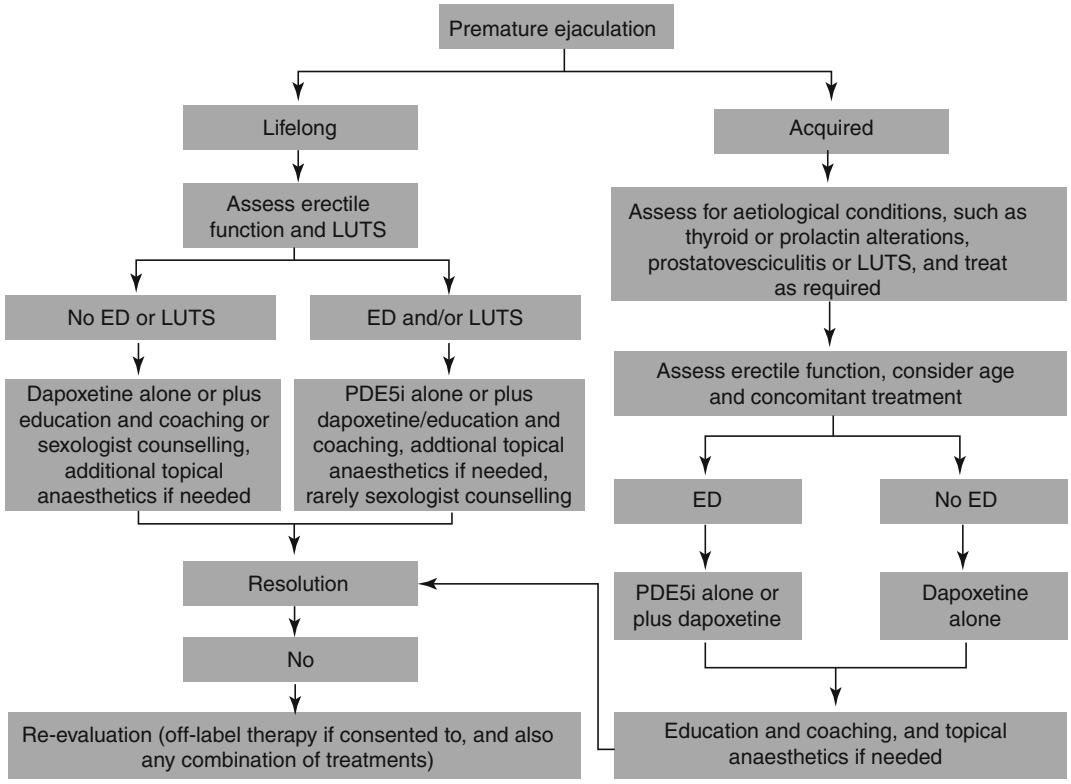

Fig. 7.1 An algorithm for the management of men with premature ejaculation. *Abbreviation*: *ED* erectile dysfunction, *LUTS* lower urinary tract symptoms, *PDE-5i* phosphodiesterase type 5 inhibitors

7.2.1.1 Premature Ejaculation Profile

The PEP consists of four items that participants respond to on a 5-grade Likert scale ranging from 1 to 5. Lower scores indicate more severe EE-related problems. PEP has been shown to have good psychometric properties (test-retest reliabilities ranging from .66 to .83 across items in two different samples).

7.2.1.2 Premature Ejaculation Diagnostic Tool

PEDT consists of five items responded to on a 5-grade Likert scale from 1 to 5, with higher values indicating more EE problems. It has also been shown to have good psychometric properties (e.g. Cronbach's $\alpha = .77$)

7.2.1.3 Multiple Indicators of Premature Ejaculation

MIPE consists of seven items, of which five are responded to on 5-grade, and two on three-grade, scales. MIPE has not been subject to case-controlled validity analyses, but extensive confirmatory factor analyses suggest good reliability (Fig. 7.1).

7.3 Treatment

7.3.1 Psychosexual Counselling

In many relationships, PE causes few if any problems. In others, the couple may reach an accommodation of the problem through various strategies—young men with a short refractory period may often experience a second and more controlled ejaculation during a subsequent episode of lovemaking. Frequently, however, PE eventually leads to significant relationship problems with partners regarding the man as selfish and developing a pattern of sexual avoidance. This only worsens the severity of the prematurity on the occasions when intercourse does occur.

The cornerstones of behavioural treatment are the Seman's "stop-start" manoeuvre and its modification proposed by Masters and Johnson, the squeeze technique. Both are based on the theory that PE occurs because the man fails to pay sufficient attention to preorgasmic levels of sexual tension. As most men with PE are aware of their anxiety, the sources of such anxiety being relatively superficial, treatment success with these behavioural approaches is relatively good in the short term though convincing long-term treatment outcome data is absent.

7.3.2 Pharmacological Treatment

Pharmacological modulation of ejaculatory threshold represents a novel and refreshing approach to the treatment of PE and a radical departure from the psychosexual model of treatment, previously regarded as the cornerstone of treatment. The introduction of SSRIs has revolutionized the approach to and treatment of PE. SSRIs consist of five compounds (citalopram, fluoxetine, fluvoxamine, paroxetine and sertraline) with a similar pharmacological mechanism of action. Although the methodology of the initial drug treatment studies was rather poor, later double-blind and placebo-controlled studies replicated the genuine effect of clomipramine and SSRIs to delay ejaculation. In spite of an increasing inclination towards research into more evidence-based drug treatment, the majority of studies still lack adequate design and methodology. A recent meta-analysis of all drug treatment studies demonstrated that only 14.4 % had been performed according to the established criteria of evidence-based medicine. Open-design studies and studies using subjective reporting or questionnaires showed a higher variability in ejaculation delay than double-blind studies in which the ejaculation delay was prospectively assessed with a stopwatch.

7.3.3 Daily Treatment with Selective Serotonin Reuptake Inhibitors

Paroxetine 20–40 mg, clomipramine 10–50 mg, sertraline 50–100 mg and fluoxetine 20–40 mg can be used for daily treatment. Paroxetine appears to exert the strongest ejaculation delay, increasing IELT approximately 8.8-fold over baseline. Ejaculation delay usually occurs within 5–10 days but may occur earlier. Adverse effects are usually minor, start in the first week of treatment, gradually disappear within 2–3 weeks and include fatigue, yawning, mild nausea, loose stools or perspiration. Diminished libido or mild ED is not reported frequently. Significant agitation is reported by a small number of patients and treatment with SSRIs should be avoided in men with a history of bipolar depression.

7.3.4 On-Demand Treatment with Selective Serotonin Reuptake Inhibitors

Administration of clomipramine, paroxetine, sertraline and fluoxetine 4–6 h before intercourse is efficacious and well tolerated but is associated with less ejaculatory delay than with daily treatment. Daily administration of an SSRI is associated with superior fold increases in IELT compared to on-demand administration. This is due to greatly enhanced 5-HT neurotransmission resulting from several adaptive processes which may include presynaptic 5-HT1a and 5-HT1b/1d receptor desensitization. On-demand treatment may be combined with either an initial trial of daily treatment or concomitant low-dose daily treatment.

7.3.5 On-Demand Treatment with Dapoxetine

A number of rapid-acting, short half-life SSRIs are under investigation as on-demand treatments for PE. Dapoxetine hydrochloride (Priligy; Janssen Pharmaceutica NV, Beerse, Belgium), a selective serotonin reuptake inhibitor (SSRI), was the first drug originally approved for the on-demand treatment of premature ejaculation (PE) by seven European countries (Austria, Finland, Germany, Italy, Portugal, Spain and Sweden) in 2008. Since then, it has received marketing authorization in 59 countries worldwide.

An integrated analysis from five phase-three trials concluded that dapoxetine 30 and 60 mg significantly improved all aspects of PE compared to placebo, including intravaginal ejaculatory latency time, PE profile questionnaire items and Clinical Global Impression of Change in PE (Althof et al. 2014). The geometric mean fold increases were 2.5, 3.0 and 1.6 with dapoxetine 30, dapoxetine 60 mg and placebo, respectively.

The safety profile of antidepressant SSRIs has never been comprehensively studied in men with PE. It consists only of safety data from clinical studies and spontaneously reported adverse events in men with psychiatric disorders. Although dapoxetine differs from other drugs within the SSRI class, due to its rapid onset of action and elimination profile enabling on-demand use, its mechanism of action theoretically could result in adverse events similar to other available SSRIs. The safety assessment currently available for dapoxetine is based on data from the clinical development programme that included >6,000 patients. In phase 3 studies, several well-recognized side effects of SSRIs (i.e. akathisia, withdrawal syndrome and mood-related changes) were not reported for dapoxetine use. A low rate of vasovagal syncope was reported in phase 3 studies, and the premarketing safety profile did not show evidence of serious cardiovascular (CV) events or arrhythmias. The primary objectives of this study were to characterize the safety profile of dapoxetine when used to treat men with PE in routine clinical practice and to report the incidence, severity and type of adverse events (serious adverse events and/or adverse events of special clinical interest). Dapoxetine is a potent SSRI (pKi = 8 nM), which is structurally similar to fluoxetine. Equilibrium radioligand-binding studies using human cells demonstrate that dapoxetine binds to 5-HT, norepinephrine (NE) and dopamine (DA) reuptake transporters and inhibits uptake in the following rank order of potency: NE < 5-HT >> DA. Brain PET studies have demonstrated significant displaceable binding of radiolabelled dapoxetine in the cerebral cortex and subcortical grey matter.

Dapoxetine undergoes rapid absorption and elimination resulting in minimal accumulation and has dose-proportional pharmacokinetics, which are unaffected by multiple dosing. The pharmacokinetic profile of dapoxetine suggests that it is a candidate for on-demand treatment of PE. The pharmacokinetics of both single doses and multiple doses over 6–9 days (30, 60, 100, 140 or 160 mg) of dapoxetine have been evaluated. Dapoxetine has a T_{max} of 1.4–2.0 h and rapidly achieves peak plasma concentration (Cmax) following oral administration. Both plasma concentration and area under the curve (AUC) are dose dependent up to 100 mg. The mean half-life of dapoxetine after a single dose is 0.5–0.8 h and plasma concentrations rapidly decline to about 5 % of Cmax at 24 h. The pharmacokinetics of dapoxetine and its metabolites were not affected by repeated daily dosing, and steady-state plasma concentrations were reached within 4 days, with only modest accumulation of dapoxetine (approximately 1.5-fold). Food does not have a clinically significant effect on dapoxetine pharmacokinetics.

No drug-drug interactions associated with dapoxetine have been reported. Coadministration of dapoxetine with ethanol did not produce significant changes in the pharmacokinetics of dapoxetine and its metabolites. Drug interaction studies demonstrate that tadalafil, a phosphodiesterase-5 inhibitor used in the treatment of ED, did not affect the pharmacokinetics of dapoxetine, whereas sildenafil increased the dapoxetine AUC by 22 %. However, this was not regarded as clinically important. Dapoxetine did not appear to affect the pharmacokinetics of tadalafil or sildenafil.

The data from a postmarketing observational study from Mirone et al. demonstrate that dapoxetine for treatment of PE has a good safety profile and low prevalence of TEAEs in routine clinical practice. Key study design features that differed from previous phase 3 studies in the clinical development programme were a lack of strict patient-exclusion criteria (e.g. age <18 years, comorbid erectile dysfunction, psychiatric or CV disorders) and the ability of participating physicians to select the starting dose of dapoxetine and adjust the dosage during the course of the study.

An important strength of this study was the thorough and comprehensive collection of

adverse event data. Compared with former studies, fewer patients were lost to follow-up (6.2 % vs. 3.9 %, respectively), and fewer patients prematurely withdrew from the study because of the onset of a side effect induced by the drug (approximately 31 % vs. approximately 11 %, respectively).

Among a total of 6,081 subjects in the phase 3 studies, of whom 4,224 subjects were treated with dapoxetine, the incidence of syncope was similar in patients receiving placebo and in those treated with dapoxetine 30 mg (0.05 % vs. 0.06 %, respectively), although greater in subjects treated with the 60 mg dose (0.23 %). In comparison, based on this large observational study of 6,128 patients treated with dapoxetine, it was observed that the incidence of syncope was zero, with the upper bound of the 95 % confidence limit around 2.0 per 1,000 person-years. One syncope case (alternative care/nondapoxetine) occurred in the context of 3,315 patients (<0.1 %) and was generally consistent with the literature reports of a background rate of vasovagal syncope of 1.31–6 per 1,000 person-years and 0.13 % per patient.

7.3.6 On-Demand Treatment with Tramadol

The efficacy of on-demand tramadol in the treatment of PE was recently reported. Tramadol is a centrally acting synthetic opioid analgesic with an unclear mode of action which is thought to include binding of the parent compound and M1 metabolite to μ-opioid receptors and weak inhibition of reuptake of norepinephrine and serotonin. Serotonin syndrome has been reported as an adverse effect of tramadol alone or in combination with SSRI class drugs. In this double-blind, placebo-controlled study, the on-demand use of 50 mg tramadol, taken 2 h prior to intercourse, exerted a clinically relevant ejaculation delay in men with PE with a 12.7 fold increase in IELT [91]. Additional flexible dose studies and long-term follow-up studies to evaluate the risk of opioid addiction are required.

7.3.7 Anaesthetic Topical Ointments

The use of topical local anaesthetics such as lignocaine and/or prilocaine as a cream, gel or spray is well established and is moderately effective in retarding ejaculation. A recent study reported that a metered-dose aerosol spray containing a eutectic mixture of lidocaine and prilocaine produced a 2.4 fold increase in baseline IELT and significant improvements in ejaculatory control and the sexual quality of life of both patients and their partners. They may be associated with significant penile hypoanaesthesia and possible transvaginal absorption, resulting in vaginal numbness and resultant female anorgasmia unless a condom is used.

7.3.8 Phosphodiesterase Inhibitors

Medications that inhibit the phosphodiesterase type-5 isoenzyme (PDE-5), such as sildenafil, tadalafil and vardenafil, are effective treatments for ED. Several authors have reported their experience with PDE-5 inhibitors alone or in combination with SSRIs as a treatment for PE. The putative role of PDE-5 inhibitors as a treatment for PE is based upon the role of the NO/cGMP transduction system as a central and peripheral mediator of inhibitory nonadrenergic, noncholinergic, nitrergic neurotransmission in the urogenital system. Several studies suggest that elevation of extracellular nitric oxide (NO) in the MPOA accelerates dopamine release and facilitates male copulatory behaviour of rats, whereas a decrease of NO reduces their copulatory behaviour. Hull et al. demonstrated that microinjection of the NO synthase inhibitor N-nitro-L-arginine methyl ester (NAME) not only decreased the number of erections but also increased the number of seminal emissions and decreased the latency to the first seminal emission. The results indicate that not only does nitric oxide promote erection in intact male rats but it may also inhibit seminal emission.

Nitric oxide synthase isoenzymes are present in human seminal vesicle smooth muscle. Several authors have reported the effects of NO donor drugs on electrically induced contractions and on

tissue levels of cyclic guanosine monophosphate (cGMP) and cyclic adenosine monophosphate (cAMP) of isolated human seminal vesicle smooth muscle preparations. These authors have concluded that NO might be involved in the control of secretory activity and smooth muscle function of human seminal vesicles. Consistent with this notion, Kriegsfeld reported that mice homozygous for eNOS gene deletion have striking ejaculatory anomalies. A significantly higher percentage of mice with eNOS gene deletion, as compared to normal controls, ejaculated during the testing period, requiring less stimulation and fewer mounts and intromissions.

A recent systematic review of 14 studies published in peer-reviewed journals or the proceedings of major international and regional scientific meetings on the PDE-5i treatment of premature ejaculation examined the role of NO as a neurotransmitter. This role was examined in central and peripheral control of ejaculation, the methodology of phosphodiesterase type 5 inhibitor (PDE-5i) treatment studies for PE, the adherence of methodology to the contemporary consensus of ideal PE drug trial design, the impact of methodology on treatment outcomes and the role of PDE-5i drugs in the treatment of PE. These studies comprise a total of 1,102 subjects suffering from PE and treated with sildenafil, tadalafil or vardenafil either as monotherapy or in combination with SSRI drugs, clomipramine or topical anaesthetics.

Most of these studies support a role for PDE-5i in the treatment of PE and speculate multiple mechanisms for their efficacy. These include (1) a central effect involving increased NO and reduced sympathetic tone, (2) smooth muscle dilatation of the vas deferens and seminal vesicles and (3) reduced performance anxiety. The smooth muscle dilatation of the vas deferens and seminal vesicles may oppose the sympathetic vasoconstriction and delay ejaculation. Better erections and downregulation of the erectile threshold to a lower level of arousal resulting in the requirement of increased levels of arousal to achieve the ejaculation threshold ultimately result in reduced performance anxiety.

The small number of publications and the lack of sufficient data preclude any meta-analysis of results. However, examination of the methodology of these studies, the adherence of methodology to the contemporary consensus of ideal clinical trial design and the impact of study methodology on treatment outcomes fail to provide any robust empirical evidence to support a role of PDE-5 inhibitors in the treatment of PE with the exception of men with PE and comorbid ED. Of the 14 studies reviewed, only one fulfilled these criteria and this study failed to confirm any significant treatment effect on IELT.

Caution should be exercised in interpreting PDE-5i and on-demand SSRI treatment data in inadequately designed studies, and their results must be regarded as unreliable. The extremely broad range of IELT fold increases reported with sildenafil (2.7–15.0, mean 6.6), combined sildenafil and on-demand sertraline (3.3–10.0, mean 6.9) and combined sildenafil and on-demand paroxetine (6.6–14.9, mean 10.7) in this systematic review is proof of the unreliability of inadequate study design. In contrast to these findings, the range of placebo IELT fold increases was relatively narrow (IELT range 1.2–1.6, mean 1.4) and was identical with the mean 1.4 IELT fold increase reported in a meta-analysis of other PE drug studies.

References

Althof S, Rosen R, Symonds T, Mundayat R, May K, Abraham L (2006) Development and validation of a new questionnaire to assess sexual satisfaction, control and distress associated with premature ejaculation. J Sex Med 3:465–475

Althof SE et al (2014) An update of the International Society of Sexual Medicine's guidelines for the diagnosis and treatment of premature ejaculation (PE). J Sex Med 11(6):1392–1422. doi:10.1111/jsm.12504

Atan A, Basar MM, Tuncel A, Ferhat M, Agras K, Tekdogan U (2006) Comparison of efficacy of sildenafil-only, sildenafil plus topical EMLA cream and topical EMLA-cream-only in treatment of premature ejaculation. Urology 67:388–391

Busato W, Galindo CC (2004) Topical anaesthetic use for treating premature ejaculation: a double-blind, randomized, placebo-controlled study. BJU Int 93: 1018–1021

Buvat J, Tesfaye F, Rothman M, Rivas DA, Giuliano F (2009) Dapoxetine for the treatment of premature ejaculation: results from a randomized, double-blind, placebo-controlled phase 3 trial in 22 countries. Eur Urol 55:957–968

Corona G, Jannini EA, Mannucci E et al (2008) Different testosterone levels are associated with ejaculatory dysfunction. J Sex Med 8:1991–1998

Corona G, Mannucci E, Jannini EA, Lotti F, Ricca V, Monami M et al (2009) Hypoprolactinemia: a new clinical syndrome in patients with sexual dysfunction. J Sex Med 6:1457–1466

de Carufel F, Trudel G (2006) Effects of a new functional-sexological treatment for premature ejaculation. J Sex Marital Ther 32:97–114

Dinsmore WW, Ralph DJ, Kell P, Wylie KR, Dean JP, Novak C et al (2006) Evaluation of the sexual assessment monitor, a diagnostic device used to electronically quantify ejaculatory latency time: findings from three studies. BJU Int 98:613–618

Dinsmore WW, Hackett G, Goldmeier D, Waldinger M, Dean J, Wright P et al (2007) Topical eutectic mixture for premature ejaculation (TEMPE): a novel aerosol-delivery form of lidocaine-prilocaine for treating premature ejaculation. BJU Int 99:369–375

Dresser MJ, Desai D, Gidwani S, Seftel AD, Modi NB (2006) Dapoxetine, a novel treatment for premature ejaculation, does not have pharmacokinetic interactions with phosphodiesterase-5 inhibitors. Int J Impot Res 18:104–110

Fatt QK, Atiya AS, Heng NG, Beng CC (2007) Validation of the hospital anxiety and depression scale and the psychological disorder among premature ejaculation subjects. Int J Impot Res 19:321–325

Hatzimouratidis K, Amar E, Eardley I et al (2010) Guidelines on male sexual dysfunction: erectile dysfunction and premature ejaculation. Eur Urol 57: 804–814

Laumann EO, Nicolosi A, Glasser DB, Paik A, Gingell C, Moreira E et al (2005) Sexual problems among women and men aged 40–80 y: prevalence and correlates identified in the Global Study of Sexual Attitudes and Behaviors. Int J Impot Res 17:39–57

Machtens S, Ckert S, Stief CG, Tsikas D, Frlich JC, Jonas U (2003) Effects of various nitric oxide-donating drugs on adrenergic tension of human seminal vesicles in vitro. Urology 61:479–483

Mamas MA, Reynard JM, Brading AF (2003) Nitric oxide and the lower urinary tract: current concepts, future prospects. Urology 61:1079–1085

McMahon CG, Stuckey B, Andersen ML, Purvis K, Koppiker N, Haughie S et al (2005) Efficacy of viagra: sildenafil citrate in men with premature ejaculation. J Sex Med 2:368–375

McMahon CG, McMahon CN, Leow LJ, Winestock CG (2006) Efficacy of type-5 phosphodiesterase inhibitors in the drug treatment of premature ejaculation: a systematic review. BJU Int 98:259–272

Mirone V, Arcaniolo D et al (2014) Results from a prospective observational study of men with premature ejaculation treated with dapoxetine or alternative care: the PAUSE study. Eur Urol 65:733–739. doi:10.1016/j.eururo.2013.08.018

Mondaini N, Ponchietti R, Muir GH, Montorsi F, Di Loro F, Lombardi G et al (2003) Sildenafil does not improve sexual function in men without erectile dysfunction but does reduce the postorgasmic refractory time. Int J Impot Res 15:225–228

Patrick DL, Althof SE, Pryor JL, Rosen R, Rowland DL, Ho KF et al (2005) Premature ejaculation: an observational study of men and their partners. J Sex Med 2(3):358–367

Porst H, McMahon CG, Althof SE et al (2010) Baseline characteristics and treatment outcomes for men with acquired or lifelong premature ejaculation with mild or no erectile dysfunction: integrated analyses of two phase 3 dapoxetine trials. J Sex Med 7:2231–2242

Pryor JL, Althof SE, Steidle C, Rosen RC, Hellstrom WJ, Shabsigh R et al (2006) Efficacy and tolerability of dapoxetine in treatment of premature ejaculation: an integrated analysis of two double-blind, randomised controlled trials. Lancet 368:929–937

Riley A, Riley E (2005) Premature ejaculation: presentation and associations. An audit of patients attending a sexual problems clinic. Int J Clin Pract 59:1482–1487

Rowland DL, Cooper SE, Schneider M (2001) Defining premature ejaculation for experimental and clinical investigations. Arch Sex Behav 30:235–253

Rowland D, Barada J, Bull S (2004) Ratings of factors contributing to overall sexual satisfaction in men with and without self-reported premature ejaculation. J Sex Med 1:58,094

Safarinejad MR, Hosseini SY (2006) Safety and efficacy of tramadol in the treatment of premature ejaculation: a double-blind, placebo-controlled, fixed-dose, randomized study. J Clin Psychopharmacol 26:27–31

Salonia A, Maga T, Colombo R, Scattoni V, Briganti A, Cestari A et al (2002) A prospective study comparing paroxetine alone versus paroxetine plus sildenafil in patients with premature ejaculation. J Urol 168:2486–2489

Sommer F, Klotz T, Mathers MJ (2005) Treatment of premature ejaculation: a comparative vardenafil and SSRI crossover study. J Urol 174:202

Waldinger MD (2002) The neurobiological approach to premature ejaculation. J Urol 168:2359–2367

Waldinger MD (2003) Towards evidenced based drug treatment research on premature ejaculation: a critical evaluation of methodology. Int J Impot Res 15:309–313

Waldinger MD, Zwinderman AH, Schweitzer DH, Olivier B (2004) Relevance of methodological design for the interpretation of efficacy of drug treatment of premature ejaculation: a systematic review and meta-analysis. Int J Impot Res 16:369–381

Yanez D, Castelo-Branco C, Hidalgo LA, Chedraui PA (2006) Sexual dysfunction and related risk factors in a cohort of middle-aged ecuadorian women. J Obstet Gynaecol 26:682–686

Yao B, Li XY, Zhao ZM et al (2007) Semen biochemical markers and their significance in the patients with premature ejaculation. Zhonghua Nan Ke Xue 13(12):1084–1086

Male Sexual Desire Disorder

8

Eric J.H. Meuleman and Jacques J.D.M. van Lankveld

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8.1 Introduction

In the literature hypoactive sexual desire is the most frequently studied entity in the male sexual desire domain. In this chapter it is extensively discussed. Moreover, some facets of male hyperactive sexual desire are discussed.

8.2 Phenomenology

According to the definition in the DSM-IV-TR (American Psychiatric Association 2000), hypoactive sexual desire disorder (HSDD) is characterised by persistently or recurrently deficient (or absent) sexual fantasies and desire for sexual activity, taking into account factors that can influence sexual functioning such as age, gender and lifestyle. To confirm the diagnosis the disturbance must cause marked distress or interpersonal difficulty and not be better accounted for by another axis I disorder (except by another sexual dysfunction) and is not due exclusively to the direct physiological effects of a substance (e.g. a drug of abuse, medication) or a general medical condition. In older literature, the term 'loss of libido' is used. This term is part of the psychodynamic explanatory model of sexual functioning and sexual disorders that has been abandoned due to the absence of empirical evidence to support it.

V. Mirone (ed.), *Clinical Uro-Andrology*,
DOI 10.1007/978-3-662-45018-5_8,

8.3 Prevalence/Incidence

In population-based studies prevalence rates of male hypoactive sexual desire between 0 and 3 % are found. (Simons and Carey 2001). In general and clinical practices (Bovée et al. 2004; Kedde et al. 2005), incidence rates between 16 % (Rosser et al. 1997) and 56 % (Segraves and Segraves 1991) are found.

It is more common in older men in comparison with younger men, independent of the severity of comorbid erectile dysfunction (Gralla et al. 2008). There are indications that there is a higher prevalence of hypoactive sexual desire in homosexual men than in the general population (Sandfort and De Keizer 2001). Depression is probably a common cause of this problem in homosexual men.

8.4 Etiology

8.4.1 Models

Sexual desire is the conscious experience of being sexually motivated. The majority of studies on the mechanism of motivation, which ensures that the individual reacts to the perception of an adequate sexual stimulus, have been conducted in animals (Beach 1956).

It has been demonstrated in the brains of several mammals (rats, hamsters, mice) that the motivational and the so-called consummatory part (commencing at penetration and ending at ejaculation) of this behavioural cycle have distinct representations in the brain and are mediated by several neurotransmitters (Everitt 1990, 1995; Pfaus 1999, 2009). There are indications that this also applies to humans (Hamann et al. 2004). These findings from animal studies suggest a delicate interplay between steroid hormones and neurotransmitters in the central nervous system that serve to integrate the potential for arousal ('central sexual arousability') with personal, rewarding sexual experiences. These experiences, in men without complaints, create the basis for the expectation that one will be capable of successful sexual functioning in a certain situation (sexual desire, erection, penetration and ejaculation).

The (linear) model of the human sexual response cycle, which was formulated by Masters and Johnson (1966), has long dominated clinical thinking and research. It describes a fixed order of response phases: sexual excitement, plateau, orgasm and resolution. The original model did not include sexual desire or problems with hypoactive sexual desire. This is likely a consequence of the fact that Masters and Johnson studied subjects who were very motivated to be sexually active. The concept of 'sexual desire' was only later added to the response cycle model (Kaplan 1977, 1979; Lief 1977). However, even with this addition it remained a linear model that states that desire is necessary to initiate the next phase of excitement, followed by orgasm. According to Kaplan and Lief, sexual desire is characterised by sexual thoughts and fantasies and the (innate) need to experience sexual excitement and release. Daily reality, however, shows that sexual motivation in men is not only characterised by initial and intrinsic sexual desire (Meston and Buss 2007). Many of the motives to engage in sexual activity are not sexual, such as wanting to please a partner or simply to dispel boredom. This realisation led to the presumption of the existence of receptive-reactive desire, alongside proactive sexual desire (Basson 2002). This made way for circular or multifactorial hypotheses on the relationship between sexual desire, subjective and physiological excitement and how it is influenced by unconscious, involuntary and automatic processes, alongside the conscious motives and considerations (Janssen et al. 2000).

In the two-phase model by Janssen and colleagues, subliminal sexual stimuli in the first phase prepare the body's sexual system for the genital arousal reaction (Janssen et al. 2000; Öhman et al. 1989). When – through sufficient processing of the sexual stimuli in the limbic system of the brain – the commencement of excitement is consciously experienced, the individual can further focus his attention on sexual stimuli. An increase of excitement or inhibition then takes place. What happens next depends on whether these stimuli invoke only erotic associations or multiple associations,

including negative ones (especially in men with sexual dysfunction). The first phase of the motivational process in this model comprises the unconscious sensitisation of the sexual system and the automatic initiation of the sexual motivation mechanism. However, all sorts of psychological factors (such as negative outcome expectations or a depressed mood) and biological factors (hormonal disorders, chronic disease) can inhibit the activation of the sexual system. In the second phase excitement increases further. The man can become aware of his motivation and can experience the desire to continue sexual stimulation, the purpose of which is to heighten sexual tension and to experience pleasant feelings. Thus, in the two-phase model sexual stimuli are already processed at an unconscious level, and excitement can precede desire. The two-phase model needs further empirical validation, but for the present discussion, it can serve as an adequate framework for decreased sexual desire in men. The most important predictions based on the two-phase model of Janssen et al. (2000) are: (1) unconscious and automatic preparation of the genital reactions takes place in response to (subliminal) perception of erotic stimuli; (2) there is a circular relationship between sexual desire and sexual excitement, wherein sexual excitement can also precede sexual desire; (3) mental preoccupation and nonsexual and negative sexual thoughts have potentially inhibiting effects on sexual desire and excitement.

8.4.2 Testosterone

In men the androgenic hormone testosterone (T) is essential for the development and preservation of the reproductive organs and sexual behaviour (Mooradian et al 1987). T has a primarily modulating effect on the central excitement mechanism, i.e. sexual desire, and, secondarily, on the different phases of the sexual response cycle (Bancroft 2005). In animal models structural changes in the anatomical and functional integrity of the penis have only been witnessed at extremely low T levels (i.e. following castration) (Traish 2009).

Over 95 % of the circulating testosterone is secreted by the Leydig cells in the testes, which produce an average 6–7 mg of T per day (Coffey 1988). In addition the adrenal cortex contributes to T production. However, the production of T is not limited to these classic endocrine glands; small amounts are produced locally in the central nervous system. Although this local contribution to the total circulating amount of T is small, it is of physiological importance especially when the total circulating level is low (Baulieu 1997).

The fact that T is also produced locally makes the concentration of circulating T an unreliable measure of the availability of biologically active T in tissue. This unreliability is heightened by other factors such as the binding of T to transport proteins in the serum (sex hormone-binding globulin (SHBG) and albumin), T's interaction with the androgen receptor (androgen receptivity) in tissue and the local T metabolism, such as the conversion to the more active dihydrotestosterone (DHT) in the prostate and hair roots and the conversion to estrogen in the central nervous system.

The biological effect of different T levels on sexuality can be observed in different stages of life. Prepubertal boys with their extremely low T levels are not sexually active outside a playful context. In puberty, when the testes starts to secrete T, and there is a sharp rise in T levels, secondary sex characteristics develop and a strong urge and motivation arises to be sexually active (Davidson et al. 1983). After the age of 40, the T levels decrease (a physiological decrease of about 1.5 % a year) (Gray et al. 1991) and a gradual decline of psychosomatic functions and concomitant symptoms occurs. As demonstrated in Fig. 8.1, the symptoms occur in a certain order, whereby decreased sexual desire and a feeling of reduced vitality are among the first symptoms of (too) low levels of testosterone (hypogonadism) (Table 8.1).[1]

Symptomatic hypogonadism with an onset after the age of 40 is referred to as symptomatic late-onset hypogonadism (SLOH) (Morales et al. 2006). In medical practice this is by far the most common form of hypogonadism. Common risk factors are: chronic disease, type II diabetes

[1] The term hypogonadism is used when the measured T levels are below 8 nmol/l.

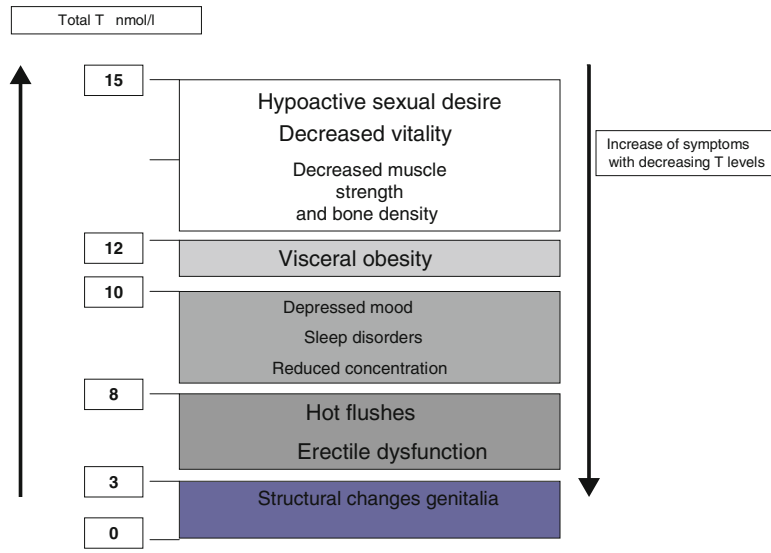

Fig. 8.1 Symptoms of decreasing T levels (Zitzmann et al. 2006)

Table 8.1 Prevalence of hypogonadism in screening of American population

Age	<40 years	40–50 years	50–70 years	>70 years
% Hypogonadism (T <8.0 nmol/l)	7.7	11.7	17.4	26.0

Morales and Lunenfeld (2002)

mellitus, metabolic syndrome (MetS)[2] and depression (Joshi et al. 2010).

Because SLOH often occurs alongside other (chronic) conditions (comorbidity), the causal direction is often difficult to establish; hypogonadism, hypoactive sexual desire and a (chronic) condition are, after all, age-related conditions that are themselves interrelated. That is to say that hypogonadism may lead to hypoactive sexual desire but, inversely, that visual erotic stimulation may lead to an increase in T levels (Carani et al 1990). Moreover, disease causes a decrease in T levels and vice versa (Corona et al. 2006; Guay and Jacobson 2007). But also disease itself can be a causal factor of the decreased sexual desire (Fig. 8.2).

The use of some drugs (medications) can reinforce this mechanism. One example is the use of antipsychotic medication, as a result of which 30–60 % of patients experience hypoactive sexual desire and SLOH. Especially antipsychotics with a high antagonistic affinity for dopamine receptors and/or antipsychotics that strongly raise prolactin levels are notorious in this respect (Knegtering et al 2007). The drugs described in the current literature as (possible) risk factors for decreasing T levels are listed in Table 8.2.

In contrast to the gradually increasing SLOH in men over 40, the symptoms of hypogonadism in younger men who had a normal pubertal development are much more severe and the course is more abrupt. In addition, the above-mentioned comorbidity is usually absent in these men. They present with severe sexual dysfunction, such as the complete absence of sexual desire, and erectile and ejaculatory dysfunction up to and including anorgasmia. On testing they often prove to have extremely low T levels. Due to their inability to ejaculate intravaginally, their request for care is often related to the desire to have children. The cause is almost always a pituitary tumour which, through its volume and possible

[2] MetS comprises a cluster of cardiovascular risk factors, such as type II diabetes mellitus, abdominal obesity, dyslipidemia and high blood pressure (AHA/NHLBI/ADA Conference Proceedings 2004). The mass of abdominal fat is the basis for the MetS. Abdominal fat performs endocrine activity: it converts the circulating T into the sex hormone estradiol (Diaz-Arjonilla et al. 2009). Furthermore, it excretes substances that cause a chronic inflammatory reaction in the vessel wall (atherosclerosis) (Matarese et al. 2007).

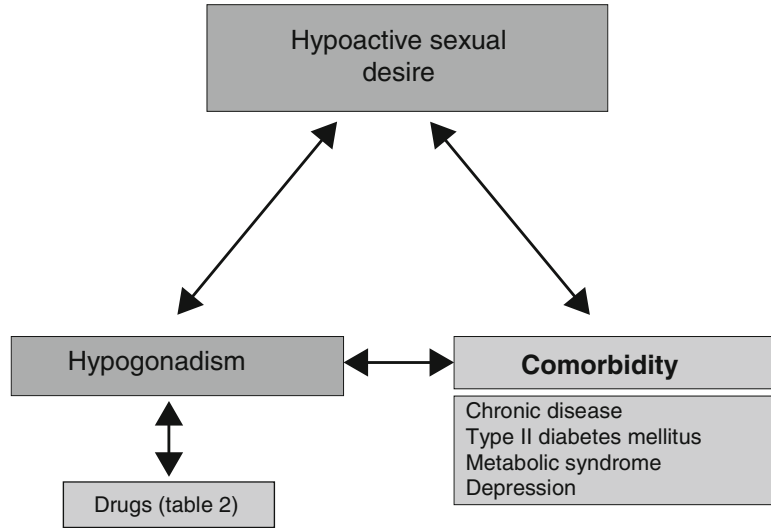

Fig. 8.2 The relationship between hypoactive sexual desire, hypogonadism and comorbidity

Table 8.2 Drugs which inhibit the production and/or action of testosterone

Spironolactone	Progesterone
Chemotherapeutics	Estrogens
Ketoconazole	GnRH agonists, antagonists
Metronidazole	Prolactin
Flutamide	Phenothiazine
Bicalutamide	Tricyclic antidepressants
Cimetidine	Reserpine
Cyproterone	Opioids
Cocaine	Anabolic steroids
Alcohol	Risperidone

secretion of prolactin, leads to hypopituitarism and hypogonadism. Furthermore, the increased prolactin levels themselves have an inhibitory effect on sexuality through the depression and anxiety which they can cause.

Men with congenital hypogonadism such as M. Klinefelter,[3] Kallmann syndrome[4] or bilateral testis atrophy with onset in childhood, such as can occur after a bilateral testicular torsion, usually seek help in or before puberty due to the lack of development of secondary sex characteristics.

8.4.3 Relational Problems and Psychiatric Disorders

Comorbid psychiatric problems and relational problems are frequently encountered in men with hypoactive sexual desire, just as other sexual disorders, such as erectile dysfunction and premature ejaculation (Segraves and Segraves 1991). Cause and effect are sometimes difficult to distinguish, especially in long-standing complaints.

8.4.3.1 Relational Problems

A man may find it difficult to acknowledge his lack of sexual desire when there are serious relationship problems or if he finds his partner less physically attractive. Myths about masculinity in many cultures dictate that a man is

[3] Klinefelter's syndrome is a genetic condition in males in which the cells contain at least one extra X chromosome. The syndrome has multiple variations, of which the least complex is the 47, XXY karyotype, in which there are 47 chromosomes per cell of which XXY are the sex chromosomes. Therefore, this variation is also known as the XXY syndrome. The Klinefelter variations 48, XXXY and 49, XXXXY with even more extra X chromosomes have similar clinical presentations. The syndrome was first described by Harry Klinefelter in 1942. It occurs in 1 in 500 to 1,000 male births.

[4] Kallmann syndrome starts before birth when a part of the brain that is used for olfaction is not formed. Because of this there also is no connection in the part of the brain between hypothalamus and pituitary. Consequentially the pituitary cannot receive any signals from the hypothalamus and therefore no LH and FSH are secreted. The consequence of the lack of LH secretion is that there is no production of sex hormones so that puberty does not commence. In addition, it causes infertility. The disorder occurs in 1 in 10,000 males and in approximately 1 in 70,000 females.

always prepared to have sex, even under such adverse circumstances. On the other hand he may conclude that the fact that he has little desire to have sex with his partner must prove that his love for her is over.

This implies that in men with decreased sexual desire, in whom relationship problems are not evident, the sexual history needs to be thorough and assessment without the partner present are necessary. Anger and rage can inhibit sexual desire and excitement (Bozman and Beck 1991). There are indications from experimental research in women that both anger and fear can reduce sexual desire, but the effect of anger seems to be strongest. In men the same effects were found, but with less difference between fear and anger. More women than men indicate they would discontinue lovemaking if feelings of anger or rage arise (Beck and Bozman 1995).

8.4.3.2 Psychiatric Disorders

Hypoactive sexual desire is the most common sexual problem in individuals with psychiatric disorders. In most cases the cause of the sexual difficulties is multidimensional: the psychiatric problem in itself and the pharmacological treatment both play a part, besides other possible physical factors. Hypoactive sexual desire is most often reported by men with a psychotic disorder. The highest prevalence is found in schizophrenic patients with chronic neuroleptic use; sexual dysfunction occurs less frequently in medication-free schizophrenic patients (Knegtering et al. 2003; Kockott and Pfeiffer 1996). A large part of the antisexual side effects of these antipsychotic drugs can be explained by their prolactin-increasing effect (Knegtering et al. 2008).

Hypoactive sexual desire occurs in more than 40 % of men with depressive disorders (Kennedy et al. 1999; van Lankveld and Grotjohann 2000). However, Bancroft and colleagues (2003a, c, 2004) discovered that in a minority of heterosexual (9.4 %) and homosexual (16 %) men, *hyper*active sexual desire occurred in depression. According to Bancroft and colleagues, this increase in sexual desire in reaction to depression can be explained by the fact that in men with a lower tendency toward sexual inhibition and a stronger tendency toward sexual excitement, the depressed mood occurs in conjunction with an increased need for intimacy and self affirmation. Sexual contact can provide this. Heightened sexual activity can also be the consequence of reduced concern about sexual risks, brought about by the depressive state. In cross-sectional research, increased sexual desire during depressed mood coincided with a higher frequency of risky sexual behaviour (Bancroft et al. 2003b, 2004). Men with a strong dispositional tendency toward inhibition see their sexual desire decreased when in a depressed mood. Bipolar (manic-depressive) disorder is characterised by hypersexual desire, especially during manic episodes.

Sexual dysfunctions are a well-known side effect of antidepressant medication. Although depressed patients attach importance to their sexual functioning, they can be reluctant when it comes to taking the initiative to mention decreased desire to their health-care professional. Most likely decreased sexual desire is underreported and this could result in undisclosed lack of medication compliance with possible relapse into depression as a result (Finn et al. 1990).

The sexual side effects of different antidepressants vary strongly and in the literature this is often neglected. For example, the tricyclic antidepressants, SSRIs and venlafaxine cause sexual side effects more often than bupropion, reboxetine, mirtazapine or agomelatine (Coleman et al. 2001; Hindmarch 1998; Schweitzer et al. 2009; Waldinger 1999).

If the intake consult reveals that a man with hypoactive sexual desire has a depressive disorder, this needs to be prioritised and treated first (with medication or cognitive behavioural therapy). In case of depressive symptoms or dysthymia without a full-blown major depressive episode, it should be discussed with the patient and his partner (if present) which concerns carry more weight.

8.4.4 Other Sexual Dysfunctions

Hypoactive sexual desire in men often occurs concurrent with other sexual dysfunctions, especially with erectile dysfunction and orgasmic

disorder (Segraves and Segraves 1991). The relationship between cause and effect is unclear.

8.4.5 Physical Factors and Disease

As described above age, especially in combination with comorbidity, is an important risk factor for the complaint hypoactive sexual desire. From the age of 40 onward, sexual desire in men decreases slowly and sometimes unnoticeably. Although aging men usually do not have the strong sexual interest they felt at a younger age, most men retain a recognisable level of sexual desire (Schiavi and Rehman 1995). However, decreased or absent sexual desire is often reported by men with chronic physical diseases such as cardiovascular disease (Bernardo 2001), diabetes, kidney failure and HIV (Dove et al. 2009). It is not always clear whether this change should be contributed to the disease, the treatment with medication, chemotherapy or radiation therapy, hypogonadism or to the changes that occur in the relationship during sickness. Three quarters of the men with an HIV infection experience a sexual problem after they start treatment; in 9 out of 10 patients this includes low sexual desire (Lallemand et al. 2002). Men with a chronic kidney disease often complain of a lack of sexual desire but they sometimes attribute it to their fatigue and exhaustion (Toorians et al. 1997). Men with kidney failure who are being treated with haemodialysis (56 %) or peritoneal dialysis (48 %) were shown to have decreased sexual desire more often than men who had undergone a kidney transplant (41 %) or male rheumatoid arthritis patients (Diemont et al. 2000). *Hyper*active sexual desire is a common but not always recognised side effect of the treatment of Parkinson's disease with dopamine agonists, especially levodopa. This side effect is not life-threatening but can strongly influence the quality of life of the patient and his or her partner. The effect can probably be attributed to the dopaminergic effect (Jimenez-Jimenez et al. 2002; van Deelen et al. 2002). Men often experience decreased sexual desire after a cortical cerebral infarction (Duits et al. 2009); however, case reports describe that some men with a comparable affliction have hypersexual episodes (Monga et al. 1986). Patients with isolated symmetrical amygdala damage, including the cortical connections, can, besides other complaints, exhibit hypersexual behaviour, such as occurs in the Kluver-Bucy syndrome. This syndrome is characterised by behavioural disorders due to damage of the right and left medial temporal lobes of the brain. This behavioural change comprises among other features, including changes in eating pattern (bulimia or the eating of inedible objects), strong oral fixation and neuropsychological disorders such as the inability to recognise familiar faces. This clinical pattern of behavioural changes suggests a role for the amygdalae in both hemispheres (Hayman et al. 1998).

Absent sexual desire is seen relatively frequently in body builders and men with eating disorders (Mangweth et al. 2001). The eating and exercising routines of body builders can be as obsessive as that of men with an eating disorder, but their goal is build-up of muscle mass and not weight loss as in an eating disorder.

8.5 Specific Diagnostics

Hypoactive sexual desire has a broad range of biological and psychological causes (Rosen 2000). There are various questionnaires that can quantify the problem, such as the Sexual Desire Inventory (King and Allgeier 2000; Spector et al. 1996) and the International Index of Erectile Function (Rosen et al. 1997); however, at present there is no gold standard for the diagnosis of hypoactive sexual desire in men (Rosen et al. 2002). In most cases health-care professionals can only identify hypoactive sexual desire if they ask their patients or clients direct and clear questions about their sexual desire and motivation. Often they will only reveal sexual difficulties if they ask supplementary questions (Meuleman and van Lankveld 2005; van Lankveld and van Koeveringe 2003).

Examples of questions from the Questionnaire for Screening of Sexual Dysfunctions (QSSD, Vroege 2003) on problems with sexual desire are:

1. Do you ever find someone (your partner or someone other than your partner) sexually attractive?
2. Do you ever come across something while reading or watching television which sexually arouses you?
3. Do you ever seek out things (situations, images etc.) which sexually arouse you?
4. Do you ever have sexual fantasies or sexual daydreams?

If these questions indicate the presence of low sexual desire and sexual activity both with a partner and masturbation, a physical exam and laboratory testing is indicated. The doctor inspects the habitus and the external genitalia for possible signs of hypogonadism (secondary sex characteristics, muscle atrophy, testicle and penis size). Laboratory testing of the T levels and, if these are too low, measuring the prolactin level is also indicated.

As described, in older men with evident hypoactive sexual desire, distinguishing between the causes of the deterioration of sexual function, including (1) physiological aging, (2) hypogonadism, (3) comorbidity (e.g. metabolic syndrome or depression), chronic disease, medication or a combination of these factors, is often difficult. In clinical practice it is important to address all these factors in the diagnostic process and the management plan.

8.6 Management

There is a range of intervention options to choose from. The PLISSIT model (Annon 1974) can be used a guideline, see Table 8.3. This is in accordance with a stepped-care approach to sexual health care, which starts with care of limited intensity that requires a maximal effort on the

Table 8.3 Summary of diagnostics and interventions in decreased sexual desire

	Process	Intervention	Result
Step 1 *Intake diagnostics*	Determining the complaints and focus of the request for help and the causative and sustaining factors	Patient history: direct questions concerning all the aspects of sexual functioning and perception, including relationship satisfaction, comorbid psychological/psychiatric and somatic problems	Complaints and focus of the request for help have been clarified
		Physical examination: in complete absence of desire and activity – inspection of external genitalia for signs of hypogonadism Questionnaire: QSSD, GRISS, IIEF *Laboratory testing:* T and prolactin levels	Diagnosis made according to the DSM-IV-R and/or description of predisposing, triggering and sustaining factors
	Assessment	Formulate *working hypothesis* Discussion of the findings and treatment options Establishing *management plan*	Management *Referral:* in case of comorbid physical (i.e. DM) or psychiatric problems – referral to adequate care. In case of stable chronic comorbid problems – consultation with treating health-care professional for possible adjustment of medication

Table 8.3 (continued)

	Process	Intervention	Result
Step 2 *Permission and Limited Information (PLI)*	Normalise Permit Inform	*Psychoeducation sexuality:* explain the circular model of sexuality; existence of proactive and reactive sexual desire; if applicable the roll of hormones, chronic) disease, psychological and relationship problems and psychiatric medication	Dysfunction resolved Dysfunction unresolved
Step 3 *Specific Suggestions (SS)*	Modification of important sustaining or causative factors in case of little or no comorbidity	*Counselling* Lifestyle adjustments Psychoeducation sexuality and communication *Simple medication interventions:* in established hormonal disorders – T therapy, prolactin decreasing medication (i.e. bromocriptine) (first: MRI sella turcica to exclude prolactinoma)	Dysfunction resolved Dysfunction unresolved
Step 4 *Intensive Therapy (TT)*	Modification of complex interdependent sustaining or causative factors	Sex therapy CBT Psychotherapy *Relationship therapy*: targeted at communication about emotions, sexual preferences and boundaries, negotiating, power struggle Medication interventions: (i.e. T substitution in T deficit, prolactin decreasing medication; antidepressants + PDE-5 inhibitor in depressive disorder)	Dysfunction resolved Dysfunction unresolved
Step 5 *Evaluation*	Evaluation and redefining goal	Psychotherapy Practical support *Pharmacotherapy:* in established medication effects re-evaluation, medication adjustment, possibly temporary medication cessation, supporting pro-sexual medication; continuous monitoring of sexual side effects	Acceptance of the dysfunction Start treatment of other problem

PLI, *SS*, and *IT* are separate phases of the *PLISSIT* strategy (Annon 1974) (see Sec 8.6).

part of the individual and his own problem-solving capacities. When this has insufficient effect, a more intensive (and therefore often more expensive) kind of management is indicated. The PLISSIT model distinguishes, in order of intensity, permission and psycho-education (PLI: permission and limited information), specific advice (SS: specific suggestions) and intensive therapy (IT: intensive therapy).

8.6.1 Permission and Psycho-education

By giving 'permission', i.e. reassuring the man that hypoactive sexual desire is not an abnormal complaint, the health-care professional can reduce insecurity and tension. This includes explanation on what is normal, what one can expect in case of disease, grieving, medication or depression. The

reversibility of decreased sexual desire, once the inhibiting factor is removed, can also be discussed. In addition, the information that sexual desire can follow sexual arousal by erotic stimuli, instead of preceding it, can be discussed.

The help seeker can be stimulated to gather further adequate information on the subject through books and websites.

8.6.2 Specific Suggestions and Advice

This part comprises among other things, simple interventions from sex therapy. The man can, for example, be given an exploration exercise to discover new kinds of erotic stimulation and rediscover forgotten ones.

Against the backdrop of the hypothesis that sexual desire can arise secondarily to, or can increase as a response to rewarding experiences with sexual arousal, simple touching and caressing exercises with the partner can be advised.

8.6.3 Intensive Therapy

This step can be applied when simpler, short-term and less demanding interventions produce insufficient results. Psychological interventions, medication or treatment with a combination of both is possible.

8.6.3.1 Hormonal and Drug Therapy

Classic indications for treatment with T are Klinefelter's syndrome, Kallmann syndrome, idiopathic hypogonadotropic hypogonadism, anorchism and pituitary disorders. Because treatment with testosterone inhibits the spermatogenesis through a negative feedback mechanism to the pituitary (T is used as a contraceptive in males) (Mommers et al. 2008), patients with a dysfunction of the hypothalamus or pituitary who want to reproduce are temporarily treated with gonadotropin (hCG/hMG) or pulsatile GnRH. When pregnancy is achieved the treatment regimen can be readjusted to treatment with T (Depenbusch et al. 2002). Although there is general agreement that patients with classic types of hypogonadism should be treated with T, the question whether the same should apply to older men with sexual complaints and SLOH cannot yet be answered decisively: firstly, because the symptoms are difficult to distinguish from the signs of physiological aging and secondly because the long-term side effects of treatment with T are not yet well known (Barrett-Connor and Bhasin 2004; Kaufman and Vermeulen 2005; Liu et al. 2004; Snyder 2004).

The current literature and recent intervention studies do not provide convincing evidence for the effectiveness of T therapy on sexual dysfunction in men with SLOH (Isidori et al. 2005; Legros et al. 2009). Although recent research does not demonstrate a relationship between T therapy, prostate cancer and exacerbation of micturition complaints (Morgentaler and Schulman 2009), the fact that the effectiveness of T treatment in men with SLOH has not (yet) been proven convincingly has lead to a reluctance to apply it.

An interesting new insight is that T therapy improves components of the metabolic syndrome (Caminiti et al. 2009; Dhindsa et al. 2004; Gooren 2001; Kapoor et al. 2005). This insight suggests that the improvement of sexual function under influence of T therapy is an indirect effect of the improvement of the metabolic status and that other interventions targeted at improving MetS, such as weight loss, could lead to more sexual desire.

In clinical practice this implies that older men with the sexual complaint of absent desire for sex deserve differentiated treatment, targeted at risk factors. This could comprise a trial regimen of T.

It is important that health-care professionals discuss the sexual functioning of depressed patients during intake consultation and continue to monitor it during treatment. When considering and implementing drug treatment, it is important to take the importance a depressed patient and his partner attach to sexuality into account. Treatment with antidepressants that have less sexual side effects can be considered as well as additional treatment with, for example, a PDE-5 inhibitor (Rothschild 2000). Improvement of sexual functioning is more likely than deterioration through treatment with antidepressants. In patients who experience deterioration, the orgasm is the most often affected aspect. Hypersexual desire during manic episodes in men

with a bipolar disorder can be reduced by adequate treatment with lithium.

8.6.3.2 Sex Therapy

In the absence of (indications of) biological causes, comorbid psychiatric problems or serious relational conflicts, which could explain the lack of sexual desire, both individual- and couple-based therapies are possible. When biological and/or psychiatric factors are present, the relative weight of these problems is assessed together with the patient. If a clearly dominant problem is present, this deserves priority. Individual- or couple-based therapy can be indicated to help partners rediscover their sexual functioning or to learn how to cope with the impairments that have arisen within their sexual relationship, either running parallel to or following the treatment of the other factors

Cognitive restructuring is an option within individual treatment. This targets inhibiting cognitive processes, such as low self-esteem as a sexual partner ('I am not a good partner for her; I probably will not find her sexy enough') or as a man in general ('if I was a real man, I would feel like having sex much more often'), inhibiting cognitions about sexual initiative ('if I touch her, it has to lead to sex' or 'if I might stop because I don't feel comfortable after all, I better had not started it in the first place') or about the quality of the sexual interaction ('it won't be any good anyway').

In couple therapy, therapeutic options are sensate focus therapy (Hawton et al. 1991; McCarthy and McDonald 2009; Schover and LoPiccolo 1982), a systemic approach (Gehring 2003), or a cognitive-behavioural approach (Trudel et al. 2001). Treatment goals based on the patient history and a meeting with the partner can be: reassuring the man and his partner, coping with lack of initiative, taking initiative despite the lack of spontaneous sexual desire, stimulation of and 'organising' positive sexual experiences, discussing and improving communication and coping with negative emotions and negotiating wishes, desires and dislikes.

When communication problems are limited to sexual interaction, they can be addressed within sex therapy. If there are communication problems in other areas of life (recreational activities, housework, upbringing op the children, finances) or problems with reaching agreements in other areas, relationship therapy is more appropriate. However, if the history taking with both partners reveals that the problem of decreased desire has major effects on their interaction,or that the level of sexual desire in the man varies as a function of the relationship dynamics (i.e. is reduced further by relational tensions), a systemic approach is indicated.

8.7 Treatment Effects in Empirical Research

The number of well-controlled studies into pharmacological treatment of male hypoactive sexual desire is very limited (Segraves 2008). There are no studies with controls that evaluate the effect of psychological treatment of decreased sexual desire in current literature. The positive findings regarding the efficacy of cognitive behavioural therapy in women with decreased sexual desire may also be applicable to men with this problem. This would predict that cognitive behavioural therapy is an effective treatment. This observation, however, has only been made in a single study (Trudel et al. 2001).

References

Annon JS (1974) The behavioral treatment of sexual problems, vol 1, Brief therapy. Enabling Systems, Honolulu

American Psychiatric Association (2000) Diagnostic and Statistical Manual of Mental Disorders (4th Ed. text rev.) Washington; DC: Author

Bancroft J (2005) The endocrinology of sexual arousal. J Endocrinol 186(3):411–427

Bancroft J, Janssen E, Strong D, Carnes L, Vukadinovic Z, Long JS (2003a) The relation between mood and sexuality in heterosexual men. Arch Sex Behav 32(3): 217–230

Bancroft J, Janssen E, Strong D, Carnes L, Vukadinovic Z, Long JS (2003b) Sexual risk-taking in gay men: the relevance of sexual arousability, mood, and sensation seeking. Arch Sex Behav 32(6):555–572

Bancroft J, Janssen E, Strong D, Vukadinovic Z (2003c) The relation between mood and sexuality in gay men. Arch Sex Behav 32(3):231–242

Bancroft J, Janssen E, Carnes L, Goodrich D, Strong D, Long JS (2004) Sexual activity and risk taking in young

heterosexual men: the relevance of sexual arousability, mood, and sensation seeking. J Sex Res 41(2):181–192
Barrett-Connor E, Bhasin S (2004) Time for (more research on) testosterone. J Clin Endocrinol Metab 89(2):501–502
Basson R (2002) Are our definitions of women's desire, arousal and sexual pain disorders too broad and our definition of orgasmic disorder too narrow? J Sex Marital Ther 28:289–300
Baulieu EE (1997) Neurosteroids: of the nervous system, by the nervous system, for the nervous system. In: Conn PM (ed) Recent Prog Horm Res 52:1–52
Beach FA (1956) Characteristics of masculine "sex drive". In: Jones MR (ed) Nebraska Symposium on motivation, vol 4. University of Nebraska Press, Lincoln, pp 1–31
Beck JG, Bozman AW (1995) Gender differences in sexual desire: the effects of anger and anxiety. Arch Sex Behav 24(6):595–612
Bernardo A (2001) Sexuality in patients with coronary disease and heart failure. Herz 26(5):353–359
Bovée B, Lagro-Janssen T, Vergeer M (2004) Seksuele problemen en hulpvraaggedrag bij diabetici, hypertensieven en patiënten met chronische obstructieve longziekten in een huisartspraktijk. Tijdschrift voor Seksuologie 28:134–139
Bozman AW, Beck JG (1991) Covariation of sexual desire and sexual arousal: the effects of anger and anxiety. Arch Sex Behav 20(1):47–60
Caminiti G, Volterrani M, Iellamo F, Marazzi G, Massaro R, Miceli M et al (2009) Effect of long-acting testosterone treatment on functional exercise capacity, skeletal muscle performance, insulin resistance, and baroreflex sensitivity in elderly patients with chronic heart failure a double-blind, placebo-controlled, randomized study. J Am Coll Cardiol 54(10):919–927
Carani C, Bancroft J, Granata A, Del Rio G, Facchinetti F, Marrama P (1990) The endocrine effects of visual erotic stimuli in normal men. Psychoneuroendocrinology 15:207–216
Coffey DS (1988) Androgen action and the sex accessory tissues. In: Knobil E, Neill J (eds) The physiologuy of reproduction. Raven, New York, pp 1081–1119
Coleman CC, King BR, Bolden-Watson C, Book MJ, Segraves RT, Richard N et al (2001) A placebo-controlled comparison of the effects on sexual functioning of bupropion sustained release and fluoxetine. Clin Ther 23(7):1040–1058
Corona G, Mannucci E, Schulman C, Petrone L, Mansani R, Cilotti A et al (2006) Psychobiologic correlates of the metabolic syndrome and associated sexual dysfunction. Eur Urol 50(3):595–604; discussion 604
Davidson JM, Chen JJ, Crapo L, Gray GD, Greenleaf WJ, Catania JA (1983) Hormonal changes and sexual function in aging men. J Clin Endocrinol Metab 57: 71–77
Depenbusch M, von Eckardstein S, Simoni M, Nieschlag E (2002) Maintenance of spermatogenesis in hypogonadotropic hypogonadal men with human chorionic gonadotropin alone. Eur J Endocrinol 147(5): 617–624
Dhindsa S, Prabhakar S, Sethi M, Bandyopadhyay A, Chaudhuri A, Dandona P (2004) Frequent occurrence of hypogonadotropic hypogonadism in type 2 diabetes. J Clin Endocrinol Metab 89(11):5462–5468
Diaz-Arjonilla M, Schwarcz M, Swerdloff RS, Wang C (2009) Obesity, low testosterone levels and erectile dysfunction. Int J Impot Res 21(2):89–98
Diemont WL, Vruggink PA, Meuleman EJ, Doesburg WH, Lemmens WA, Berden JH (2000) Sexual dysfunction after renal replacement therapy. Am J Kidney Dis 35(5):845–851
Dove LM, Rosen RC, Ramcharran D, Wahed AS, Belle SH, Brown RS et al (2009) Decline in male sexual desire, function, and satisfaction during and after antiviral therapy for chronic hepatitis C. Gastroenterology 137(3):873–884
Duits A, van Oirschot N, van Oostenbrugge RJ, van Lankveld JJDM (2009) The relevance of sexual responsiveness to sexual function in male stroke patients. J Sex Med 6(12):3320–3326
Everitt BJ (1990) Sexual motivation: a neural and behavioural analysis of the mechanisms underlying appetitive and copulatory responses of male rats. Neurosci Biobehav Rev 14(2):217–232
Everitt BJ (1995) Neuroendocrine mechanisms underlying appetitive and consummatory elements of masculine sexual behaviour. In: Bancroft J (ed) The pharmacology of sexual function and dysfunction. Excerpta Medica, Amsterdam, pp 15–31
Finn SE, Bailey JM, Schultz RT, Faber R (1990) Subjective utility ratings of neuroleptics in treating schizophrenia. Psychol Med 20(4):843–848
Gehring D (2003) Couple therapy for low sexual desire: a systemic approach. J Sex Marital Ther 29(1):25–38
Gooren LJG (2001) Visceral obesity, androgens and the risk of cardiovascular disease and diabetes mellitus. Aging Male 4:30–38
Gralla O, Knoll N, Fenske S, Spivak I, Hoffmann M, Ronnebeck C et al (2008) Worry, desire, and sexual satisfaction and their association with severity of ED and age. J Sex Med 5(11):2646–2655
Gray A, Feldman HA, McKinlay JB, Longcope C (1991) Age, disease, and changing sex hormone levels in middle-aged men: results of the Massachusetts Male Aging Study. J Clin Endocrinol Metab 73(5): 1016–1025
Guay A, Jacobson J (2007) The relationship between testosterone levels, the metabolic syndrome (by two criteria), and insulin resistance in a population of men with organic erectile dysfunction. J Sex Med 4 (4 Pt 1):1046–1055
Hamann S, Herman RA, Nolan CL, Wallen K (2004) Men and women differ in amygdala response to visual sexual stimuli. Nat Neurosci 7(4):411–416
Hawton K, Catalan J, Fagg J (1991) Low sexual desire: sex therapy results and prognostic factors. Behav Res Ther 29(3):217–224

Hayman LA, Rexer JL, Pavol MA, Strite D, Meyers CA (1998) Kluver-Bucy syndrome after bilateral selective damage of amygdala and its cortical connections. J Neuropsychiatry Clin Neurosci 10(3):354–358

Hindmarch I (1998) The behavioural toxicity of antidepressants: effects on cognition and sexual function. Int Clin Psychopharmacol 13(Suppl 6):S5–S8

Isidori AM, Giannetta E, Gianfrilli D, Greco EA, Bonifacio V, Aversa A, Isidori A, Fabbri A, Lenzi A (2005) Effects of testosterone on sexual function in men: results of a meta-analysis. Clin Endocrinol (Oxf) 63(4):381–394, Review

Janssen E, Everaerd W, Spiering M, Janssen J (2000) Automatic processes and the appraisal of sexual stimuli: toward an information processing model of sexual arousal. J Sex Res 37(1):8–23

Jimenez-Jimenez FJ, Sayed Y, Garcia-Soldevilla MA, Barcenilla B (2002) Possible zoophilia associated with dopaminergic therapy in Parkinson disease. Ann Pharmacother 36(7–8):1178–1179

Joshi D, van Schoor NM, de Ronde W, Schaap LA, Comijs HC, Beekman AT, Lips P (2010) Low free testosterone levels are associated with prevalence and incidence of depressive Symptoms in older men. Clin Endocrinol (Oxf) 72(2):232–240

Kaplan HS (1977) Hypoactive sexual desire. J Sex Marital Ther 3(1):3–9

Kaplan HS (1979) Disorders of sexual desire. Brunner/Mazel, New York

Kapoor D, Malkin CJ, Channer KS, Jones TH (2005) Androgens, insulin resistance and vascular disease in men. Clin Endocrinol (Oxf) 63(3):239–250

Kaufman JM, Vermeulen A (2005) The decline of androgen levels in elderly men and its clinical and therapeutic implications. Endocr Rev 26(6):833–876

Kedde H, Vroege JA, Vanwesenbeeck I, Bartelds A (2005) De incidentie van seksuele problemen in de huisartsenpraktijk – gegevens uit de Continue Morbiditeits Registratie Peilstations Nederland. Tijdschrift voor Seksuologie 29:143–149

Kennedy SH, Dickens SE, Eisfeld BS, Bagby RM (1999) Sexual dysfunction before antidepressant therapy in major depression. J Affect Disord 56(2–3):201–208

King BE, Allgeier ER (2000) The Sexual Desire Inventory as a measure of sexual motivation in college students. Psychol Rep 86(1):347–350

Knegtering H, van der Moolen AE, Castelein S, Kluiter H, van den Bosch RJ (2003) What are the effects of antipsychotics on sexual dysfunctions and endocrine functioning? Psychoneuroendocrinology 28(Suppl 2):109–123

Knegtering H, Bruggeman R, Castelein S, Wiersma D (2007) Antipsychotics and sexual functioning in persons with psychoses. Tijdschr Psychiatr 49(10):733–742

Knegtering H, van den Bosch R, Castelein S, Bruggeman R, Sytema S, van Os J (2008) Are sexual side effects of prolactin-raising antipsychotics reducible to serum prolactin? Psychoneuroendocrinology 33(6):711–717

Kockott G, Pfeiffer W (1996) Sexual disorders in non-acute psychiatric outpatients. Compr Psychiatry 37(1):56–61

Lallemand F, Salhi Y, Linard F, Giami A, Rozenbaum W (2002) Sexual dysfunction in 156 ambulatory HIV-infected men receiving highly active antiretroviral therapy combinations with and without protease inhibitors. J Acquir Immune Defic Syndr 30(2):187–190

Legros JJ, Meuleman EJ, Elbers JM, Geurts TB, Kaspers MJ, Bouloux PM (2009) Oral testosterone replacement in symptomatic late-onset hypogonadism: effects on rating scales and general safety in a randomized, placebo-controlled study. Eur J Endocrinol 160(5):821–831

Lief HI (1977) Inhibited sexual desire. Med Aspects Human Sexuality 7:94–95

Liu PY, Swerdloff RS, Veldhuis JD (2004) Clinical review 171: the rationale, efficacy and safety of androgen therapy in older men: future research and current practice recommendations. J Clin Endocrinol Metab 89(10):4789–4796

Mangweth B, Pope HG Jr, Kemmler G, Ebenbichler C, Hausmann A, De Col C et al (2001) Body image and psychopathology in male bodybuilders. Psychother Psychosom 70(1):38–43

Masters WH, Johnson VE (1966) Human sexual response. Little, Brown & Co., Boston

Matarese G, Mantzoros C, La Cava A (2007) Leptin and adipocytokines: bridging the gap between immunity and atherosclerosis. Curr Pharm Des 13(36):3676–3680

McCarthy B, McDonald D (2009) Assessment, treatment, and relapse prevention: male hypoactive sexual desire disorder. J Sex Marital Ther 35(1):58–67

Meston CM, Buss DM (2007) Why humans have sex. Arch Sex Behav 36(4):477–507

Meuleman EJ, van Lankveld JJDM (2005) Hypoactive sexual desire disorder: an underestimated condition in men. BJU Int 95(3):291–296

Mommers E, Kersemaekers WM, Elliesen J, Kepers M, Apter D, Behre HM, Beynon J, Bouloux PM, Costantino A, Gerbershagen HP, Grønlund L, Heger-Mahn D, Huhtaniemi I, Koldewijn EL, Lange C, Lindenberg S, Meriggiola MC, Meuleman E, Mulders PF, Nieschlag E, Perheentupa A, Solomon A, Väisälä L, Wu FC, Zitzmann M (2008) Male hormonal contraception: a double-blind, placebo-controlled study. J Clin Endocrinol Metab 93(7):2572–2580

Monga TN, Monga M, Raina MS, Hardjasudarma M (1986) Hypersexuality in stroke. Arch Phys Med Rehabil 67(6):415–417

Mooradian AD, Morley JE, Korenman SG (1987) Biological actions of androgens. Endocr Rev 8:1–27

Morales A, Lunenfeld B (2002) International Society for the Study of the Aging Male. Investigation, treatment and monitoring of late-onset hypogonadism in males. Official recommendations of ISSAM. International Society for the Study of theAging Male. Aging Male 5(2):74–86

Morales A, Schulman CC, Tostain J, C W Wu F (2006) Testosterone Deficiency Syndrome (TDS) needs to be named appropriately–the importance of accurate terminology. Eur Urol 50(3):407–409

Morgentaler A, Schulman C (2009) Testosterone and prostate safety. Front Horm Res 37:197–203, Review

Öhman A, Dimberg U, Esteves F (1989) Preattentive activation of aversive emotions. In: Archer T, Nilsson LG (eds) Aversion, avoidance and anxiety: perspectives on aversively motivated behavior. Erlbaum, Hillsdale, pp 169–193

Pfaus JG (1999) Neurobiology of sexual behavior. Curr Opin Neurobiol 9(6):751–758

Pfaus JG (2009) Pathways of sexual desire. J Sex Med 6(6):1506–1533

Rosen RC (2000) Prevalence and risk factors of sexual dysfunction in men and women. Curr Psychiatry Rep 2(3):189–195

Rosen RC, Riley A, Wagner G, Osterloh IH, Kirkpatrick J, Mishra A (1997) The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. Urology 49(6):822–830

Rosen RC, Cappelleri JC, Gendrano N 3rd (2002) The International Index of Erectile Function (IIEF): a state-of-the-science review. Int J Impot Res 14(4): 226–244

Rosser BR, Metz ME, Bockting WO, Buroker T (1997) Sexual difficulties, concerns, and satisfaction in homosexual men: an empirical study with implications for HIV prevention. J Sex Marital Ther 23(1):61–73

Rothschild AJ (2000) New directions in the treatment of antidepressant-induced sexual dysfunction. Clin Ther 22(Suppl A):A42–A57; discussion A58–61

Sandfort TGM, De Keizer M (2001) Sexual problems in gay men: an overview of empirical research. Annu Rev Sex Res 12:93–120

Schiavi RC, Rehman J (1995) Sexuality and aging. Urol Clin North Am 22(4):711–726

Schover LR, LoPiccolo J (1982) Treatment effectiveness for dysfunctions of sexual desire. J Sex Marital Ther 8(3):179–197

Schweitzer I, Maguire K, Ng C (2009) Sexual side-effects of contemporary antidepressants: review. Aust N Z J Psychiatry 43(9):795–808

Segraves RT (2008) Management of hypoactive sexual desire disorder. Adv Psychosom Med 29:23–32

Segraves K, Segraves RT (1991) Hypoactive sexual desire disorder: prevalence and comorbidity in 906 subjects. J Sex Marital Ther 17(1):55–58

Simons JS, Carey MP (2001) Prevalence of sexual dysfunctions: results from a decade of research. Arch Sex Behav 30(2):177–219

Snyder PJ (2004) Hypogonadism in elderly men–what to do until the evidence comes. N Engl J Med 350(5): 440–442

Spector IP, Carey MP, Steinberg L (1996) The sexual desire inventory: development, factor structure, and evidence of reliability. J Sex Marital Ther 22(3):175–190

Toorians AW, Janssen E, Laan E, Gooren LJ, Giltay EJ, Oe PL et al (1997) Chronic renal failure and sexual functioning: clinical status versus objectively assessed sexual response. Nephrol Dial Transplant 12(12):2654–2663

Traish AM (2009) Androgens play a pivotal role in maintaining penile tissue architecture and erection: a review. J Androl 30(4):363–369

Trudel G, Marchand A, Ravart M, Aubin S, Turgeon L, Fortier P (2001) The effect of a cognitive-behavioral group treatment program on hypoactive sexual desire in women. Sexual Relationship Ther 16(2):145–164

van Deelen RA, Rommers MK, Eerenberg JG, Egberts AC (2002) Hypersexuality during use of levodopa. Ned Tijdschr Geneeskd 146(44):2095–2098

van Lankveld JJDM, Grotjohann Y (2000) Psychiatric comorbidity in heterosexual couples with sexual dysfunction assessed with the Composite International Diagnostic Interview. Arch Sex Behav 29(5):479–498

van Lankveld JJDM, van Koeveringe GM (2003) Predictive validity of the Golombok Rust Inventory of Sexual Satisfaction (GRISS) for the presence of sexual dysfunctions within a Dutch urological population. Int J Impot Res 15:110–116

Vroege JA (2003) De Vragenlijst voor het signaleren van Seksuele Dysfuncties (VSD). Bruikbaarheid in de klinische praktijk [The Questionnaire for Screening Sexual Dysfunctions (QSSD). Usability in clinical-practice]. RNG-studies 4, Delft: Eburon.

Waldinger MD (1999) Sexual side effects of antidepressants. Ned Tijdschr Geneeskd 143(37):1853–1857

Zitzmann M, Faber S, Nieschlag E (2006) Association of specific symptoms and metabolic risks with serum testosterone in older men. J Clin Endocrinol Metab 91(11):4335–4343

Female Sexual Dysfunction (FSD)

9

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9.1 Background and Definition of Women's Sexual Dysfunction

Sexual dysfunction (SD) in women is defined as disorders of *sexual desire, arousal, orgasm, and/or sexual pain*, which result in significant personal distress and may have a negative effect on a woman's health and an impact on the quality of life (Basson et al. 2000, 2004). Even more than in men, sexual dysfunction in women is a multifactorial condition with anatomical, physiological, medical, psychological, and social components.

Historically, US population census data suggest that approximately ten million American women aged 50–74 self-report or complain of diminished vaginal lubrication, pain and discomfort during intercourse, decreased arousal, and difficulty in achieving orgasm (Laumann et al. 1999). Among women with any SD, on average, 64 % (range: 16–75 %) experienced desire difficulty, 35 % (16–48 %) experienced orgasm difficulty, 31 % (12–64 %) experienced arousal impairment, and 26 % (7–58 %) complained of sexual pain. Only a few epidemiological studies also assessed the proportion of women with SD-related distress, showing a prevalence ranging between 12 and 67 % (Hayes et al. 2006; Shifren et al. 2008).

Laumann et al. (1999) reported that SD is even more prevalent in women (43 %) than in men (31 %) and is associated with various psycho-demographic characteristics such as age,

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V. Mirone (ed.), *Clinical Uro-Andrology*,
DOI 10.1007/978-3-662-45018-5_9, © Springer-Verlag Berlin Heidelberg 2015

education, and poor physical and emotional health. Frank et al. (1978) had previously demonstrated similar data among the so-called "normal" couples, where 40 % of the male partners suffered from erectile dysfunction (ED) or ejaculatory disorders (EjDs), and up to 63 % of the female partners complained of either arousal or orgasmic problems or both.

Since the early descriptions of the sexual response cycle by Masters and Johnson (1966) and, later, Kaplan (1974), the originally suggested stages have been challenged (Basson 2000); substantial advances have occurred in the understanding of physiological aspects of female sexual function and dysfunction, mainly driven by more and more sophisticated methods of their measurement. In this context, rate of SD in women increases along with age; moreover, sexual functioning impairment is significantly associated with the menopausal transition and the menopausal period itself (Dennerstein et al. 2003, 2007; Goldstein and Teng 1991; Nappi et al. 2010a). In this context, for instance postmenopausal women often complain of low sexual desire, discomfort with intercourse, dryness, and diminished arousal of the vagina (Nappi et al. 2010b; Rosen et al. 2012; Mongomery and Studd 1991; Semmens and Semmens 1984).

Although FSD is a very prevalent, multifaceted problem, it continues to be under-recognized and undertreated (Giraldi et al. 2011; Bitzer et al. 2013a, b; Fugl-Meyer et al. 2013); healthcare professionals are aware of the high prevalence of SD among women but infrequently initiate a discussion of sexual function (SF) with their female patients or conduct a comprehensive evaluation for SD (Bachmann 2006).

Women's sexual function is a complex neurovascular phenomenon under psychologic and hormonal control that could be divided at least into three moments:

(i) *Sexual desire* could be described as consisting of biological roots, which are partially based on hormones (i.e., androgen, estrogen), as well as of motivational roots, which are also based on intimacy, pleasure, and both relationship and cognitive issues (i.e., risk and wish related with sexual activities) (Maserejian et al. 2010; Brotto et al. 2010, 2011);

(ii) *Sexual arousal* is the state with specific feelings and physiologic changes, usually associated with sexual activity involving the genitals. Women's sexual arousal is the final expression of a complex process involving sexual stimulation, ascending/descending steady control by the central nervous system (both supraspinally and spinally), a peripheral neurovascular pathway, and an important hormonal milieu. Sexual arousal is also a hemodynamic process, involving increased arterial inflow, coordinated with clitoris smooth muscle relaxation. When describing the physiological fundament of arousal, it is certainly noteworthy to stress that it is difficult to retrieve an exhaustive definition for female sexual arousal (Basson et al. 2004); in the literature this is often based on what is considered dysfunctional. It is mandatory to stress that in women changes in physiology do not necessarily induce SD, while sexual problems may occur despite an apparent normal sexual physiology. In this context, it has been suggested to subdivide female sexual arousal into an objective (namely, both genital and "extragenital") and a subjective part. Genital sexual arousal may be described as "a combination of objective and subjective signs; the bodily reactions as vulvar swelling, vaginal lubrication, heavy breathing and increased sensitivity of the genitalia, combined with the subjective experience of feeling pleasure and excitement" (Basson et al. 2004). Thus, women's sexual arousal dysfunction must consider the potential absence of coordination between an objective genital activation (i.e., with vasocongestion, enhanced local hyperemia, and an increased lubrication) and/or extragenital activation (i.e., skin sensitivity, mammary tension, and increased scent perception toward pheromones) and the woman's subjective perception of the arousal itself (Brotto et al. 2010; Salonia et al. 2010). Some women, indeed, especially in the premenstrual period, do not seem to focalize their attention on the potentially pleasant sensations delivered by the genital

and nongenital excitement (i.e., nipples, skin, etc.) due to the distraction/distress provided by negative emotions (i.e., anxiety, gut feeling, etc.).

(iii) *Orgasm*, in contrast, may be defined as "a variable, transient peak sensation of intense pleasure, creating an altered state of consciousness, usually accompanied by involuntary, rhythmic contractions of the pelvic striated circumvaginal musculature, with concomitant uterine and anal contractions and myotonia that resolves the sexually induced vasocongestion (sometimes only partially), usually with an induction of well-being and contentment" (Meston et al. 2004; Ishak et al. 2010; Salonia et al. 2010). A so-called orgasmic platform, potentially responsible of either the genital pleasure at the acme and a possible biological basis for the greater capacity for multiple orgasm, has been suggested in women as the result of genital sexual arousal (Masters and Johnson 1966; Laan and Everaerd 1998). Sensory trigger points have been advocated at the orgasmic platform level, including the clitoris and vagina, clitoral and periurethral glans, cervix, uterus, anal mucosa, and proprioceptive stimuli from the levator ani and perivaginal muscles (Goldstein et al. 1999). Nongenital trigger points are, for instance, the breast and nipples, skin, and sensory organs (Mah and Binik 2001). At least two major situations have been described anatomically: clitoral vs. vaginal orgasm (Masters and Johnson 1966; Goldstein et al. 1999; Mah and Binik 2001). Both anatomic and functional biologic modifications of these triggers points and areas can significantly affect the women's orgasmic phase.

Therefore, based on the previous classification criteria and more recent reconsiderations of the available clinical observations (Basson et al. 2003; Clayton 2007), female SD are subdivided into:

- Sexual desire/interest disorders
- Arousal disorders (subjective sexual arousal disorder, genital sexual arousal disorder, combined sexual arousal disorder, persistent sexual arousal disorder, genital arousal disorders, generalized sexual arousal disorders, missed sexual arousal)
- Orgasm disorders
- Vaginismus
- Dyspareunia

All of these result in significant personal distress and may have a negative effect on women's health and an impact on the quality of life. Although each specific condition can be separately defined in medical terms, there is significant clinical overlap in affected patients. Similarly, each of these "categories" involves both psychological and physiological aspects and needs subjective and objective evaluations.

9.2 Sexual Desire/Interest Disorders

Sexual desire is something difficult to be comprehensively defined; indeed, there is not a complete and official definition in literature of what it is or how it works. In the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR), a person is considered affected by hypoactive sexual desire disorder (HSDD) when "desire for and fantasy about sexual activity are chronically or recurrently deficient or absent."

Many clinicians consider desire as a distinct aspect from arousal in both animals and humans, consistent with the DSM's categorization of arousal disorders as different from desire disorders; when considering arousal disorders, attention is focused on problems in the blood flow to genitals and erectile tissues, while when thinking about sexual desire disorders, the complaints mostly relate to a lack of sexual interest. In practical terms, however, desire may be informed and probably confirmed by the presence of autonomic and central responses that define arousal and so, despite of the two different definitions, desire and arousal may be parts of one another (Brotto et al. 2010; Giuliano et al. 2010).

Sexual desire/interest disorders may be further stratified into the following.

HSDD (hypoactive sexual desire disorder) – HSDD in women is, at its most basic level, a lack

of sexual desire that causes distress. The last published edition of the DSM IV-TR (DSM-IV-TR 2000) defines HSDD as: "Persistent or recurrently deficient (or absent) sexual fantasies and desire for sexual activity. The disturbance causes marked distress or interpersonal difficulty," and "is not due exclusively to the direct physiological effects of a substance or a general medical condition." HSDD has been included in the International Classification of Diseases (ICD-10, F52.0) and it has also been also recognized by the American Urological Association Foundation (Basson et al. 2003).

HSDD receives particular attention under the banner of female SD due to its higher prevalence. Estimates of HSDD vary widely according to the population studied, menopausal status, whether menopause was natural or surgical, and the criteria used to define HSDD, but it is thought that at least between 7 and 26 % of women may experience HSDD throughout their life span (Dennerstein et al. 2006; Leiblum et al. 2006; Hayes et al. 2008a; West et al. 2008; Burri and Spector 2011). A recent health policy statement from the International Society of Sexual Medicine (ISSM) on HSDD quotes a figure of 10 % of women across all age groups (ISSM Health Policy Statement 2011).

Most women with HSDD are in long-term partner relationships with high levels of overall relationship satisfaction. Postmenopausal women are more likely to seek help for their disorder, despite similarly high levels of distress associated with HSDD (Rosen et al. 2012).

HSDD often occurs in association with other FSD, such as arousal or lubrication problems, particularly in individuals who rate their HSDD as being severe (Maserejian et al. 2012). Whereas no single causative factor has been identified in HSDD, a considerable amount of research has been performed in the past 15–30 years, with a focus on the exploration of the physiological, psychological, and sociocultural aspects of female sexual desire.

The age-related changes in sexual function in women are proposed to have a physiological basis, which has been theorized to be due to the marked fall in estradiol levels around and beyond the time of menopause (Davis et al. 2004), with the age-related decline in androgen levels also likely to be contributing (Davison et al. 2005). Whereas the falling of estradiol levels around menopause is associated with a varying incidence and severity of somatic symptoms that may contribute to lowered libido in the majority of women – thus, including sleep deprivation and vaginal dryness – the fall in androgens is more gradual, with a steep decline in testosterone and its precursor hormones seen even from adult women in the early reproductive years (Davison et al. 2005). Testosterone levels at age 40 are on average half of those at 20 years and continue to fall until a nadir is reached at age 65. Bilateral oophorectomy is further associated with a 50 % or more reduction in androgen levels (Kingsberg et al. 2008) and a higher prevalence of HSDD in some studies, particularly in younger women (Dennerstein et al. 2006; Leiblum et al. 2006; Hayes et al. 2008a; West et al. 2008). Whereas a link between testosterone precursor hormones and a number of aspects of sexual functioning has been made, the largest cross-sectional study reporting sexual desire in relation to androgen levels in women has not made a clear-cut link with endogenous testosterone levels (Davis et al. 2005). However, it is certainly possible that the combination of the fall in estradiol levels around the time of menopause and the age-related decline in androgen levels in some women may cause them to be highly susceptible to a fall in sexual desire and in those cases that cause distress, a diagnosis of HSDD.

Several other biologically active entities are believed to have an important role in sexual function in women, including the pro-sexual effects of dopamine (Graham and Pfaus 2010), noradrenaline (Wiedeking et al. 1979), melanocortins, serotonin acting via 5-hydroxytryptamine1A (5-HT1A) and 5-HT2C (Pfaus 2009), and oxytocin (Blaicher et al. 1999; Salonia et al. 2005). Gamma-amino butyric acid has an inhibitory effect on sexual function as does the action of serotonin at other receptors (Argiolas and Melis 2003). In recent years, these molecules, or their associated pathways, have provided a focus for the development of medical therapies for HSDD. Indeed, it is proposed that a complex

relationship between neurotransmitters, various peptides, and hormones exists with other factors, such as the environment, with regard to the net effect on sexual functioning (Basson 2009).

Therapeutic strategies for impaired sexual function have included, in peri- or postmenopausal women, the introduction of vaginal or systemic estrogen therapy (the latter including progestogen treatment in those with intact uteri).

- Systemic hormone replacement therapy (HRT) is effective in treating vasomotor and other symptoms around the time of the menopause and may have an effect on sexual desire indirectly by reducing vasomotor symptoms, improving sleep quality, and general well-being (Hickey et al. 2012). Similarly, vaginal estrogen is effective in addressing vaginal dryness due to atrophic changes, which may secondarily improve sexual desire. While HRT users in some studies have been reported to have higher sexual desire compared to nonusers (Leiblum et al. 2006; Davison et al. 2008), a similar effect of HRT was not seen for those who met the criteria for HSDD (Leiblum et al. 2006). Overall data would suggest that there is no definitive evidence to suggest there is a significant effect of HRT on sexual desire, arousal, and orgasmic response (North American Menopause Society 2012).
- The majority of studies of androgen therapy have been focused on testosterone, either administered by tablet, injection, subcutaneous pellet, or "implant" and, in more recent studies, as transdermal patch, cream, or gel. Most studies have been performed in surgically postmenopausal women and have involved dosing with testosterone in addition to systemic estrogen. More recent studies of testosterone have been in naturally menopausal women (Shifren et al. 2006) and of testosterone use alone (Davis et al. 2008a). Only a few studies have been performed in premenopausal women (Goldstat et al. 2003; Chudakov et al. 2007; Davis et al. 2008b). Overall, most studies showed an improvement in sexual function after testosterone replacement, even including a number of satisfying sexual events, which eventually represent the criteria by which the US Food and Drug Administration (FDA) (2000) draft guidance for clinical trials in the area of FSD has specified an improvement should be seen.

  Side effects after testosterone replacement are in general minimal; increased hair growth and acne are the most frequently reported from randomized placebo-controlled trials (Davis and Braunstein 2012). Nevertheless, criticisms regarding the use of testosterone in women have included the risk of reaching supra-physiological levels of testosterone, the presence of a strong placebo response, scant data in premenopausal women, and the lack of actual data on long-term effects (Davison and Davis 2011). Conversely, a study of a large cohort of women who had used testosterone for a median of 1.3 years reported no increase in the incidence of breast cancer (Davis et al. 2009); moreover, the longest follow-up of women using testosterone for 4 years was recently reported, with the most common adverse effects including application site reactions and unwanted hair growth (Nachtigall et al. 2011). The other pertinent issue in studies of testosterone in women is whether improvements in sexual function are a direct effect or due secondarily to improvements in overall well-being (Shifren et al. 2000).
- Placebo-controlled studies do not report an improvement in sexual function in women treated with physiological doses of dehydroepiandrosterone (DHEA) (Panjari and Davis 2007).
- A combination of testosterone 0.5 mg and sildenafil 50 mg (commercially called Lybrido), is a novel on-demand drug actually under evaluation as an effective compound to increase central sexual motivation in women with HSDD; it has been demonstrated that premenopausal women with HSDD with a relatively insensitive system for sexual cues had increased preconscious attention allocation, genital arousal, and sexual desire vs. placebo (Bloemers et al. 2013; Poels et al. 2013). Positive results seem to be obtained in women with HSDD and maladaptive sexual inhibitory mechanisms with an association of testosterone

0.5 mg and buspirone 10 mg (commercially termed Lybridos) (Bloemers et al. 2013; Poels et al. 2013).

- Bupropion is an antidepressant agent which functions as a dopamine agonist by blocking dopamine and noradrenaline reuptake. Whereas combination treatment with a selective serotonin reuptake inhibitor (SSRI) resulted in an increase in sexual desire in one study (Clayton et al. 2004), a lack of effect on sexual desire was seen with bupropion in women with HSDD (Segraves et al. 2004). However, the latter study did report increases in sexual receptivity and arousability associated with bupropion use in women with HSDD.

  Flibanserin acts as a postsynaptic agonist at the5-HT1A receptor and an antagonist at the 5-HT2C receptor (Stahl et al. 2011). Data from premenopausal women with HSDD treated with flibanserin 100 mg showed consistent improvements in terms of sexual desire and satisfying sexual events, along with reduced levels of sexual distress, as compared with women in the placebo group (Goldfischer et al. 2011; Derogatis et al. 2012; Thorp et al. 2012). Fatigue, somnolence, and dizziness were reported in around 10 % of participants on flibanserin. Flibanserin is yet to be approved for the treatment of HSDD.
- Bremelanotide is a cyclic melanocortin peptide that acts as a melanocortin-receptor-4 and 3 agonist to modulate pathways involved in sexual response. It induces erections in healthy male rats, in healthy men and in men with mild-to-moderate ED, and in men who do not respond well to PDE-5 inhibitors, as well. Moreover, bremelanotide has been demonstrated to improve sexual response also in female rats (Pfaus et al. 2007). It has been also shown that this drug, self-administered in premenopausal women at 1.25 and 1.75 mg SC, may be effective in treating both HSDD and mixed HSDD/arousal disorders individuals. Intranasal 10 mg bremelanotide has produced statistically significant improvements from baseline in terms of arousal success rate, desire success rate, levels of arousal and desire, and overall success and satisfaction rate in both pre- and postmenopausal women, with more robust response in the second group (74) (Levine et al. 2008).
- Gepirone is a selective 5-HT1A receptor partial agonist that is under development for the treatment of anxiety and depression. Gepirone has been associated with a higher rate of reversal of HSDD compared to placebo and SSRI-treated women with depression, mainly if premenopausal women (Fabre et al. 2011).
- Cognitive behavioral therapy may be a useful strategy in women with HSDD, especially for those who have lowered mood, depression, or anxiety. Few studies of psychological therapeutic interventions have been performed (Brotto et al. 2010; ter Kuile et al. 2010). Improved sexual function scores were reported in women with SD who underwent a group psychoeducational intervention (Smith et al. 2008). Similarly, a study of group cognitive behavioral therapy in couples reported an improvement in sexual desire that was maintained in over 60 % of the individuals at 1 year (Trudel et al. 2001). Likewise, an Internet-based psychological treatment program consisting of communication skills training, sensate focus exercises, and contact with a therapist in women with SD vs. controls has reported improved sexual and relationship functioning in the treatment group (Jones and McCabe 2011).

9.3 Sexual Arousal Disorders

The DSM-IV-TR defines Female Sexual Arousal Disorder (FSAD) (2000) as the "persistent or recurrent inability to attain, or to maintain until completion of the sexual activity an adequate lubrication-swelling response to sexual excitement. The disturbance causes marked distress or interpersonal difficulty. The sexual dysfunction is not better accounted for by another AXIS I disorder (except another sexual dysfunction) and is not due to the direct physiological effects of substance abuse or a general medical condition" (Giraldi et al. 2013).

FSAD can be described "as the absence or malfunction of component parts." The comprehensive analysis of the different components of arousal which are either missing or that do not work properly – allows to stratify women with FSAD in different subtypes (Basson 2002a). Among them:

- *Genital sexual arousal disorders* – The exact definition of these disorders is "complaints of absent or impaired genital sexual arousal. Self-report may include minimal vulval swelling or vaginal lubrication from any type of sexual stimulation and reduced sexual sensations from caressing genitalia. Subjective sexual excitement still occurs from non-genital sexual stimuli"(Giraldi et al. 2013). This is the group composed, for instance, by women with multiple sclerosis or women who had undergone radical hysterectomy with autonomic nerve damage, who may eventually complain of loss of their enjoyable genital response. In this context, although their minds are sexually aroused, these women feel a sort of "genital deadness" (Basson 2001, 2002b).

  Moreover, a specific vascular version of genital arousal disorder has been also described (Traish et al. 2010). In this context, when compared to control animals, rabbits with atherosclerotic lesions have been demonstrated to have significantly reduced vaginal and clitoral blood flow following pelvic nerve stimulation, as well as decreased development of pressure in vaginal and clitoral tissues (Park et al. 1997). Upon histological examination, clitoral and vaginal tissues from atherosclerotic animals exhibited diffuse fibrosis. In another study, clitoral corpus cavernosum tissue from atherosclerotic animals was found to have significantly decreased smooth muscle content with a concomitant increase in connective tissue (Park et al. 2000). While specific pathophysiological processes have yet to be explicitly demonstrated in vaginal or clitoral tissues, it seems likely that the development of atherosclerotic plaques within the blood vessels feeding the genital tissues and the progression of disease would be similar to what has been described in the heart and coronary vessels (Plutzky 2003). Atherosclerotic blood vessels with significant stenosis may not be able to maintain sufficient perfusion and so female genital tissues are exposed to consequent chronic ischemia and hypoxia.

  A further significant contributor to vascular disease is a dysfunctional endothelium. A healthy endothelium is necessary to provide an antithrombotic, anti-inflammatory, and antiatherogenic surface and also to regulate vascular tone and permeability. Diseased or damaged endothelium may be a major contributor to vascular insufficiency of female genital tissues. Endothelium-dependent relaxation of blood vessels has been shown to be compromised in animal models of atherosclerosis, hypertension, diabetes, aging, smoking, and renal failure. While it remains unclear whether endothelial dysfunction is a cause or a consequence of any of these disease states, its existence as a common pathological state warrants consideration and further investigation. Considered the vascular nature of genital tissue and the importance of blood flow during the genital arousal response, perturbations in endothelial function are likely to be important mechanisms mediating genital arousal dysfunction (Triggle et al. 2003).

  Overall, although vascular insufficiency has been linked with disorders and diseases of the heart, brain, eye, bladder as well as ED in male patients, its impact on impairment of genital sexual arousal in women remains to be established (Giraldi et al. 2013; Salonia et al. 2010).
- *Subjective arousal disorder* – This kind of sexual disorder is defined as the "absence of or markedly diminished feelings of sexual arousal (sexual excitement and sexual pleasure) from any type of sexual stimulation. Vaginal lubrication or other signs of physical response still occur" (American Psychiatric Association 2000; Giraldi et al. 2013).
- *Combined genital and subjective arousal disorder* – This condition is usually defined as the "absence of or markedly diminished feelings of sexual arousal (sexual excitement and sexual pleasure) from any type of sexual stimulation as well as complaints of absent or

impaired genital sexual arousal (vulval swelling, lubrication)" (American Psychiatric Association 2000; Giraldi et al. 2013).

- *Missed sexual arousal* – This is the most prevalent subtype of FSAD identified in laboratory studies. Women are not subjectively aroused but are physiologically congesting (Basson 2001, 2002b).

Further subtypes are:

- *Persistent sexual arousal disorder* – Persistent genital arousal disorder (PGAD) is a relatively rare condition characterized by unwanted genital arousal that occurs in the absence of sexual desire, that is, without any subjective sense of sexual excitement, and that does not easily subside. It usually causes a lot of suffering and it has been described to be often associated with social withdrawal and even suicidal thoughts. Theories exist regarding causes, triggers, and pathophysiology, but nothing is known for sure (Brotto et al. 2010; Waldinger et al. 2009a, b, c). Consequently, no therapy has been established so far, and treatment is extremely difficult. The "dual control model" could help to understand what happens in PGAD: it suggest that there could be a loss of balance between excitation and inhibition elements, with an increase of stimulation factors (anxiety, high-tone pelvic floor dysfunction, dopamine, oxytocin, melanocortin, noradrenalin, thyroid hormone) and a decrease of inhibition elements (decrease of genital sensation, prolactin, opioids, endocannabinoids). So the starting point for therapy can be to adopt strategies to reduce anxiety and conservative measures such as heating pad, warm bath, yoga, and acupuncture. Another step could be the decrease of pudendal nerve sensation, that could be carried out with different techniques, from the simple stand least invasive such as topical application of lidocaine to the transcutaneous electrical nerve stimulator (TENS) technique and the pudendal nerve blocks. Duloxetine (a serotonin-norepinephrine reuptake inhibitor (SNRI) drug used to treat depression and generalized anxiety disorders but also diabetic neuropathy pain), pregabalin (an anticonvulsant drug used to relieve neuropathic diabetic pain and to treat fibromyalgia), and tramadol (a centrally acting synthetic opioid analgesic) have been also shown to exert some success in women with PGAD (Philippsohn and Kruger 2012).

The prevalence of sexual arousal disorders ranges between 6 and 28 %, with most of the studies highlighting a prevalence of 13–24 % (Laumann et al. 1999; Brotto et al. 2010; Giraldi et al. 2013). Several studies have demonstrated that the prevalence of arousal problems increases along with ageing, peaking after the age of 50 years (Shifren et al. 2008). More specifically, in a large US study, the overall prevalence of sexual arousal problems was 27 %. When adjusted for distress the prevalence of sexual arousal disorder was decreased to a range 3.3 % (age group 18–44 years) and 7.5 % (45–64 years) of the recruited women. Consequently, the prevalence of FSAD is almost constant between age groups as women report more arousal problems with increased age but is less distressed by the condition (Shifren et al. 2008; Hayes et al. 2008a).

Existing data indicate that a transcultural difference may also impact on the prevalence of arousal problems. For instance, cross-cultural studies on women aged 40–80 years indicate that women from the Middle East and East and Southeast Asia reported lubrication problems significantly more often (23–38 %) as compared with women from Europe and North America (16–27 %) (Laumann et al. 2005).

Postmenopausal vaginal atrophy (VA) is a chronic condition with symptoms that include vaginal dryness, soreness, itching, burning, and dyspareunia. In this context, FSAD mostly represented by vaginal dryness symptoms has a prevalence of up to 55 % in postmenopausal women (Palacios 2009; Nappi et al. 2013; Kingsberg et al. 2013a, b). Vulvovaginal atrophy is mainly caused by decreased estrogen levels in postmenopausal women. Although the changes in hormonal milieu occurring throughout the menopausal period significantly impact upon the sexual arousal response, studies on the relationship between FSAD and decline in estrogens have been eventually inconclusive.

Though the arousal response is thought mainly to be mediated by estrogens, testosterone may

also have an effect by enhancing vaginal blood flow and lubrication. The effect may be due to a direct effect or conversion of testosterone to estradiol (Davison and Davis 2011). Recently, the level of the steroid-precursor DHEA has been proposed as crucial for development of postmenopausal vaginal atrophy, as DHEA is found to have a protective effect (Labrie et al. 2009; Labrie et al. 2010). Labrie et al. showed that intravaginal DHEA (commercially termed as Prasterone®) used as one ovule 0.0, 0.5, 1.0, or 1.8 % resulted in a significant decrease of vaginal pH in only 7 days, with serum estradiol and testosterone level that remained within normal postmenopausal values at all DHEA doses (Kim et al. 2012).

Various medical diseases involving the autonomic nervous and vascular system are known risk factors for FSAD. These include diabetes, which may affect sexual arousal function directly through impairments in the vascular system or through neuropathy (Giraldi and Kristensen 2010), moreover, neurological disorders such as multiple sclerosis and spinal cord injuries.

Surgery over the pelvic and genital organs, which may cause nerve damage, and radiation therapy on genital and pelvic structures, which may promote significant damages of tissues, vessels, and autonomic nerves, are also potentially associated with FSAD.

Recurrent urinary tract infections also affect the arousal response as well as recurrent vaginal infections, which creates irritative symptoms and decreased lubrication (Shifren 2011; Basson et al. 2010).

Antiestrogenic treatment for hormone-sensitive breast cancer is a further substantial risk factor; similarly, both the antiandrogens and the aromatase inhibitors that inhibit estrogen-synthesizing enzymes may eventually negatively impact on sexual arousability (Mok et al. 2008).

Cognitive-affective mechanisms can affect people's responses to stimuli, including sexual stimuli (Nobre and Pinto-Gouveia 2009). For example, studies have shown that negative views about the sexual self (negative sexual attitudes) or negative expectations about sexual encounters are associated with less subjective sexual arousal during exposure to sexual stimuli in the laboratory (Middleton et al. 2008). Interestingly, the negative schemas were associated with the subjective but not the physiological arousal sexual responses, thus corroborating the hypothesis that physiological/subjective sexual arousal is, at least in part, an automatic response that receives only minor input from psychological processes.

Several epidemiological studies have shown that depression is associated with arousal problems in women, often coexisting with desire problems (Angst 1998; Kennedy et al. 1999; Shifren et al. 2008); however, the relationship between mood deflection/affect and sexual arousal is far from being understood.

Many studies found higher levels of anxiety in women with sexual problems (for review see Brotto et al. 2010), and women with anxiety disorders are found to have higher rates of SD, including arousal disorders (Kalmbach et al. 2012).

Experiences of sexual abuse are associated with lower physiological sexual arousal responses and greater rates of FSAD (Rellini 2008). Theoretically, given the important relational components of sexuality, it is feasible that the disruption caused by childhood abuse on the ability of the individual to form meaningful relationships may impact the development of trust, thus promoting fear during intimate situations, which – in turn – can inhibit sexual arousal. Individuals with major depressive disorder or posttraumatic stress disorder in response to a history of abuse should be treated for these conditions first or concurrent with the sexual arousal disorder.

Sexuality, in addition to being affected by psychological factors relevant to the individual, is also heavily dependent on the psychological well-being of the couple and the condition of the partner.

Specifically, relationships can play a role in sexual arousal functioning if the woman is unable to communicate her preferred types and intensity of stimulations to the partner (Kelly et al. 2006). However, it is also important to note that a review of epidemiological studies reported that sexual arousal disorder is less affected by relationship

problems as compared with HSDD (Hayes et al. 2008b); therefore, relationship issues should be considered, but healthcare providers should not assume that any relationship difficulty may automatically lead to problems with becoming sexually aroused.

A considerable number of studies have shown that sexual dysfunction of the male partner, especially ED and premature ejaculation (PE), have a negative impact on the female partner's sexuality, including FSAD (Oberg et al. 2005). A number of studies have shown that successfully addressing ED may eventually restore a woman's sexual quality of life (Rubio-Aurioles et al. 2009). On the other hand, a pharmacologically induced erection has also been found to lead to resistance in some women, as it is perceived that the erection is unrelated to her partner's desire for her (Muller et al. 2001).

Therapeutic strategies for impaired sexual arousal start considering that arousal and arousal problems are best assessed using a biopsychosocial approach exploring predisposing, precipitating, and maintaining factors with the woman. Ideally, the healthcare provider can go through all factors as described, but this will depend on his/her expertise, time, and experience and needs to be adjusted to the clinical situation. A full assessment includes a thorough medical and sexological history and a medical examination. Finally, the degree of distress should be evaluated.

If possible, treatment for FSAD should be focused on the most likely causal factor, taking into consideration the interplay between biological, psychological, and relational factors.

In the clinical scenario, arousal disorders are often combined with desire and/or orgasmic disorders; a more integrative treatment will then focus on the other disorders that may have led to arousal disorder (see SOPs on desire, orgasm, and pain disorders).

In general, very little evidence exists on especially nonpharmacological treatment modalities and even the pharmacological treatment possibilities have been scanty analyzed.

Women with *subjective arousal problems* may benefit from a treatment focused on promoting awareness of genital responses and becoming subjectively aroused. The techniques that can be used are cognitive-behavioral techniques and/or traditional sex therapy, with sensate focus or psychodynamic treatment and as a newly introduced, mindfulness (Brotto et al. 2008).

Women with *genital arousal disorder* may benefit from pharmacological treatment enhancing lubrication as well as focus on more adequate sexual stimulation.

Pharmacological treatment of arousal disorders can be *hormonal* and *nonhormonal*.

Several studies have shown that topical or systemic estrogens may improve vaginal lubrication and decrease vaginal irritation and dryness in those women who are estrogen deficient (Basson 2009). A Cochrane review showed that a regular and continuous topical application of estrogens in women with vaginal atrophy had a positive effect on dryness and dyspareunia, regardless of the modality of local application (creams, vaginal tablets, or vaginal ring) (Suckling et al. 2003). Oral estrogens require achievement of serum estradiol levels of 35–55 pg/mL for optimal vaginal symptom relief; moreover, systemic estrogen, even at higher doses, fails to relieve symptoms in 10–25 % of women (Long et al. 2006). Therefore, local vaginal estrogen therapy may be preferred to systemic therapy. Estrogen administered via the vaginal route bypasses gastrointestinal tract; in this way thin atrophic vaginal epithelium may absorb locally applied estrogen faster than after the epithelium has been estrogenized, and there is less conversion of the drug in liver. Estrogen lowers vaginal pH, increases subepithelial capillary growth, thickens the epithelium itself, raises level of vaginal secretions, and may increase the transvaginal potential difference, thus alleviating subjective vaginal symptoms of dryness, soreness, irritation, pruritus, and dyspareunia (Archer 2010). On the other hand, estrogens applied vaginally with vaginal tablets are effective at lower doses and with minimal elevation of serum estradiol levels. Indeed, circulating estradiol levels with vaginal tablets are typically stable within the postmenopausal range of 3–10 pg/mL (Bachmann et al. 2008).

In conclusion, the advantages of using vaginal estradiol tablets are an enhanced control of a

uniform dose, a reduced potential for systemic absorption, and the increased adherence compared with vaginal creams; conversely, potential disadvantages are their less introital effect, the difficulty to individualize the right dose, the not eco-friendly applicators, and the higher costs (Shulman et al. 2008).

Estrogen creams applied vaginally can be administered in doses sufficiently high to relieve vasomotor symptoms. In one study, use of local vaginal cream was associated with better symptoms relief than oral dose, even with lower systemic levels seen. They are effective in producing vaginal maturation in 1/4 of the dose of oral therapies. In conclusion, the advantages of estrogen creams are the individualization and flexibility of dosing – that can be useful to treat from the introitus to the apex – the emollient effect of vehicle, while disadvantages are the risk of a poor compliance, of systemic absorption, the potential endometrial effects, and the costs (Krychman 2011).

- Vaginal rings represent another option for local estrogen therapy. A vaginal ring consists in a central drug-containing core surrounded by drug-free membrane that releases a steady concentration of estrogen to effectively treat vulvovaginal atrophy symptoms. It must be inserted approximately every 3 months, and estradiol levels reach highest plasma concentrations shortly after insertion, within approximately 3 h. Thereafter, they fall and stay within the menopausal range below 20 pg/mL (<73.2 pmol/L) (Dennerstein et al. 2003; Dezarnaulds and Fraser 2003).
- Low-dose estradiol vaginal ring studied in postmenopausal women older than 60 years exerted beneficial effects in different areas, such as forearm bone density and serum low-density lipoprotein levels, thus suggesting that systemic effects are possible even with low-dose vaginal rings (Naessen et al. 2001; Panay and Maamari 2012).
- Systemic treatment with estrogens is an alternative option and has been shown to decrease vaginal dryness, irritation, and pain as compared with placebo in both surgical and natural postmenopausal women, although a large inter-patient variability has been observed (Dennerstein et al. 1980; Nathorst-Boos et al. 1993; Kovalevsky 2005). The Women's Health Initiative (WHI) drew attention to long-term effects of systemic estrogen therapy; therefore, a number of recommendations and treatment of women with arousal problems who may benefit from estrogen therapy were proposed (9,162).
- Ospemifene is a once-daily oral selective estrogen receptor modulator (SERM) that exerts positive tissue selective effects on the vaginal epithelium with minimal effect on the endometrium. It has been shown in Phase 3 studies to improve both the physiologic changes (pH, superficial and parabasal cells) and symptoms (above all dyspareunia) seen with vulvovaginal atrophy.
- Phosphodiesterase type 5 inhibitors (PDE5Is) have been investigated in several studies as a treatment for FSAD, mainly with a demonstration of therapeutic inefficacy in the clinical setting (Chivers and Rosen 2010; Alexander et al. 2011; Leddy et al. 2012; Ückert et al. 2013). Likewise, women with HSDD showed limited efficacy, which can be explained by the absence of a centrally acting mechanism. Smaller studies in special populations of women with a medical condition have shown more consistent positive effects (i.e., women with multiple sclerosis, diabetes, and with SSRI-induced SD). Overall, PDE5Is may be beneficial in specific groups of women with genital arousal disorder (Basson and Brotto 2003).
- Vaginal lubricants, applied intravaginally to temporarily relieve vaginal dryness during intercourse, could be helpful and are often used in the clinical setting. Lubricants are characterized by short duration of action, and thus, they must be applied frequently when considered as sexual aids. Lubricants minimize friction and irritation, they are applied around the clitoris, labia and vaginal entrance, or even on both partners' genitals. They can be gel or liquid, water based, oil based, and silicone based. Clinically it must be kept in consideration that latex condom integrity and efficacy is compromised by oil-based lubricants; moreover, lubricants may affect sperm

integrity and function, thereby decreasing fertilization potential (Agarwal et al. 2008).

- Vaginal moisturizers are promoted as providing long-term relief from vaginal dryness; they need to be continuously used, several times a week, and so they can be seen as everyday aids. Vaginal moisturizers are bioadhesive-based polymers that attach to mucin and epithelial cells on the vaginal wall; it carries up to 60 times its weight in water and holds water in place on vaginal epithelial surface until it is sloughed off. They require only two to three applications a week, without the need for recurrent topical application before sexual intercourses (Sinha and Ewies 2013).

9.4 Female Orgasmic Disorders

DSM-IV-TR defines female orgasmic disorder (FOD) as a persistent or recurrent delay in, or absence of, orgasm *following a normal sexual excitement phase*, causing marked distress or interpersonal difficulty (American Psychiatric Association 2000; Laan et al. 2013). The diagnosis is based on a clinical judgment that the ability of a woman to experience orgasm is less than would be reasonable for her age, sexual experience, and the adequacy of the sexual stimulation she receives. The international classification committee, sponsored by the American Urological Association Foundation, defined FOD as either lack of orgasm, markedly diminished intensity of orgasmic sensations, or marked delay of orgasm from any kind of stimulation, *despite the self-report of high sexual arousal/excitement* (Basson et al. 2003). The International Classification of Diseases (ICD) 9 and 10 specified that the disorder should impair the patient's ability to participate in a sexual relationship in the way she would like, occurs frequently, and has been present for at least 6 months.

In both the DSM-IV-TR and ICD ten definitions, three groups of specifiers are identified for FOD:

(i) Lifelong (primary) or acquired (secondary)
(ii) Generalized or situational
(iii) Psychological or combined

In the lifelong subtype, FOD has always been present, whereas in the acquired subtype, FOD occurs after a period of functionally normal orgasmic response. In the generalized subtype, FOD occurs with all stimulations, situations, and partners, whereas in the situational subtype, it only occurs within specific conditions. For the psychological subtype, specific cognitive, affective (e.g., anxiety), or relational factors are usually implicated with the onset, severity, exacerbation, or maintenance of orgasmic difficulties, in the absence of medical conditions or substance contributors. For the combined FOD subtype, psychological factors contribute to the orgasmic difficulties in addition to medical conditions or substance use.

A review of research on the prevalence and incidence of FOD shows that this disorder is the second most common among women, closely following HSDD (Lewis et al. 2010). Reported prevalence figures for FOD range from 16 to 28 % in the United States, Europe, and Central/South America; conversely prevalence rates are as high as 30–46 % in Asia.

As with all other sexual disorders, the proportion of women with problems reaching an orgasm is double that for women with this difficulty who also report FOD-associated distress. There is some preliminary evidence for a genetic influence on the ability to reach orgasm, with an estimated heritability variation of 34 % for difficulty reaching orgasm during sexual intercourse and 45 % for difficulty reaching orgasm with masturbation (Dunn et al. 2005; Burri et al. 2012).

A factor that impacts the assessment and treatment of this condition is the relatively common occurrence of other concurrent sexual dysfunctions (Segraves and Segraves 1991). It has been estimated that among women with FOD, 31 % also report difficulties with sexual arousal, 18 % with lubrication, 14 % with desire, 12 % with pain, and 0.9 % with vaginismus (Nobre et al. 2006). Because of this high level of comorbidity, it is often hard to determine risk factors and treatment efficacy specific to FOD. It also means that most women will present with a complex combination of problems, requiring a comprehensive assessment that takes into consideration the

known correlates of FOD, as well as other relevant biopsychosocial factors, in an appropriate cultural context.

Physiologically speaking, there is a large variability in the type and intensity of tactile stimulation that is required to produce an orgasm in women. Historically, Hite showed that 30 % of women climax reliably during intercourse (Hite 2005). Almost all women in her study who reached orgasm through stimulation from coitus alone had experienced orgasm through masturbation. Many women needed additional manual stimulation to become orgasmic during coitus, and an even larger number was unable to orgasm during intercourse. Sexual intercourse alone had appeared not to be a very effective stimulus for enabling orgasm in women. Similarly, Lloyd concluded after an extensive review of the literature that only a quarter of women always or nearly always experience orgasm during intercourses (Lloyd 2005).

The limited evidence-based research does not allow for formulation of clear criteria for FOD (Brotto et al. 2010). Women frequently habituate to patterns of sexual stimulation and may be unaware or unwilling to explore more effective forms of sexual stimulation, particularly if they also experience problems with arousal. In general, women seem relatively unaware of their own genital changes, particularly at the early stages of sexual response, and therefore may lack the proprioceptive feedback that could further increase their arousal (Laan and Everaerd 1995). It is therefore important to rule out insufficient and/or inadequate stimulation before assigning a FOD diagnosis. For example, case studies and quantitative empirical studies have indicated that women in a relationship with men with ED and/or PE are likely to experience problems reaching orgasm. The orgasm problems may have started as a lack of adequate stimulation, although a careful assessment needs to identify whether other maintenance factors have also developed with time. If the inability to reach an orgasm is a function of inability to become sexually aroused given appropriate stimulation, then refer to the SOP for arousal disorders. A consistent finding in the literature has been that only about half of women experiencing orgasm difficulties also report associated distress (Hayes et al. 2008a). Overall, available data suggest that sexual satisfaction and orgasm frequency are interdependent but not identical (Philippsohn and Hartmann 2009).

The view that clitoral and vaginal orgasms are distinct phenomena has been debated (Laan et al. 2013; Kingsberg et al. 2013a, b). Evidence suggests that the "clitoral complex" is also stimulated during vaginal penetration. A recent empirical study that divided types of orgasm in terms of pleasure and satisfaction women experienced showed that orgasms achieved during intercourse were not necessarily reported as more pleasurable than those achieved through the stimulation of the clitoris during oral sex or masturbation (King et al. 2011).

Some risk factors should be considered in the assessment and treatment of FOD (Laan et al. 2013). A number of psychosocial factors interfere with women's capacity for orgasm such as low educational level, religiosity, and feeling guilty about sex (Meston et al. 2004). In this context, over 27 % of women with FOD suffer from anxiety (Shifren et al. 2008). Anxiety associated with sexual experiences can interfere with the ability to relax and can lead to attention to a number of (nonsexual) concerns resulting in inhibition of sexual arousal and orgasm (Van den Hout and Barlow 2000). Depression is also commonly associated with orgasmic problems, with one study reporting that out of 1,315 women who qualified for a diagnosis of FOD, 53 % met the criteria for depression (Shifren et al. 2008). The tendency to ruminate over negative events, the inability to redirect attention toward the present, and negative expectations toward the future, the world, and the self are cognitive styles of people with depression that could also interfere with sexual functioning. Women who feel that they must remain in control, and who may have learned to fear the loss of control at high levels of arousal, are more likely to have difficulties in focusing their attention to sexual stimuli and their own subsequent bodily sensations ("solo"-phase) (Heiman 2000). Likewise, couples where the female partner is anorgasmic report more problems with sexual communication

than couples without sexual difficulties or couples experiencing chronic illness (Kelly et al. 2006). Male partners of women with FOD experience greater discomfort discussing sexual problems as compared with controls, thus suggesting that inability to effectively and openly communicating about sex should be addressed at the couple level (Kelly et al. 2006).

A large body of literature correlates orgasm to childhood sexual abuse. Studies on clinical cases of women who experienced rape (sexual abuse with the use of physical violence) tend to report greater effects on sexual functioning, including orgasmic disorder, than studies utilizing the college population (Leonard and Follette 2002; Rellini and Meston 2007). It is important to note that not all women with a history of sexual abuse develop orgasmic disorders and that the etiology of the orgasmic disorder should not be automatically assumed to be the experience of abuse. A recent study showed that the tendency to avoid interpersonal connections and experiences mediated the relationship between a history of childhood sexual abuse and low orgasmic functioning (Staples et al. 2012), suggesting that increasing a woman's openness to positive sexual experiences could be useful to reduce the orgasmic difficulties experienced after sexual abuse that occurred prior to age 16 years.

Large epidemiological studies in the United States have shown an association between orgasmic functioning and chronic medical conditions, such as arthritis, hypertension, chronic medical conditions, chronic pain, thyroid problems, asthma, diabetes, and coronary heart disease or other heart conditions (Meston et al. 2004; Shifren et al. 2008). It is often unclear whether it is the medical condition per se, the treatment, or the psychological side effects of such conditions that eventually affect the orgasmic functioning. Medications such as antipsychotics, mood stabilizers, cardiovascular medications, chemotherapeutic agents, and hypertension drugs have also been flagged for their potential negative effects on orgasm functioning (Clayton and Balon 2009). However, factors associated with the reasons for taking the medications (e.g., nerve damage, anxiety, and depression) also affect orgasmic functioning and are often hard to distinguish from the impact of the medications themselves.

- In cases where the orgasmic problems are acquired, or manifest themselves only during partnered sex, the partner should be involved in the assessment and treatment or at least included in the communication training related to sexual problems. Cognitive and behavioral psychotherapies should be utilized to address distressing cognitions, emotions, and behaviors.
- Among the different cognitive and behavioral techniques, directed masturbation (DM) training is the approach that has been mostly recommended. DM training is a largely behavioral technique, usually conducted for 4–16 weekly therapy sessions. It involves graded exposure to genital stimulation, may include role playing orgasm response, use of sexual fantasy and/or vibrators to facilitate heightened arousal and orgasm. It has shown well-established efficacy when administered in a variety of modalities: group, individual, couples therapy, and bibliotherapy. The success rates for DM training (either administered individually or in groups, with or without involvement of the partner) in women with primary anorgasmia are generally high; 60–90 % of the women become orgasmic with masturbation and 33–85 % will become orgasmic with partnered sexual activity.
- Sensate focus (SF) is a useful adjunct for the treatment of FOD. It consists of graded exposure from nonsexual to sexual touching, to acquaint sexual pleasure with trust and effective communication between the couple. It reduces distractions and spectatoring (the tendency to evaluate oneself from a third person perspective during sex) by increasing attention to pleasurable sensual and sexual sensations during partnered sexual activity. Across all comparison-controlled studies, DM plus SF has proved to be more effective than DM alone (Heiman and Meston 1997).
- Mindfulness and yoga practice may be considered as possible adjuncts to DM and SF, which enable attentional focus to be directed to "being in the moment without judgment." DM

in conjunction with other interventions such as sex education, anxiety reduction techniques, and cognitive behavior therapy (CBT) is the main therapeutic tool.

- Hormonal treatment for (postmenopausal) women with low testosterone/low estrogen levels may be indicated, although more research on the efficacy of hormonal replacement treatment on orgasm functioning is certainly warranted. For instance, it has been shown that intranasal testosterone gel (tbs−2), an innovative formulation of testosterone for nasal administration that exploits the nasal mucosa which offers an alternative route of administration with its high permeability and ease of administration with rapid absorption into the systemic circulation, may be effective in alleviating FOD, thus avoiding chronic exposure to testosterone (Tkachenko et al. 2013).
- The recommended first line of action in the presence of medication-induced FOD is waiting for tolerance to develop, and the second-line approach is to either switch the patient to a different medication with lower side effects or to reduce the medication dose. More research is recommended to investigate the efficacy of the addition of PDEI5s to counteract the sexual side effects of medications.

9.5 Sexual Pain Disorders

9.5.1 Vaginismus

Vaginismus is the recurrent or persistent involuntary spasm of the musculature of the third outside of the vagina that interferes with vaginal penetration, inducing personal distress. Sometimes this is described as a spasm so prolonged and severe enough to induce the occurrence of pain. The definition of vaginismus may be partially extended also considering the concept of difficulty – persistent or recurrent – experienced by the woman in allowing not only vaginal penetration of the penis as well as digits or any other object despite willingness of the woman. Therefore, vaginismus, also known as vaginal penetration disorder, represents an aversion to any form of vaginal penetration as a result of painful attempts and a fear of anticipated pain. It is involuntary and uncontrolled and functions much the same as any reflex to avoid injury. It is the most common reason for unconsummated marriages.

Vaginismus is a poorly understood condition affecting approximately 1–7 % of women worldwide (Pacik 2011).

The etiology is thought to be unknown. Numerous papers note a history of religious or strict sexual upbringing or aversion to penetration because of perceived pain and bleeding with first-time intercourse. Sexual molestation may be more prevalent in this group of patients (Lahaie et al. 2010; van Lankveld et al. 2010; Melnik et al. 2012).

In the clinical practice, the ability to make a diagnosis of vaginismus can be compromised by inability to perform a satisfactory gynecologic examination, especially in the more severe cases of the disorder. For this reason, a detailed history is of paramount importance. Vaginismus should be part of the differential diagnosis for patients who have an aversion to vaginal penetration, of any type (thus, including a penetration with tampon, finger, speculum, dilator, or penis), and for those who have never had pain-free intercourse.

Dyspareunia, a term of ancient Greek origin meaning "difficult mating" (Graziottin 2001), means painful intercourses, which can range from mild to severe. A woman who has never had pain-free intercourse is considered to have vaginismus, and this disorder may also manifest mild to severe. In severe cases of vaginismus, any form of intercourse usually is impossible, and burning pain can last for days for some women who make the attempt. A history of never having had comfortable intercourse is important in differentiating vaginismus from dyspareunia. Indeed, a woman with primary vaginismus has never had comfortable penetration, and this is the most common reason for unconsummated marriages. Conversely, a woman with secondary vaginismus has experienced normal sexual relations and often has given birth to a child, but some happening such as an infection or childbirth has triggered current pain with attempted penetration.

Vulvodynia is a chronic vulvar pain condition of uncertain etiology (Moyal-Barracco and Lynch 2004). Vulvodynia is pain involving any part of the vulva that may or may not be associated with vaginismus. Vestibulodynia, formerly known as *vulvar vestibulitis syndrome* (VVS), represents the most common form of vulvodynia (Haefner 2007; Goldstein and Burrows 2008) and is the most frequent cause of dyspareunia in young women (Harlow and Stewart 2003; Danielson et al. 2003). Provoked vestibulodynia (PVD) is a condition in which pain is triggered by simple physical contact, touch, pressure, or stretching of the tissue around the vaginal opening, eventually resulting in an inability to engage in both coital and noncoital sexual attempts (Friedrich 1987; Goldstein and Burrows 2008). PVD is often acquired, and dyspareunia may appear after a period of pain-free sexual intercourse (Bornstein et al. 2001; Granot et al. 2004).

Some researchers argue that vaginismus and dyspareunia may be impossible to differentiate because vaginal penetration problems are not specific to vaginismus but frequently present also as a symptom of dyspareunia (de Kruiff et al. 2000; Engman et al. 2004; Reissing et al. 2004; Binik 2010). The presence of vestibulodynia adds a further difficulty in making a precise diagnosis of vaginismus. Vulvodynia, if present, is specified as an associated (secondary) medical condition because vaginismus is the primary event; vaginal penetration disorder and dyspareunia are mutually exclusive diagnoses (Reissing et al. 2004). With dyspareunia, penetration is painful, whereas with vaginismus, penetration has never been comfortable. In severe cases of vaginismus, penetration is almost ever impossible.

Before recommending treatment, it is vital to stratify the severity of vaginismus. Patients who have had many years of failed treatments may have an undiagnosed severe form of vaginismus. Historically, Lamont (1978) classified vaginismus according to the patient's history and behavior during a gynecologic examination. With the mildest form of vaginismus, *grade 1*, the patient is noted to have tight vaginal muscles but is able to relax enough with coaxing to have a gynecologic examination. With *grade 2* vaginismus, muscles are noted to be tight, and the patient is unable to relax, but examination can be still done. The woman with *grade 3* vaginismus elevates her buttocks to avoid examination. With the most severe form of vaginismus, *grade 4*, the patient elevates her buttocks, retracts, and adducts her thighs to avoid being examined.

The use of graduated dilators, first described by Sims in his 1861 publication, is likely the most commonly used treatment plan.

Milder cases of vaginismus may respond to Kegel exercises encouraging relaxation of the pelvic floor, psychotherapy, sex counseling, cognitive behavioral therapy, hypnotherapy, support groups, physical therapy to stretch the vaginal muscles, biofeedback to reduce pelvic floor tension, lubricants often containing topical anesthetics, muscle relaxants, antianxiety medications, antidepressants, and tranquilizers. These various methods of treatment are aimed at getting the patient to a point at which she can begin using dilators.

More severe cases often are refractory to treatment, resulting in a great deal of frustration and upheaval in relationships and marriage.

Hymenectomy may be performed but vaginismus due to an intact hymen is rare. Vestibulectomy, when performed, is sometimes done as a last resort, and several patients have failed this treatment too. The use of Botox to treat vaginismus was first reported by Brin and Vapnek (1997). Botox injections have been reported to be useful for the more severe forms of vaginismus or for those patients whose condition has been refractory to other treatments. The use of a comprehensive program, consisting of vaginal Botox injections, bupivacaine injections, progressive dilation under anesthesia, and postprocedure counseling including dilation and progression to intercourse, is an effective means of allowing even the most severe vaginismus patients to achieve pain-free intercourse (Pacik 2011).

9.5.2 Dyspareunia

Dyspareunia is defined as "persistent or recurrent pain occurring with either attempted or complete vaginal entry and/or penile vaginal intercourse."

Like all the other sexual disorders, it could be described as lifelong vs. acquired, generalized vs. situational, and organic, psychogenic, mixed, or of unknown etiology (Basson et al. 2003). Further classification of dyspareunia is based on anatomic location (superficial vs. deep pain conditions); superficial dyspareunia (entry dyspareunia) is defined as pain with initial penetration of the vaginal introitus; conversely, deep dyspareunia is defined as pain with deep vaginal penetration (Ferrero et al. 2008).

The lack of standard criteria and overlapping descriptors for sexual pain dysfunction negatively affects our understanding of the etiology of this troublesome and distressful disorder.

In this context, proposed precipitating factors for vulvar pain syndromes are numerous and have historically included histories of recurrent vaginal infections (most commonly, vulvovaginal candidiasis and bacterial vaginosis), use of oral contraceptives (particular early use), and destructive treatments (for instance, exposure to irritant agents such as trichloroacetic acid). Moreover, a number of disorders are associated with or contribute to deep dyspareunia; among these, dyspareunia has been observed in women with endometriosis, pelvic congestion syndrome, interstitial cystitis, levator ani muscle myalgia, and uterine retroversion. Other conditions, such as the presence of uterine myomas or adenomyosis, or a history of pelvic inflammatory disease (PID) or irritable bowel disease, are either more controversial with respect to an association with deep dyspareunia or have not been investigated in large epidemiological studies (Ferrero et al. 2008; Burrows et al. 2012; Dhingra et al. 2012).

The role of psychologic factors in sexual pain seems to vary with the underlying sexual pain etiology (rather than sexual pain itself); overall, women with dyspareunia have been found to have elevated rates of depression and anxiety disorders.

Diagnosis of sexual pain is initially entertained by asking women open-ended questions about pain during sexual intercourse. If sexual pain is identified, further directive questions should be undertaken in a nonjudgmental manner to identify the underlying etiology, including location (deep vs. superficial, localized vs. generalized), timing (provoked vs. consistent, present in all situations or in selected relationships, lifelong or acquired), and aggravating and alleviating factors.

The lack of a single etiology for deep dyspareunia makes the diagnosis difficult to be conclusively obtained. Deep dyspareunia is a frequent component of both endometriosis-related pain and pelvic congestion syndrome, affecting approximately 50–90 % of women seeking care for surgical or medical management of endometriosis and between 27 and 61 % of women being treated for pelvic congestion syndrome (Ferrero et al. 2008).

In this context, treatment of deep dyspareunia should be directed at identified causative factors (i.e., endometriosis).

References

Agarwal A, Deepinder F, Cocuzza M et al (2008) Effect of vaginal lubricants on sperm motility and chromatin integrity: a prospective comparative study. Fertil Steril 89:375–379

Alexander MS, Rosen RC, Steinberg S et al (2011) Sildenafil in women with sexual arousal disorder following spinal cord injury. Spinal Cord 49:273–279

American Psychiatric Association (2000) Diagnostic and statistical manual of mental disorders: DSM-IV-TR, 4th edn. text revision ed. American Psychiatric Association, Washington, DC

Angst J (1998) Sexual problems in healthy and depressed persons. Int Clin Psychopharmacol 13(suppl 6):S1–S4

Archer DF (2010) Efficacy and tolerability of local estrogen therapy for urogenital atrophy. Menopause 17: 194–203

Argiolas A, Melis MR (2003) The neurophysiology of the sexual cycle. J Endocrinol Invest 26(Suppl 3):20–22

Bachmann G (2006) Female sexuality and sexual dysfunction: are we stuck on the learning curve? J Sex Med 3:639–645

Bachmann G, Lobo RA, Gut R et al (2008) Efficacy of low-dose estradiol vaginal tablets in the treatment of atrophic vaginitis: a randomized controlled trial. Obstet Gynecol 111:67–76

Basson R (2000) The female sexual response: a different model. J Sex Marital Ther 26:51–65

Basson R (2001) Female sexual response: the role of drugs in the management of sexual dysfunction. Obstet Gynecol 998:350–353

Basson R (2002a) The complexities of female sexual arousal disorder: potential role of pharmacotherapy. World J Urol 20:119–126

Basson R (2002b) A model of woman's sexual arousal. J Sex Marital Ther 28:1–10
Basson R (2009) Pharmacotherapy for women's sexual dysfunction. Expert Opin Pharmacother 10: 1631–1648
Basson R, Brotto LA (2003) Sexual psychophysiology and effects of sildenafil citrate in oestrogenised women with acquired genital arousal disorder and impaired orgasm: a randomized controlled trial. BJOG 110: 1014–1124
Basson R, Berman J, Burnett A et al (2000) Report of the international consensus development conference on female sexual dysfunction: definitions and classifications. J Urol 163:888–893
Basson R, Leiblum S, Brotto L et al (2003) Definitions of women's sexual dysfunction reconsidered: advocating expansion and revision. J Psychosom Obstet Gynaecol 24:221–229
Basson R, Leiblum S, Brotto L et al (2004) Revised definitions of women's sexual dysfunction. J Sex Med 1:40–48
Basson R, Rees P, Wang R et al (2010) Sexual function in chronic illness. J Sex Med 7:374–388
Binik YM (2010) The DSM diagnostic criteria for vaginismus. Arch Sex Behav 39:278–291
Bitzer J, Giraldi A, Pfaus J (2013a) Sexual desire and hypoactive sexual desire disorder in women. Introduction and overview. Standard operating procedure (SOP Part 1). J Sex Med 10:36–49
Bitzer J, Giraldi A, Pfaus J (2013b) A standardized diagnostic interview for hypoactive sexual desire disorder in women: standard operating procedure (SOP Part 2). J Sex Med 10:50–57
Blaicher W, Gruber D, Bieglmayer C et al (1999) The role of oxytocin in relation to female sexual arousal. Gynecol Obstet Invest 47:125–126
Bloemers J, van Rooij K, Poels S et al (2013) Toward personalized sexual medicine (part 1): integrating the "dual control model" into differential drug treatments for Hypoactive Sexual Desire Disorder and female sexual arousal disorder. J Sex Med 10:791–809
Bornstein J, Maman M, Abramovici H (2001) "Primary" vs "secondary" vulvar vestibulitis: one disease, two variants. Am J Obstet Gynecol 184:28–31
Brin MF, Vapnek JM (1997) Treatment of vaginismus with botulinum toxin injections. Lancet 349: 252–253
Brotto LA, Krychman M, Jacobson P (2008) Eastern approaches for enhancing women's sexuality: mindfulness, acupuncture, and yoga (CME). J Sex Med 5:2741–2748
Brotto LA, Bitzer J, Laan E et al (2010) Women's sexual desire and arousal disorders. J Sex Med 7(1 Pt 2): 586–614
Brotto LA, Petkau AJ, Labrie F et al (2011) Predictors of sexual desire disorders in women. J Sex Med 8: 742–753
Burri A, Spector T (2011) Recent and lifelong sexual dysfunction in a female UK population sample: prevalence and risk factors. J Sex Med 8:2420–2430
Burri A, Greven C, Leupin M et al (2012) A multivariate twin study of female sexual dysfunction. J Sex Med 9:2671–2681
Burrows LJ, Basha M, Goldstein AT (2012) The effects of hormonal contraceptives on female sexuality: a review. J Sex Med 9:2213–2223
Chivers ML, Rosen RC (2010) Phosphodiesterase type 5 inhibitors and female sexual response: faulty protocols or paradigms? J Sex Med 7:858–872
Chudakov B, Ben Zion IZ, Belmaker RH (2007) Transdermal testosterone gel prn application for hypoactive sexual desire disorder in premenopausal women: a controlled pilot study of the effects on the arizona sexual experiences scale for females and sexual function questionnaire. J Sex Med 4:204–208
Clayton AH (2007) Epidemiology and neurobiology of female sexual dysfunction. J Sex Med 4(Suppl 4):260–268
Clayton AH, Balon R (2009) The impact of mental illness and psychotropic medications on sexual functioning: the evidence and management. J Sex Med 6:1200–1211
Clayton AH, Warnock JK, Kornstein SG et al (2004) A placebo-controlled trial of bupropion SR as an antidote for selective serotonin reuptake inhibitor induced sexual dysfunction. J Clin Psychiatry 65:62–67
Danielson I, Sjoberg I, Stenlund H et al (2003) Prevalence and incidence of prolonged and severe dyspareunia in women: results from a population study. Scand J Public Health 31:113–118
Davis SR, Braunstein GD (2012) Efficacy and safety of testosterone in the management of hypoactive sexual desire disorder in postmenopausal women. J Sex Med 9:1134–1148
Davis SR, Guay AT, Shifren JL et al (2004) Endocrine aspects of female sexual dysfunction. J Sex Med 1:82–86
Davis SR, Davison SL, Donath S et al (2005) Circulating androgen levels and self-reported sexual function in women. JAMA 294:91–96
Davis SR, Moreau M, Kroll R et al (2008a) Testosterone for low libido in postmenopausal women not taking estrogen. N Engl J Med 359:2005–2017
Davis S, Papalia MA, Norman RJ et al (2008b) Safety and efficacy of a testosterone metered-dose transdermal spray for treating decreased sexual satisfaction in premenopausal women: a randomized trial. Ann Intern Med 148:569–577
Davis SR, Wolfe R, Farrugia H et al (2009) The incidence of invasive breast cancer among women prescribed testosterone for low libido. J Sex Med 6:1850–1856
Davison SL, Davis SR (2011) Androgenic hormones and aging: the link with female sexual function. Horm Behav 59:745–753
Davison SL, Bell R, Donath S et al (2005) Androgen levels in adult females: changes with age, menopause, and oophorectomy. J Clin Endocrinol Metab 90:3847–3853
Davison SL, Bell RJ, Lachina M et al (2008) Sexual function in well women: stratification by sexual satisfaction, hormone use, and menopause status. J Sex Med 5:1214–1222

de Kruiff ME, ter Kuile PTM, Weijenborg PTM et al (2000) Vaginismus and dyspareunia: is there a difference in clinical presentation? J Psychosom Obstet Gynecol 21:149–155

Dennerstein L, Burrows GD, Wood C et al (1980) Hormones and sexuality: effect of estrogen and progestogen. Obstet Gynecol 56:316–322

Dennerstein L, Alexander JL, Kotz K (2003) The menopause and sexual functioning: a review of the population-based studies. Annu Rev Sex Res 14:64–82

Dennerstein L, Koochaki P, Barton I et al (2006) Hypoactive sexual desire disorder in menopausal women: a survey of Western European women. J Sex Med 3:212–222

Dennerstein L, Lehert P, Guthrie JR, Burger HG (2007) Modeling women's health during the menopausal transition: a longitudinal analysis. Menopause 14:53–62

Derogatis LR, Komer L, Katz M et al (2012) Treatment of hypoactive sexual desire disorder in premenopausal women: efficacy of flibanserin in the VIOLET study. J Sex Med 9:1074–1085

Dezarnaulds G, Fraser IS (2003) Vaginal ring delivery of hormone replacement therapy–a review. Expert Opin Pharmacother 4:201–212

Dhingra C, Kellogg-Spadt S, McKinney TB et al (2012) Urogynecological causes of pain and the effect of pain on sexual function in women. Female Pelvic Med Reconstr Surg 18:259–267

Dunn KM, Cherkas LF, Spector TD (2005) Genetic influences on variation in female orgasmic function: a twin study. Biol Lett 1:260–263

Engman M, Lindehammar H, Wijma B (2004) Surface electromyography diagnostics in women with partial vaginismus with or without vulvar vestibulitis and in asymptomatic women. J Psychosom Obstet Gynecol 25:281–294

Fabre LF, Brown CS, Smith LC et al (2011) Gepirone-ER treatment of hypoactive sexual desire disorder (HSDD) associated with depression in women. J Sex Med 8:1411–1419

Ferrero S, Ragni N, Remorgida V (2008) Deep dyspareunia: causes, treatments and results. Curr Opin Obstet Gynecol 20:394–399

Frank E, Anderson C, Rubinstein D (1978) Frequency of sexual dysfunction in "normal" couples. N Engl J Med 299:111–115

Friedrich EG Jr (1987) Vulvar vestibulitis syndrome. J Reprod Med 32:110–114

Fugl-Meyer KS, Bohm-Starke N, Damsted Petersen C et al (2013) Standard operating procedures for female genital sexual pain. J Sex Med 10:83–93

Giraldi A, Kristensen E (2010) Sexual dysfunction in women with diabetes mellitus. J Sex Res 47:199–211

Giraldi A, Rellini A, Pfaus JG et al (2011) Questionnaires for assessment of female sexual dysfunction: a review and proposal for a standardized screener. J Sex Med 8:2681–2706

Giraldi A, Rellini AH, Pfaus J et al (2013) Female sexual arousal disorders. J Sex Med 10:58–73

Giuliano F, Pfaus J, Balasubramanian S et al (2010) Experimental models for the study of female and male sexual function. J Sex Med 7:2970–2995

Goldfischer ER, Breaux J, Katz M et al (2011) Continued efficacy and safety of flibanserin in premenopausal women with Hypoactive Sexual Desire Disorder(HSDD): results from a randomized withdrawal trial. J Sex Med 8:3160–3172

Goldstat R, Briganti E, Tran J et al (2003) Transdermal testosterone therapy improves well being, mood, and sexual function in premenopausal women. Menopause 10:390–398

Goldstein AT, Burrows L (2008) Vulvodynia. J Sex Med 5:5–14

Goldstein MK, Teng NN (1991) Gynecologic factors in sexual dysfunction of the older women. Clin Geriatr Med 7:41–61

Goldstein I, Graziottin A, Heiman JR et al (1999) First international consultation on erectile dysfunction, Chapter 14, pp 507–556

Graham MD, Pfaus JG (2010) Differential regulation of female sexual behaviour by dopamine agonists in the medial preoptic area. Pharmacol Biochem Behav 97:284–292

Granot M, Friedman M, Yarnitsky D et al (2004) Primary and secondary vulvar vestibulitis syndrome: systemic pain perception and psychophysical characteristics. Am J Obstet Gynecol 191:138–142

Graziottin A (2001) Clinical approach to dyspareunia. J Sex Marital Ther 27:489–501

Haefner H (2007) Report of the International Society for the Study of Vulvovaginal Disease terminology and classification of vulvodynia. J Low Genit Tract Dis 11:48–49

Harlow BL, Stewart EG (2003) A population-based assessment of chronic unexplained vulvar pain: have we underestimated the prevalence of vulvodynia? J Am Med Womens Assoc 58:82–88

Hayes RD, Bennett CM, Fairley CK, Dennerstein L (2006) What can prevalence studies tell us about female sexual difficulty and dysfunction? J Sex Med 3:589–595

Hayes RD, Dennerstein L, Bennett CM et al (2008a) What is the 'true' prevalence of female sexual dysfunctions and does the way we assess these conditions have an impact? J Sex Med 5:777–787

Hayes RD, Dennerstein L, Bennett CM et al (2008b) Risk factors for female sexual dysfunction in the general population: exploring factors associated with low sexual function and sexual distress. J Sex Med 5: 1681–1693

Heiman JR (2000) Orgasmic disorders in women. In: Rosen RC, Leiblum SR (eds) Principles and practices of sex therapy. Guilford Press, New York, pp 118–153

Heiman JR, Meston CM (1997) Empirically validated treatment for sexual dysfunction. Annu Rev Sex Res 8:148–194

Hickey M, Elliott J, Davison SL (2012) Hormone replacement therapy. BMJ 344:e763

Hite S (2005) The Hite report. New York: Dell; 1976.8 Lloyd EA. The case of the female orgasm: bias in the science of evolution. Harvard University Press, Cambridge, MA

Ishak WW, Bokarius A, Jeffrey JK et al (2010) Disorders of orgasm in women: a literature review of etiology and current treatments. J Sex Med 7:3254–3268

ISSM Health Policy Statement (2011) hypoactive sexual desire disorder in women. J Sex Med 8:1313

Jones LM, McCabe MP (2011) The effectiveness of an Internet-based psychological treatment program for female sexual dysfunction. J Sex Med 8:2781–2792

Kalmbach DA, Ciesla JA, Janata JW et al (2012) Specificity of anhedonic depression and anxious arousal with sexual problems among sexually healthy young adults. J Sex Med 9:505–513

Kaplan H (1974) The new sex therapy. Brunner Mazel, New York

Kelly MP, Strassberg DS, Turner CM (2006) Behavioral assessment of couples' communication in female orgasmic disorder. J Sex Marital Ther 32:81–95

Kennedy SH, Dickens SE, Eisfeld BS et al (1999) Sexual dysfunction before antidepressant therapy in major depression. J Affect Disord 56:201–208

Kim C, Kong S, Laughlin GA et al (2012) Reductions in glucose among postmenopausal women who use and do not use estrogen therapy. Menopause 20(4):393–400

King R, Belsky J, Mah K et al (2011) Are there different types of female orgasm? Arch Sex Behav 40:865–875

Kingsberg SA, Simon JA, Goldstein I (2008) The current outlook for testosterone in the management of hypoactive sexual desire disorder in postmenopausal women. J Sex Med 5(Suppl 4):182–193

Kingsberg SA, Tkachenko N, Lucas J et al (2013a) Characterization of orgasmic difficulties by women: focus group evaluation. J Sex Med 10(9):2242–2250. doi:10.1111/jsm.12224

Kingsberg SA, Wysocki S, Magnus L et al (2013b) Vulvar and vaginal atrophy in postmenopausal women: findings from the REVIVE (REal Women's VIews of Treatment Options for Menopausal Vaginal ChangEs) survey. J Sex Med 10(7):1790–1799

Kovalevsky G (2005) Female sexual dysfunction and use of hormone therapy in postmenopausal women. Semin Reprod Med 23:180–187

Krychman ML (2011) Vaginal estrogens for the treatment of dyspareunia. J Sex Med 8:666–674

Laan E, Everaerd W (1995) Determinants of female sexual arousal: psychophysiological theory and data. Annu Rev Sex Res 6:32–76

Laan E, Everaerd W (1998) Physiological measures of vaginal vasocongestion. Int J Impot Res 10(Suppl 2):S107–S110

Laan E, Rellini AH, Barnes T (2013) Standard operating procedures for female orgasmic disorder: consensus of the International Society for Sexual Medicine. J Sex Med 10:74–82

Labrie F, Archer D, Bouchard C et al (2009) Effect of intravaginal dehydroepiandrosterone (Prasterone) on libido and sexual dysfunction in postmenopausal women. Menopause 16:923–931

Labrie F, Archer D, Bouchard C et al (2010) High internal consistency and efficacy of intravaginal DHEA for vaginal atrophy. Gynecol Endocrinol 26:524–532

Lahaie MA, Boyer SC, Amsel R et al (2010) Vaginismus: a review of the literature on the classification/diagnosis, etiology and treatment. Womens Health (Lond Engl) 6:705–719

Lamont JA (1978) Vaginismus. Am J Obstet Gynecol 131:633–636

Laumann EO, Paik A, Rosen RC (1999) Sexual dysfunction in the United States. Prevalence and predictors. JAMA 281:537–544

Laumann EO, Nicolosi A, Glasser DB et al (2005) Sexual problems among women and men aged 40–80 y: prevalence and correlates identified in the Global Study of Sexual Attitudes and Behaviors. Int J Impot Res 17:39–57

Leddy LS, Yang CC, Stuckey BG et al (2012) Influence of sildenafil on genital engorgement in women with female sexual arousal disorder. J Sex Med 9:2693–2697

Leiblum SR, Koochaki PE, Rodenberg CA et al (2006) Hypoactive sexual desire disorder in postmenopausal women: US results from the Women's International Study of Health and Sexuality (WISHeS). Menopause 13:46–56

Leonard LM, Follette VM (2002) Sexual functioning in women reporting a history of child sexual abuse: review of the empirical literature and clinical implications. Annu Rev Sex Res 13:346–388

Levine SB et al (2008) Phase 2B bremelanotide study in pre- and postmenopausal women with FSAD. Poster presentation at ACOG 56th annual meeting, New Orleans, May 3–7 2008

Lewis RW, Fugl-Meyer KS, Corona G et al (2010) Definitions/epidemiology/risk factors for sexual dysfunction. J Sex Med 7:1598–1607

Lloyd EA (2005) The case of the female orgasm: bias in the science of evolution. Harvard University Press, Cambridge, MA

Long CY, Liu CM, Hsu SC et al (2006) A randomized comparative study of the effects of oral and topical estrogen therapy on the vaginal vascularization and sexual function in hysterectomized postmenopausal women. Menopause 13:737–743

Mah K, Binik YM (2001) The nature of human orgasm: a critical review of major trends. Clin Psychol Rev 21:823–856

Maserejian NN, Shifren JL, Parish SJ et al (2010) The presentation of hypoactive sexual desire disorder in premenopausal women. J Sex Med 7:3439–3448

Maserejian NN, Shifren J, Parish SJ et al (2012) Sexual arousal and lubrication problems in women with clinically diagnosed hypoactive sexual desire disorder: preliminary findings from the hypoactive sexual desire disorder registry for women. J Sex Marital Ther 38: 41–62

Masters WH, Johnson VE (1966) Human sexual response. Little; Brown, Boston

Melnik T, Hawton K, McGuire H (2012) Interventions for vaginismus. Cochrane Database Syst Rev 12:CD001760. doi:10.1002/14651858.CD001760.pub2

Meston CM, Hull E, Levin RJ et al (2004) Disorders of orgasm in women. J Sex Med 1:66–68

Middleton LS, Kuffel SW, Heiman JR (2008) Effects of experimentally adopted sexual schemas on vaginal response and subjective sexual arousal: a comparison between women with sexual arousal disorder and sexually healthy women. Arch Sex Behav 37:950–961

Mok K, Juraskova I, Friedlander M (2008) The impact of aromatase inhibitors on sexual functioning: current knowledge and future research directions. Breast 17:436–440

Mongomery JC, Studd JW (1991) Physiological and sexual aspects of the menopause. Brit J Hosp Med 45:300–302

Moyal-Barracco M, Lynch PJ (2004) 2003 ISSVD terminology and classification of vulvodynia: a historical perspective. J Reprod Med 49:772–777

Muller MJ, Ruof J, Graf-Morgenstern M et al (2001) Quality of partnership in patients with erectile dysfunction after sildenafil treatment. Pharmacopsychiatry 34:91–95

Nachtigall L, Casson P, Lucas J et al (2011) Safety and tolerability of testosterone patch therapy for up to 4 years in surgically menopausal women receiving oral or transdermal oestrogen. Gynecol Endocrinol 27:39–48

Naessen T, Rodriguez-Macias K, Lithell H (2001) Serum lipid profile improved by ultra-low doses of 17 beta-estradiol in elderly women. J Clin Endocrinol Metab 86:2757–2762

Nappi RE, Albani F, Santamaria V et al (2010a) Hormonal and psycho-relational aspects of sexual function during menopausal transition and at early menopause. Maturitas 67:78–83

Nappi RE, Albani F, Santamaria V et al (2010b) Menopause and sexual desire: the role of testosterone. Menopause Int 16:162–168

Nappi RE, Kingsberg S, Maamari R et al (2013) The CLOSER (CLarifying Vaginal Atrophy's Impact On SEx and Relationships) survey: implications of vaginal discomfort in postmenopausal women and in male partners. J Sex Med 10(9):2232–2241. doi:10.1111/jsm.12235

Nathorst-Boos J, Wiklund I, Mattsson LA et al (1993) Is sexual life influenced by transdermal estrogen therapy? A double blind placebo controlled study in postmenopausal women. Acta Obstet Gynecol Scand 72:656–660

Nobre PJ, Pinto-Gouveia J (2009) Cognitive schemas associated with negative sexual events: a comparison of men and women with and without sexual dysfunction. Arch Sex Behav 38:842–851

Nobre PJ, Pinto-Gouveia J, Gomes FA (2006) Prevalence and comorbidity of sexual dysfunctions in a Portuguese clinical sample. J Sex Marital Ther 32:173–182

North American Menopause Society (2012) The 2012 hormone therapy position statement of: the North American Menopause Society. Menopause 19:257–271

Oberg K, Fugl-Meyer K, Fugl-Meyer AR (2005) On Swedish women's distressing sexual dysfunction: some concomitant conditions and life satisfaction. J Sex Med 2:169–180

Pacik PT (2011) Vaginismus: review of current concepts and treatment using botox injections, bupivacaine injections, and progressive dilation with the patient under anesthesia. Aesthetic Plast Surg 35:1160–1164

Palacios S (2009) Managing urogenital atrophy. Maturitas 63:315–318

Panay N, Maamari R (2012) Treatment of postmenopausal vaginal atrophy with 10-μg estradiol vaginal tablets. Menopause Int 18:15–19

Panjari M, Davis SR (2007) DHEA therapy for women: effect on sexual function and well-being. Hum Reprod Update 13:239–248

Park K, Goldstein I, Andry C et al (1997) Vasculogenic female sexual dysfunction: the hemodynamic basis for vaginal engorgement insufficiency and clitoral erectile insufficiency. Int J Impot Res 9:27–37

Park K, Tarcan T, Goldstein I et al (2000) Atherosclerosis-induced chronic arterial insufficiency causes clitoral cavernosal fibrosis in the rabbit. Int J Impot Res 12:111–116

Pfaus JG (2009) Pathways of sexual desire. J Sex Med 6:1506–1533

Pfaus JG, Giuliano F, Gelez H (2007) Bremelanotide: an overview of preclinical CNS effects on female sexual function. J Sex Med 4:269–279

Philippsohn S, Hartmann U (2009) Determinants of sexual satisfaction in a sample of German women. J Sex Med 6:1001–1010

Philippsohn S, Kruger TH (2012) Persistent genital arousal disorder: successful treatment with duloxetine and pregabalin in two cases. J Sex Med 9:213–217

Plutzky J (2003) The vascular biology of atherosclerosis. Am J Med 115:55S–61S

Poels S, Bloemers J, van Rooij K et al (2013) Toward personalized sexual medicine (part 2): testosterone combined with a PDE5 inhibitor increases sexual satisfaction in women with HSDD and FSAD, and a low sensitive system for sexual cues. J Sex Med 10:810–823

Reissing ED, Binik YM, Khalife S et al (2004) Vaginal spasm, pain, and behavior: an empirical investigation of the diagnosis of vaginismus. Arch Sex Behav 33:5–17

Rellini A (2008) Review of the empirical evidence for a theoretical model to understand the sexual problems of women with a history of CSA. J Sex Med 5:31–46

Rellini A, Meston C (2007) Sexual function and satisfaction in adults based on the definition of child sexual abuse. J Sex Med 4:1312–1321

Rosen RC, Maserejian NN, Connor MK et al (2012) Characteristics of premenopausal and postmenopausal women with acquired, generalized hypoactive sexual desire disorder: the Hypoactive Sexual Desire Disorder Registry for women. Menopause 19:396–405

Rubio-Aurioles E, Kim ED, Rosen RC et al (2009) Impact on erectile function and sexual quality of life of couples: a double-blind, randomized, placebo-controlled trial of tadalafil taken once daily. J Sex Med 6:1314–1323

Salonia A, Nappi RE, Pontillo M et al (2005) Menstrual cycle-related changes in plasma oxytocin are relevant

to normal sexual function in healthy women. Horm Behav 47:164–169
Salonia A, Giraldi A, Chivers ML et al (2010) Physiology of women's sexual function: basic knowledge and new findings. J Sex Med 7:2637–2660
Segraves KB, Segraves RT (1991) Hypoactive sexual desire disorder: prevalence and comorbidity in 906 subjects. J Sex Marital Ther 17:55–58
Segraves RT, Clayton A, Croft H et al (2004) Bupropion sustained release for the treatment of hypoactive sexual desire disorder in premenopausal women. J Clin Psychopharmacol 24:339–342
Semmens JP, Semmens EC (1984) Sexual function and the menopause. Clin Obstet Gynecol 27:717–723
Shifren JL (2011) Increasing our understanding of women's sexuality at midlife and beyond. Menopause 18(11):1149–1151
Shifren JL, Braunstein GD, Simon JA et al (2000) Transdermal testosterone treatment in women with impaired sexual function after oophorectomy. N Engl J Med 343:682–688
Shifren JL, Davis SR, Moreau M et al (2006) Testosterone patch for the treatment of hypoactive sexual desire disorder in naturally menopausal women: results from the INTIMATE NM1 Study. Menopause 13:770–779
Shifren JL, Monz BU, Russo PA, Segreti A, Johannes CB (2008) Sexual problems and distress in United States women: prevalence and correlates. Obstet Gynecol 112:970–978
Shulman LP, Portman DJ, Lee WC et al (2008) A retrospective managed care claims data analysis of medication adherence to vaginal estrogen therapy: implications for clinical practice. J Womens Health (Larchmt) 17:569–578
Sims JS (1861) On vaginismus. Trans Obstet Soc Lond 3:356–367
Sinha A, Ewies AA (2013) Non-hormonal topical treatment of vulvovaginal atrophy: an up-to-date overview. Climacteric 16:305–312
Smith WJ, Beadle K, Shuster EJ (2008) The impact of a group psycho-educational appointment on women with sexual dysfunction. Am J Obstet Gynecol 198:697e1–697e6
Stahl SM, Sommer B, Allers KA (2011) Multifunctional pharmacology of flibanserin: possible mechanism of therapeutic action in hypoactive sexual desire disorder. J Sex Med 8:15–27
Staples J, Rellini AH, Roberts SP (2012) Avoiding experiences: sexual dysfunction in women with a history of sexual abuse in childhood and adolescence. Arch Sex Behav 41:341–350
Suckling J, Lethaby A, Kennedy R (2003) Local oestrogen for vaginal atrophy in postmenopausal women. Cochrane Database Syst Rev 2003;(4):CD001500
ter Kuile MM, Both S, van Lankveld JJ (2010) Cognitive behavioral therapy for sexual dysfunctions in women. Psychiatr Clin North Am 33:595–610
Thorp J, Simon J, Dattani D et al (2012) Treatment of hypoactive sexual desire disorder in premenopausal women: efficacy of flibanserin in the DAISY study. J Sex Med 9:793–804
Tkachenko N et al (2013) An open−label, single and multiple−application of intranasal testosterone gel (tbs−2) in healthy pre−menopausal female subjects at three dose levels. Annual meeting ISSWSH: New Orleans, USA
Traish AM, Botchevar E, Kim NN (2010) Biochemical factors modulating female genital sexual arousal physiology. J Sex Med 7:2925–2946
Triggle CR, Hollenberg M, Anderson TJ et al (2003) The endothelium in health and disease—a target for therapeutic intervention. J Smooth Muscle Res 39:249–267
Trudel G, Marchand A, Ravart M et al (2001) The effect of a cognitive-behavioral group treatment program on hypoactive sexual desire in women. Sex Relat Ther 16:145–164
U.S. Department of Health and Human Services, Food and Drug Administration (2000) Guidance for industry. Female sexual dysfunction: clinical development of drug products for treatment. Draft guidance. In: Center for Drug Evaluation, Research (CDER) (eds)
Ückert S, Kuczyk MA, Oelke M (2013) Phosphodiesterase inhibitors in clinical urology. Expert Rev Clin Pharmacol 6:323–332
Van den Hout M, Barlow D (2000) Attention, arousal and expectancies in anxiety and sexual disorders. J Affect Disord 61:241–256
van Lankveld JJ, Granot M, Weijmar Schultz WC et al (2010) Women's sexual pain disorders. J Sex Med 7:615–631
Waldinger MD, Schweitzer DH (2009) Persistent genital arousal disorder in 18 Dutch women: Part II. A syndrome clustered with restless legs and overactive bladder. J Sex Med 6:482–497
Waldinger MD, van Gils AP, Ottervanger HP et al (2009a) Persistent genital arousal disorder in 18 Dutch women: Part I. MRI, EEG, and transvaginal ultrasonography investigations. J Sex Med 6:474–481
Waldinger MD, Venema PL, van Gils AP et al (2009b) New insights into restless genital syndrome: static mechanical hyperesthesia and neuropathy of the nervus dorsalis clitoridis. J Sex Med 6:2778–2787
West SL, D'Aloisio AA, Agans RP et al (2008) Prevalence of low sexual desire and hypoactive sexual desire disorder in a nationally representative sample of US women. Arch Intern Med 168:1441–1449
Wiedeking C, Ziegler MG, Lake CR (1979) Plasma noradrenaline and dopamine beta-hydroxylase during human sexual activity. J Psychiatr Res 15:139–145

Part IV

Male Hypogonadism and Infertility

Testosterone Deficiency Syndrome 10

Siegfried Meryn

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10.1 General Aspects of Testosterone Deficiency

10.1.1 Definition of Hypogonadism

Hypogonadism in men is a clinical syndrome that results from failure of the testes to produce physiological levels of testosterone resulting in testosterone deficiency and in some instances normal numbers of spermatozoa (infertility) due to disruption of one or more levels of the hypothalamic–pituitary–testicular axis. The two distinct yet interdependent testicular functions,

V. Mirone (ed.), *Clinical Uro-Andrology*,
DOI 10.1007/978-3-662-45018-5_10, © Springer-Verlag Berlin Heidelberg 2015

spermatogenesis and steroidogenesis (androgen production), can fail independently.

Testosterone deficiency may be primary, due to a problem with the testes, secondary, due to a problem with the hypothalamic–pituitary–testicular axis, or combined primary and secondary. The etiology of androgen deficiency may be organic, in which there is a pathological physical change in the structure of an organ or within the hypothalamic–pituitary–testicular axis. Androgen deficiency may be functional when there is no demonstrable pathological change in the structure of an organ (stress, extreme obesity) or within the hypothalamic–pituitary–testicular axis. Organic defects are usually long lasting or permanent while functional defects are potentially reversible. Weight loss, for instance, usually raises serum testosterone levels.

10.1.2 Testosterone Production

The production of testosterone takes places in the Leydig cell. The daily production of testosterone in adulthood is about 5–7 mg. Testosterone diffuses passively into cells of the target organs of androgen. To exert its biological action, it must bind to the androgen receptor though there are also a number of biological actions of testosterone which do not require receptor activation (membrane effects). For some of its biological actions, testosterone is a prohormone. After diffusion into the cell, testosterone may be converted to 5alpha-dihydrotestosterone (DHT) or estradiol. There are two types of 5alpha-reductase enzymes which convert testosterone to DHT. DHT and testosterone bind to the same androgen receptor, although DHT has an approximately tenfold greater affinity for the receptor and its dissociation is slower, resulting in a considerably higher biopotency than testosterone. The conversion of testosterone to DHT can be viewed as an androgen amplification mechanism in organs that require strong androgen action such as the prostate. About 80 % of DHT is produced in peripheral organs/tissues and the remaining 20 % is secreted directly by the testis. Furthermore, approximately 30–40 μg of estradiol is produced by the adult male, mainly in peripheral tissues, such as adipose tissue, bone, prostate, and brain. Insight into the biological actions of estradiol in the male is of rather recent date. Estrogens have an important effect on the final phases of skeletal maturation and bone mineralization in puberty. In addition, from some studies in elderly men it appears that estrogen levels show a higher correlation with bone mineral density (BMD) than androgen levels (Laurent et al. 2014). Impaired estrogen action in men leads to dyslipidemia and to endothelial dysfunction. Observation in men with aromatase deficiency shows that these men have a complex dysmetabolic syndrome characterized by insulin resistance, diabetes mellitus type 2, acanthosis nigricans, liver steatosis hepatis, and signs of precocious atherogenesis, remedied by estrogen administration. Estrogen effects on the brain are also increasingly recognized (Cornil et al. 2012; Rochira et al. 2005). Though the effects of estrogens in the male are undeniably biologically significant, estrogen deficiency as a clinical entity is sporadic in men unless in the rare cases of aromatase deficiency or estrogen receptor abnormalities. Since testosterone is a precursor molecule for estradiol, low estradiol levels are usually associated with (severe) androgen deficiency.

10.1.3 Bioavailability of Testosterone

Testosterone is a lipophilic molecule and its solubility in blood is limited. Only ±2 % of circulating testosterone is free, non-bound to transport proteins, able to diffuse into cells, and immediately available for biological action. Approximately 60 % of circulating testosterone is bound with high affinity to sex hormone-binding globulin (SHBG) and ±38 % is loosely bound and transported by albumin. The free fraction of testosterone (±2 %) and the albumin-bound fraction (±38 %) have been termed bioavailable testosterone since these two fractions are readily available for biological action. The binding of testosterone to SHBG has a high affinity and changes in concentrations of circulating SHBG impact on the bioavailability of testosterone. SHBG is

produced by the liver. A number of conditions/hormones influence its production. Androgen and growth hormone decrease circulating SHBG and, as a result, increase bioavailable testosterone and therewith amplify the action of testosterone and the combined anabolic effects of growth hormone and testosterone. Androgen deficiency, estrogen, hyperthyroidism, and liver disease increase circulating SHBG and consequently limit its biological action. SHBG binds also estradiol but with lower affinity than testosterone. Since the binding affinity of testosterone to SHBG is higher than of estradiol, the aforementioned conditions may be associated with signs of estrogen excess in relation to the bioavailability of androgen, such as in cases of gynecomastia. Overweight with its associated hyperinsulinism, corticosteroids, and hypothyroidism reduce hepatic production and consequently circulating SHBG and result in low total plasma concentrations of testosterone and possible consequences on bioavailable testosterone.

10.1.4 The Hypothalamic–Pituitary–Testicular Axis

The secretion of testosterone from the Leydig cell is stimulated by the pituitary hormone luteinizing hormone (LH). Human chorionic gonadotropin (hCG) is chemically largely identical with LH and is equally capable of stimulating testosterone production. Follicle stimulating hormone (FSH) binds to the Sertoli cell and promotes spermatogenesis. The pituitary production of LH and FSH, in turn, is regulated by the hormone luteinizing hormone-releasing hormone (LHRH), produced in the arcuate nucleus and the preoptic area of the hypothalamus under the stimulating and inhibitory influence of local neurotransmitters. LHRH is secreted in regular pulses, with peaks in adulthood every 90–120 min, due to the intrinsic capacity of LHRH neurons to secrete episodically. The pulsatility of LHRH is essential to its gonadotropin-releasing effect. Continuous stimulation of the pituitary by LHRH leads to desensitization and to a cessation of LH and FSH release. The hypothalamus is connected with the anterior pituitary through a portal system through which LHRH reaches the pituitary. Due to this anatomical situation, the concentration of LHRH in peripheral blood is immeasurably low.

Testicular hormones exert a negative feedback control on the secretion of LH and FSH. Testosterone itself but also estradiol and DHT are involved in the negative feedback action which is exerted both at the level of the hypothalamus (reducing LHRH pulse frequency and amplitude) and at the level of the pituitary by reducing production and release of LH and FSH. The negative feedback action of estrogen on the secretion of LH and FSH is evidenced by the resulting rise of LH and FSH following administration of agents that pharmacologically reduce estrogen action (antiestrogen and aromatase inhibitors). The latter agents may have a role in treating mild forms of hypogonadism.

Testosterone secretion follows a daily rhythm with highest testosterone levels in the early morning hours then gradually declining to reach the lowest levels in the early evening. The biological significance of this diurnal rhythm has not been established. With aging the production of testosterone declines and its bioavailability is reduced and the diurnal rhythm is less pronounced.

10.2 Age-Related Decline of Serum Testosterone

10.2.1 Mechanisms of the Age-Related Decline of Serum Testosterone

The decline in testosterone production in older men is the result of age-related changes at all levels of the hypothalamic–pituitary–testicular axis (Bassil 2011; Huhtaniemi 2014; Behre et al. 2012). Testosterone production is less efficient in old age with a lower steroidogenic response to stimulation with LH or hCG. The decline of circulating testosterone is not always compensated by an increase in LH which would be expected on the basis of a decreased negative feedback signal. So it would seem that the pituitary has become more sensitive to the negative

feedback action of testosterone and its metabolites. A more important factor is probably the changes of the aging hypothalamic structures which produce LHRH. The pulsatile secretion of LHRH is attenuated and more disorderly so that stimulation of the pituitary to produce LH is less efficacious. Also, the synchrony between an LH pulse and a testosterone pulse is weakened in elderly men. The diurnal rhythm of testosterone, with higher plasma testosterone in the early morning than in the early evening, is dampened in elderly men resulting in a lower testosterone output.

Aging not only affects androgen production but also its bioavailability (Bassil 2011; Tajar et al. 2012). The levels of the testosterone-binding protein SHBG commonly rise with aging; though another common feature of aging, obesity and hyperinsulinism reduces circulating SHBG. The rise in SHBG is in the first instance associated with lower free testosterone levels. With a healthy hypothalamus–pituitary system, this would result in the compensatory secretion of LH and subsequently of testosterone. But the less efficacious aging hypothalamus–pituitary system is not always capable of this response leading to lower levels of free and bioavailable testosterone.

Many of the changes associated with aging such as loss of bone and muscle mass, increased fat mass, and deterioration of physical, cognitive, and sexual capacities are similar to the symptoms of classical hypogonadism in younger men (Bassil 2011). The decline in circulating testosterone is not universal in elderly men and of a lesser magnitude than in classical hypogonadism (Behre et al. 2012). To explain the androgen deficiency-like symptoms in aging in the presence of relatively mildly reduced testosterone levels, it has been hypothesized whether the efficacy of androgen action at the level of receptor and post-receptor mechanisms is diminished in old age compared to younger age. Arguing against this is that, with regard to the anabolic actions of testosterone on muscle, elderly men are as responsive to testosterone as young men (Bhasin and Buckwalter 2001). Also, effects on metabolic syndrome are similar in young and old men (Page et al. 2005). While male sexual functioning in (young) adulthood can be maintained with lower-than-normal values (Corona et al. 2013a), there are indications that the threshold required for behavioral effects of testosterone increases with aging (Schiavi and Rehman 1995), confirmed in a laboratory setting indicating that libido and erectile function require higher testosterone levels in old age compared to younger age (Gray et al. 2005) but also apparent from clinical observation (Basaria 2013) and suggested by a meta-analysis (Jain et al. 2000).

10.2.2 Nomenclature

When it became established statistically that serum testosterone decline with age, parallels with female reproductive endocrinology were sought and terms as male climacterium or male menopause were proposed, but they must be regarded as misnomers since the patterns of decline of serum testosterone in male menopause bear no resemblance to female menopause (Morales et al. 2006). Instead, the terminology (partial) androgen deficiency of the aging male (ADAM or PADAM) was thought to be more accurate. But, in fact, serum testosterone starts to decline from the fourth decade of life, well before aging, so it seemed that aging should not be part of the definition, and the focus of these definitions is not sufficiently on testosterone, rather on androgen in general. Late-onset hypogonadism, also termed symptomatic late-onset hypogonadism, indicates that clinical symptoms of testosterone deficiency must be present for the diagnosis to be accepted. The term hypogonadism is traditionally used synonymously with a pathological testosterone deficiency state arising from specific diseases or dysfunctions of the hypothalamic–pituitary–testicular axis which generally require specialized investigations. This is not the case with age-related decline in testosterone in terms of both etiology and severity. Therefore, a case has been made for the term testosterone deficiency syndrome (TDS) (Morales et al. 2006). TDS specifies that testosterone is the main male hormone. In addition, TDS does not carry the

connotation that it is obligatorily restricted to elderly men. The clinical picture of TDS, composed of symptoms and signs of variable severity, is well known and widely accepted. It is also recognized that the diagnosis, normally, requires the combination of clinical manifestations and biochemical confirmation in the laboratory.

10.2.3 Who Is Truly Testosterone-Deficient in Old Age?

As indicated above, circulating levels of testosterone show a statistically significant decline with aging. The vast majority of men will have circulating testosterone values which are 5–20 % below reference values for men. And it has been difficult to draw a clear dividing line between blood levels of testosterone which represent a truly hypogonadal state and a eugonadal state (Traish et al. 2011; Corona et al. 2013a). This problem is compounded by the fact that serum testosterone thresholds for androgen deficiency, though highly consistent within a person, differ between people (Kelleher et al. 2004). Hypogonadal men who receive androgen treatment perceive the threshold for androgen deficiency symptoms at highly reproducible blood testosterone levels. This distinctively individual trigger level for androgen deficiency symptoms differs widely between men. The threshold values vary from very low to above the lower limit of the eugonadal reference range. On average, it approximates the lower limit of the eugonadal reference range for young men (Kelleher et al. 2004). The factors which define this symptomatic threshold are as yet unknown, but it is reasonable to assume that genetic polymorphisms of the androgen receptors influencing androgen sensitivity play a significant role (Zitzmann 2007). There are (subtle) genetic differences in androgen receptor properties in men. The androgen receptor gene contains in exon 1 a polymorphic trinucleotide CAG repeat. The length of the (CAG)n polymorphism of the gene is negatively associated with transcriptional activity of the androgen receptor. In other words, an androgen receptor with fewer CAG repeats mediates a stronger androgen effect than a receptor with more CAG repeats. Some studies have found that men with fewer CAG repeats, subject to enhanced androgen action, are more liable to develop prostate cancer. Other reports fail to confirm this (for review: Zitzmann 2007). A similar controversy surrounds the relevance of the number of CAG repeats for the severity of symptoms of the age-associated decline of testosterone (Harkonen et al. 2003). For the time being determination of the number of CAG repeats is not part of routine clinical assessment of the hypogonadal male, young or old.

The impact of the aging process and the accumulation of acquired chronic diseases with aging on the threshold for androgen deficiency symptoms are beginning to be understood (Kelleher et al. 2004; Cattabiani et al. 2012; Fillo et al. 2012).

10.2.4 Thresholds and Dose-Response Relationships of Androgen Effects

The concept of different threshold values of circulating testosterone on the manifestation of the different symptoms of androgen deficiency is only beginning to be supported by empirical studies. A threshold for androgen effects on male sexual function, primarily libido, is becoming evident at the lower range of the reference value of serum testosterone concentrations (Gooren 1987; Bagatell et al. 1994). These studies failed to define a threshold with precision. By contrast, the muscle appears to exhibit linear dose-response relationship to testosterone from below to above the eugonadal reference range for blood testosterone concentrations (Woodhouse et al. 2004). One study has suggested a dose-response relationship for the effects of normalization of circulating testosterone on the features of metabolic syndrome (Corona et al. 2013b), but an optimal range for those beneficial effects was not established in this study. Whether linear dose-response or threshold models apply to other androgen-sensitive tissues, such as bone and prostate, psychosexual and cardiovascular effects remain to be

determined. From recent studies of elderly men, it has become apparent that complaints of testosterone deficiency cannot be related to a specific single-value threshold of testosterone concentration but that thresholds vary with the various symptoms of testosterone deficiency (Zitzmann et al. 2006). In a cohort of men, androgen-related loss of libido or vigor became more prevalent when testosterone concentrations fell below 15 nmol/l, while depression and diabetes mellitus type 2 (also in nonobese men) became only significantly more present in men with testosterone concentrations below 10 nmol/l. Symptoms related to androgen deficiency in this study could be subdivided in three independent groups: psychosomatic complaints, metabolic disorders, and sexual health problems. Patients suffering from one of these three groups exhibit distinct features in terms of androgen levels, age, and body mass index. Therefore, complaints are not only linked to androgen levels but age and body mass index carried weight as well in the manifestation of the signs and symptoms of androgen deficiency (Zitzmann et al. 2006). To further complicate the matter of the relationship between testosterone levels on the one hand and symptoms of testosterone deficiency on the other, the authors have drawn attention to the multifactorial impact on certain androgen-related functions (Zitzmann et al. 2006). Erectile dysfunction may serve as an example of a composite dysfunctionality in which, apart from testosterone concentrations, other hormones (prolactin, estradiol), arterial endothelial function, neuronal integrity, and psychological factors play pivotal roles, almost precluding the establishing of a straightforward relationship between testosterone levels and erectile dysfunction (Bancroft 2005). In the study of Zitzmann et al. (2006), erectile dysfunction was identified as a composite pathology of metabolic risk factors, smoking, and depression, and only testosterone concentrations below 8 nmol/l contributed to that symptom. So the various symptoms of testosterone deficiency might start at various circulating concentrations of androgen. As a result, with a given plasma testosterone level, some complaints might be present and others not. This has also been confirmed in other studies establishing symptom-specific thresholds of androgen levels (O'Donnell et al. 2004, Feldman et al. 2002). It, therefore, comes as no surprise that there is a significant variation among clinics and European countries in their application of threshold values of testosterone signifying hypogonadism which range from 7.5 to 12.0 nmol/l (Nieschlag et al. 2004; Behre et al. 2012). Almost certainly a factor in this observation is that physicians in different countries will have different concepts of what constitute the core symptoms of hypogonadism. On the basis of the above observations, it is clear that the symptoms of testosterone deficiency are not uniformly and predictably related to values of blood testosterone, which may lead to different diagnostic criteria for testosterone deficiency. So the conclusion seems inevitable that the clinical manifestations of hypogonadism are multifactorially determined and that the diagnosis should not only depend on the measurement of testosterone but proper assessment should comprise somatic and psychological aspects in addition to the measurement of testosterone (Huhtaniemi 2014; Shelton and Rajfer 2012). In an area with uncertainties regarding the diagnosis and treatment of testosterone deficiency in elderly men, guidelines drafted by groups of experts serve a useful role.

10.2.5 Guidelines for the Diagnosis and Treatment of Testosterone Deficiency in Elderly Men

Professional organizations recognize that androgen deficiency in the aging male should receive due interest and debate, not least because the demographics clearly demonstrate the increasing percentage of the population that is in the older age groups, and with age a significant percentage of men over the age of 60 years have serum testosterone levels that are below the lower limits of young adult (age, 20–30 years) men. Older hypogonadal men might well benefit from testosterone treatment on multiple target organs of androgen, with potentially similar beneficial effects of testosterone in older similar to those in younger men. Of pivotal importance is the

question whether the functional benefits of testosterone administration would result in retarding frailty of the elderly. Evidence is accumulating that risks associated with such intervention are acceptable with the proper supervision of testosterone treatment of the elderly. Therefore, several professional bodies have formulated guidelines for the responsible use of testosterone in the elderly carefully weighing benefits against risks. Long-term data over more than 3 years on the effects of testosterone treatment in the older population are still limited, and specifically more data on the risks of prostate and cardiovascular disease are needed. A diagnosis of androgen deficiency should be based on consistent symptoms and signs and unequivocally low serum testosterone levels. It is recommended to measure morning total testosterone level by a reliable assay as the initial diagnostic test. In case there is no clear-cut outcome confirmation of the diagnosis, repeating the measurement of morning total testosterone is recommended; in some patients, this is complemented by measurement of the free or bioavailable testosterone level. The use of accurate assays is pivotal for a proper diagnosis. Testosterone therapy is given with the aim to induce and maintain secondary sex characteristics and to improve sexual function, sense of well-being, muscle mass and strength, and bone mineral density. It should be reserved for symptomatic men with androgen deficiency and who have low testosterone levels. Professional organizations have formulated guidelines/recommendations for the administration of testosterone to elderly men. One set of guidelines has been adopted by the International Society of Andrology, the International Society for the Study of the Aging Male, and the European Association of Urology (Wang et al. 2008). The other one has been proposed by a task force of the Endocrine Society (Bhasin et al. 2010).

One set of guidelines defines the reference values of testosterone as follows: normal – total testosterone >12 nmol/l (346 ng/dl) and free testosterone >250 pmol/l (72 pg/ml). Treatment may be considered if there are symptoms and the value of total testosterone is 8–12 nmol/l (231–346 ng/dl). A total testosterone value of <8 nmol/l (231 ng/dl) and free testosterone of <180 pmol/l (52 pg/ml) is an indication for treatment (Wang et al. 2008). The guidelines of the Endocrine Society specify that there is as yet no consensus on what constitutes a low testosterone value but regard a total testosterone value of <6.9–10.4 nmol/l (200–300 ng/dl) and a free testosterone value of <0.17 nmol/l (50 pg/ml) as low (Bhasin et al. 2010). According to the above guidelines, when testosterone therapy is instituted, achieved testosterone levels during treatment should be in the mid-normal range (Bhasin et al. 2010) The formulation of testosterone should be chosen on the basis of the patient's preference, consideration of pharmacokinetics, treatment burden, and cost (Bhasin et al. 2010). Men receiving testosterone therapy should be monitored using a standardized plan, detailed in the above guidelines. Testosterone treatment should not be started in patients with breast or prostate cancer, a palpable prostate nodule or induration, or prostate-specific antigen greater than 4 ng/ml or greater than 3 ng/ml in men at high risk for prostate cancer such as African-Americans or men with first-degree relatives with prostate cancer without further urological evaluation. Treatment should also be withheld if hematocrit is greater than 50 % and in case of untreated severe obstructive sleep apnea, severe lower urinary tract symptoms with International Prostate Symptom Score above 19, or uncontrolled or poorly controlled heart failure.

10.2.6 Clinical Diagnosis of Testosterone Deficiency Syndrome

The diagnosis of testosterone deficiency syndrome and, certainly, the decision to provide androgen treatment must be made with caution, taking the specific increment of symptom prevalence in relation to testosterone levels into account and the many factors interacting in androgen-dependent functions such as erectile potency (Zitzmann et al. 2006; Huhtaniemi and Forti 2011). With the above being the case, it is virtually impossible to take a blood testosterone

value solely as an indication for testosterone treatment. The presenting symptoms of hypogonadism in a man may or may not be related to testosterone value, though the lower the value of blood testosterone, the greater the likelihood. The decision to provide androgen treatment must not only be guided by the level of blood testosterone but also based on clinical judgment (Ho and Beckett 2011; Corona et al. 2013a). The lower the serum testosterone level, the greater the likelihood that the symptoms are related to that particular testosterone level. The decision to treat will have an element of arbitrariness unless serum testosterone is truly low (<6 nmol/l) or truly in the normal range (>15 nmol/l). A case can be made for a therapeutic trial of testosterone if the interpretation of clinical and laboratory data provide an ambiguous outcome (Black et al. 2004; Wang et al. 2008). In case of sexual dysfunction, this approach is helpful in treating the disorder (Reyes-Vallejo et al. 2007).

In summary, physicians have to be aware that testosterone plays a significant but not all-decisive role in older male patients and that replacement options should be based firstly on symptoms and secondly on hormone concentrations, which should be evaluated on a symptom-specific basis. Physicians treating elderly men should have expertise in the signs and symptoms of testosterone deficiency which have a broad spectrum of psychological, metabolic, and sexual symptoms. Naturally, testosterone is not a panacea of all the mental and somatic problems men encounter in the process of aging, and indiscriminate use in men who present with vague symptoms will have many failures.

In patients at risk or suspected of hypogonadism, a thorough physical and biochemical workup is necessary. Transient decreases of serum testosterone levels such as those due to acute illnesses should be excluded by careful clinical evaluations and repeated hormone measurement. Hypogonadism (primary or secondary) can occur at all ages including elderly men. Risk factors for hypogonadism in older men may include chronic illnesses including diabetes mellitus, chronic obstructive lung disease, inflammatory arthritic disease, renal disease, HIV-related disease, obesity, metabolic syndrome, and hemochromatosis. A serum sample for total testosterone determination should be obtained between 0700 and 1100 h. The most widely accepted parameters to establish the presence of hypogonadism is the measurement of serum total testosterone. There are no generally accepted lower limits of normal. There is, however, agreement that a total testosterone level above 12 nmol/l (350 ng/dl) does not require substitution (Wang et al. 2008; Bhasin et al. 2010). Similarly, based on the data of younger men, there is consensus that patients with serum total testosterone levels below 8 nmol/l (230 ng/dl) will usually benefit from testosterone treatment. If the serum total testosterone level is between 8 and 12 nmol/l, repeating the measurement of total testosterone with sex hormone-binding globulin (SHBG) to calculate total testosterone or free testosterone by equilibrium dialysis may be helpful. Measurements of serum luteinizing hormone will assist in differentiating between primary and secondary hypogonadism, and serum prolactin is indicated when the serum testosterone is lower than 5.2 nmol/l (150 ng/dl) or when secondary hypogonadism is suspected (Wang et al. 2008). Since there are known variations between assay methods, it is imperative that the practitioners utilize reliable laboratories and are acquainted with the reference ranges for testosterone from their local laboratory (Wang et al. 2008). Current immunometric methods for the measurement of testosterone can distinguish between hypogonadism and normal adult men. However, the methods based on mass spectrometry are more accurate and precise (Wang et al. 2008) and are increasingly recognized as the method of choice for serum testosterone measurement. The measurement of free or bioavailable testosterone should be considered when the serum total testosterone concentration is not diagnostic of hypogonadism, particularly in obese men. There are no generally accepted lower limits of normal for free testosterone for the diagnosis of hypogonadism. However, a free testosterone level below 225pmol/l (65 pg/ml) can provide supportive evidence for testosterone treatment (Wang et al. 2008). Threshold values for bioavailable testosterone

depend on the method used and are not generally available. Equilibrium dialysis is the gold standard for free testosterone measurement. Free testosterone assays based on analog displacement immunoassays are widely available but do not give an accurate measurement of free testosterone; thus, they should not be used (Wang et al. 2008). Alternately, measuring serum SHBG levels together with reliable serum total testosterone levels provides the data necessary for calculating free testosterone levels. Calculated free testosterone correlates well with free testosterone by equilibrium dialysis (Wang et al. 2008). Efforts to create standardization of testosterone assays, agreement on standards for testosterone measurement, and accurate reference ranges for testosterone by liquid chromatography–mass spectrometry (LC–MS)/MS are being developed. International reference standards, characterization of methodology, and population-based reference ranges for free testosterone by equilibrium dialysis are needed. Consensus on the equilibrium constants for testosterone binding to SHBG and albumin will allow improved calculation of free testosterone (Wang et al. 2008). Salivary testosterone has also been shown to be a reliable substitute for free testosterone measurements but cannot be recommended for general use at this time, since the methodology has not been standardized and adult male ranges are not available in most hospital or reference laboratories (Wang et al. 2008).

10.3 Benefits of Testosterone Replacement Therapy

10.3.1 General Aspects

There is abundant evidence that testosterone administration to hypogonadal men in adequate doses restores the manifestations of hypogonadism to normal. Hypogonadism affects many organ systems and biological functions of men. There may be beneficial effects on mood, energy level and patients' sense of well-being, sexual function, lean body mass and muscle strength, erythropoiesis and bone mineral density (BMD), cognition, and some benefits on cardiovascular risk factors. When it became clear that elderly men may suffer from a decline in serum testosterone amounting to hypogonadism, the question became pertinent whether these older men have similar benefits from restoring serum testosterone levels to the normal range as younger men do, and evidence is accumulating that this is indeed the case (Corona et al. 2013a, b).

10.3.2 Improving Metabolic Syndrome, Diabetes Type 2, and Cardiovascular Disease

It is now well established that hypogonadal men are more likely to suffer from metabolic syndrome (obesity, hypertension, dyslipidemia, impaired glucose regulation, and insulin resistance) (Shelton and Rajfer 2012; Grossmann 2014; Traish et al. 2013; Arafa et al. 2012; Garcia-Cruz et al. 2012). Testosterone concentrations are inversely related to mortality of all causes and also, more specifically, to cardiovascular diseases (Lin et al. 2011). A positive correlation between serum testosterone levels and insulin sensitivity has been found in men across the full spectrum of glucose tolerance (Pitteloud et al. 2005), and testosterone treatment improves insulin sensitivity (Corona et al. 2013a; Saad et al. 2012). There are now studies finding a favorable effect of testosterone on glycemic control, more so when combined with diet and exercise (Heufelder et al. 2009). These effects may be secondary to an increase in lean body mass and reduction of fat mass, explaining why these metabolic effects of testosterone treatment are only manifested after 6 months or more of treatment (Corona et al. 2013a; Garcia-Cruz et al. 2013). There has been a belief that testosterone administration would increase the incidence of cardiovascular disease. But a critical analysis through meta-analyses (Rao et al. 2013; Calof et al. 2005; Haddad et al. 2007; Carson and Rosano 2012) has concluded that an association between testosterone replacement and cardiac events cannot be proven. Most studies in men find either a favorable or neutral effect of normal testosterone levels

on cardiovascular pathology (Lin et al. 2011). It is safe to say that lower testosterone levels are associated with higher cardiovascular risk and to an extent with mortality in aging men (Shelton and Rajfer 2012), but adequately powered clinical trials are required to establish whether restoring testosterone to normal will indeed lead to a reduction of clinical end points such as morbidity and mortality from cardiovascular disease in men with lower-than-normal serum testosterone levels.

10.3.3 Bone Mineral Density

Hypogonadism is, both in older and younger men, associated with osteopenia, osteoporosis, and bone fractures (Meier et al. 2008). Testosterone deficiency doubles the prevalence of osteoporosis (Fink et al. 2006). Normal testosterone levels are pivotal for the development of normal bone mineral density (BMD) starting in puberty. Though hypogonadal men of all ages benefit from testosterone treatment with regard to building up bone mass, adult levels of bone mass are not always reached (Saggese et al. 1997). Further, it is critical that the doses of testosterone substitution are high enough (Aversa et al. 2012; Behre et al. 1997; Svartberg et al. 2008). In patients with prostate cancer undergoing androgen deprivation the risk of osteoporotic fracture clearly increases.

Part of androgen's effect on bone is indirect and mediated via aromatization of testosterone to estrogen (van den Beld et al. 2000; Michael et al. 2005).

The effects of testosterone occur slowly over several years, and the significance of restoring testosterone levels to normal in elderly men is rather difficult to demonstrate, but positive effects have been reported (Snyder et al. 1999; Svartberg et al. 2008). The pooled results of a meta-analysis suggest a beneficial effect on lumbar spine bone density and equivocal findings on femoral neck BMD (Tracz et al. 2006). Trials of intramuscular testosterone reported significantly larger effects on lumbar bone density than trials of transdermal testosterone (Aversa et al. 2012), particularly among patients receiving chronic glucocorticoids. None of the studies have been large enough to show clinical benefits, such as fracture risk reduction with testosterone replacement therapy.

10.3.4 Muscle Mass and Strength

When men age significant changes in body composition occur: a decrease in free fat mass and an increase and redistribution of fat mass, usually associated with functional limitations and increased morbidity (Bhasin 2003; Frontera et al. 2000). There is, independently of age, a correlation of maximal muscle strength with muscle mass (Reed et al. 1991). The age-related decline of testosterone levels is usually a factor in these changes. Testosterone has a direct effect on muscle, and it is also a factor in the expression of the effects of growth hormones on muscle via insulin-like growth factor-1. Both mechanisms lead to an increased synthesis of muscle protein and growth (Borst et al. 2014). Restoring serum testosterone to normal plays a potential role in reversing age-dependent body composition changes and associated morbidity (Hildreth et al. 2013). A large number of studies now document that treatment of hypogonadal men with testosterone improves body composition: an increase of lean body mass and a decrease of fat mass (Ferrando et al. 2003; Page et al. 2005; Harman and Blackman 2003; Svartberg et al. 2008; Aversa et al. 2010a, b). The net effect of the combination of an increase in lean body mass and a decrease of fat mass results often in no change in body weight. More significantly, grip strength improves upon testosterone treatment (Page et al. 2005; Sih et al. 1997; Morley et al. 1993). When men were treated with testosterone, skeletal muscle performance in elderly men with chronic heart failure improved (Caminiti et al. 2009), and there was prevention of loss of muscle strength of the lower limbs (Srinivas-Shankar et al. 2010). Less clear are changes in lower extremity muscle strength and physical function. But there are studies demonstrating effects of on muscle strength parameters of upper and lower extremities, manifested by leg

extensor strength and isometric hand grip strength (Perry et al. 2000). Functional parameters including the doors test, as well as "get up and go" test, and 5-chair sit/stand test improve upon normalization of testosterone (Breuer et al. 2001). There may be a potential role of testosterone in the management of frailty in elderly men (Srinivas-Shankar et al. 2010).

10.3.5 Improved Sexual Desire, Function, and Performance

The prevalence of erectile dysfunction increases markedly with age (Lyngdorf and Hemmingsen 2004; Selvin et al. 2007; Hamidi Madani et al. 2012). Serum-free testosterone is significantly correlated with the erectile and orgasmic function domains of the International Index of Erectile Function (IIEF) Questionnaire. Compared with younger men, elderly men may require higher levels of circulating testosterone for libido and erectile function (Schiavi and Rehman 1995; Gray et al. 2005). However, erectile dysfunction and/or diminished libido with or without testosterone deficiency might be related to other comorbidities or medications (Morales et al. 2004; Zitzmann et al. 2006; Tan et al. 2011; Isidori et al. 2014). Men with diminished libido and testosterone deficiency are candidates for testosterone therapy (Isidori et al. 2014). Long-term follow-up of testosterone replacement in hypogonadal males and a control group indicates that libido was significantly higher in the testosterone-treated group (Garcia-Cruz et al. 2013; Hajjar et al. 1997). Overviews of randomized controlled clinical trials indicate benefits of testosterone therapy on sexual health-related outcomes. Testosterone replacement has also been shown to enhance libido and the frequency of sexual acts and sleep-related erections (Shabsigh 1997; Morley et al. 1993).

A newer insight is that adequate testosterone treatment can restore anatomical defects of erectile tissue, such as venous leakage in the corpus cavernosum which is a frequent etiological factor in ED in elderly men (Yassin and Saad 2006; Traish 2009).

Transdermal testosterone replacement therapy, in particular, has been linked to positive effects on fatigue, mood, and sexual function, as well as significant increases in sexual activity (Meikle et al. 1996). In the presence of a clinical picture of testosterone deficiency and borderline serum testosterone levels, a short therapeutic trial of transdermal testosterone may be tried. There is evidence that the combined use of testosterone and phosphodiesterase type 5 inhibitors in hypogonadal or borderline eugonadal men has a synergetic effect (Shabsigh et al. 2004; Greenstein et al. 2005; Greco et al. 2006; Aversa et al. 2004; Buvat et al. 2011). The combination treatment should certainly be considered in hypogonadal patients with erectile dysfunction (ED) that failed to respond to either treatment alone. Testosterone produces this effect by enhancing the production of nitric oxide synthase and, in the longer term, restoring the substrate of penile erection.

10.3.6 Lower Urinary Tract Symptoms

Not only sexual function improves following testosterone treatment but also, contrary to traditional belief, urinary tract symptomatology/bladder functions by increasing bladder capacity and compliance and decreasing detrusor pressure at maximal flow in men with late-onset hypogonadism (Karazindiyanoglu and Cayan 2008; Haider et al. 2009; Francomano et al. 2014). There is now a belief that structures of the urogenital tract deteriorate when testosterone levels fall below normal. Further, not only the penis but also other parts of the urogenital tract are dependent on nitric oxide, which explains the beneficial effects of phosphordiesterase type 5 inhibitors on lower urinary tract symptoms (Brock et al. 2014).

10.3.7 Mood, Energy, and Quality of Life

Aging men whose serum testosterone levels decline often have a poorer quality of life and

complain of loss of libido, dysphoria, fatigue, and irritability (Seidman and Weiser 2013; Johnson et al. 2013). These combined complaints are similar to the signs and symptoms of depression. Indeed, studies have found an inverse correlation between bioavailable testosterone levels and depression in elderly men, independent of age and weight (Barrett-Connor et al. 1999b). These symptoms might be partially explained by the aging process, but the relationship of these symptoms with testosterone in men could be demonstrated following induced testosterone deficiency, and these depressive symptoms during the hypogonadal state could be reversed by testosterone replacement (Schmidt et al. 2004). Several studies in hypogonadal men show that testosterone replacement improves mood and well-being and reduces fatigue and irritability (Hackett et al. 2013). More specifically, when men suffer from the combination of metabolic syndrome and low testosterone levels, testosterone treatment leads to an improvement of depressive symptoms, aging male symptoms, and sexual dysfunction in hypogonadism. Remarkably, the beneficial effects of testosterone were more prominent in men with the lowest baseline total testosterone level (Giltay et al. 2010). An excess of visceral fat produces inflammatory factors which are factors in depression, and the effect of testosterone can be explained by the positive effects of testosterone on visceral fat (Giltay et al. 2010).

10.3.8 Cognitive Function

Higher bioavailable and free testosterone concentrations have each been associated with better performance in specific aspects of memory and cognitive function, with optimal processing capacity found in men ranging from 35 to 90 years of age, even after adjustment for potential confounders including age, educational attainment, and cardiovascular morbidity (Barrett-Connor et al. 1999a; Yaffe et al. 2002). Although the evidence from observational studies is not uniform, lower free testosterone appears to be associated with poorer outcomes on measures of cognitive function, particularly in older men, and testosterone therapy in hypogonadal men may have some benefit on cognitive performance.

10.3.9 Improving Anemia

Testosterone stimulates erythropoiesis. Men who are hypogonadal have a 10–20 % decrease in blood hemoglobin concentration, which can result in anemia (Spitzer et al. 2013; Spivak 2000; Coviello et al. 2008). Testosterone treatment increases red blood cell count and hemoglobin levels, which may also improve cardiovascular performance.

10.4 Safety of Testosterone Therapy

10.4.1 Prostate Pathology

There is, on the basis of traditional beliefs, a large degree of reservation with physicians to prescribe testosterone to men older than 50–60 years based on fears it will induce a malignancy of the prostate (Cooper and Page 2014). There may be also an element of legal accountability if such a cancer would develop in the course of testosterone administration. With and without testosterone administration, the likelihood of developing prostate cancer increases with age, simply because aging in itself is the strongest predictor of prostate malignancies. There are data in the recent literature that have put the potential development of prostate pathologies in a more rational perspective. It has not been found that testosterone administration to the elderly leads to a significant increase of lower urinary tract symptoms over its natural occurrence associated with aging (Calof et al. 2005; Grossmann et al. 2013). As indicated above, aging is a powerful predictor of occurrence of prostate cancer, and therefore it does not come as a surprise that prostate cancers have been reported after testosterone administration in (elderly) men, mostly in case reports (Rhoden and Morgentaler 2004). Systematic studies varying in design and formulations of testosterone over periods ranging from several months to 15 years

in men with a wide range of ages have failed to demonstrate an increase of the risk of developing prostate cancer (Morgentaler 2007). This was substantiated in a meta-analysis of studies of older men receiving testosterone treatment compared to placebo. These studies did not establish a higher risk of detection of prostate cancer (Calof et al. 2005). The credibility of this finding was strengthened by the much higher frequency of prostate biopsies in the men receiving testosterone than in the placebo group (Calof et al. 2005), thus increasing the probability of detecting a malignant process in the group treated with testosterone. At present, there are no data to prove that testosterone is the main culprit in the development or progression of malignancies of the prostate (Morgentaler and Schulman 2009; Morgentaler et al. 2011). In spite of this, many physicians do not feel confident in prescribing testosterone. They would only do so if the risk was close to zero, which is not the case because aging itself is a prominent predictor. Like in other domains of medicine, potential benefits must be rationally weighed against potential side effects (Khera et al. 2014). Another element in their trepidation is the fact that certain prostate cancers are treated with androgen ablation which makes it difficult to believe that androgen does not play a demonstrable role in cancer development. There are now several studies that demonstrate that the highest degrees of malignancies are found in men with relatively low serum testosterone (Morgentaler 2009).

It remains true that the prostate is an exquisitely sensitive organ to androgen action but as indicated above there are a number of recent insights showing that the traditional assumptions about the effects of testosterone on the prostate must be put in a radically new perspective (Morgentaler 2009). The saturation model postulates that with lower-than-normal circulating levels of testosterone, all androgen receptors are saturated. As a consequence, further increase in circulating levels of testosterone will lack the potential of further receptor-mediated androgen action on the prostate. Support for this theory comes from the observation that prostate disease (prostate cancer and benign prostate hyperplasia) usually occur in associated with age-related decline of circulating levels of testosterone, which renders it unlikely that these diseases must be primarily attributed to an excess of testosterone. But as indicated above, studies properly defining the safety of testosterone administration are still lacking but guidelines for monitoring have been developed (Bhasin et al. 2010; Wang et al. 2008) which, if rigorously applied, render testosterone treatment to be an acceptably safe therapy in men without (a prior history of) prostate cancer. Testosterone treatment of men who have had curative treatment of prostate cancer is presently evaluated (Morgentaler et al. 2011).

10.4.2 Hemoglobin and Hematocrit

Testosterone stimulates red blood cell formation, and its effects on hemoglobin and hematocrit are dose dependent (Wang et al. 2000). Relevant for this contribution is that this effect is more pronounced in elderly men (Coviello et al. 2008; Zitzmann and Nieschlag 2007; Ip et al. 2010). An elevated hematocrit is a risk factor for stroke and coronary heart disease but this has not been found by large meta-analyses of placebo-controlled trials of testosterone administration to (elderly) men (Calof et al. 2005; Fernandez-Balsells et al. 2010). In men receiving androgen administration hemoglobin levels and hematocrit must be monitored, and if necessary the dose of testosterone must be adjusted. Increases in hematocrit take place over the first 12–24 months of testosterone administration, thereafter values stabilize (Saad et al. 2011).

10.4.3 Cardiovascular Disease

Traditionally, it was believed that androgen was a factor in the etiology of cardiovascular disease (Schooling 2013). This belief was based on the skewed sex ratio of cardiovascular disease in men and women. But in recent times studies critically analyzing the relationship between androgen and cardiovascular disease have failed to demonstrate such a relationship (Traish et al. 2009; Traish and Kypreos 2011; Yeap 2014), though a report on testosterone administration to elderly frail men

by Basaria et al. (2010) has drawn new attention to the potential cardiovascular risks of testosterone, but this study has been criticized for a number of potential biases (Carson and Rosano 2012).

10.4.4 Sleep Apnea

Snoring and repetitive episodes of upper airway occlusion are characteristic of obstructive sleep apnea syndrome (OSAS) leading to hypoxemia and sleep fragmentation and excessive daytime sleepiness (Lopez-Jimenez et al. 2008). Loss of libido and erectile dysfunction are frequently encountered. (Hoekema et al. 2007). Patients are usually obese and suffer from metabolic syndrome (De Sousa et al. 2008), explaining their sexual dysfunction (Shabsigh et al. 2008). These patients have an increased risk of hypertension, arrhythmia, myocardial infarction, stroke, and sudden death. It is common to find lowered plasma testosterone levels (Barrett-Connor et al. 2008) since metabolic syndrome is associated with reduced plasma testosterone values. Similar to cardiovascular disease OSAS occurs more frequently in men than in women and therefore has been associated with testosterone. Indeed, one study administering supraphysiological doses of testosterone found that OSAS worsened (Liu et al. 2003). But over the last decade, studies on testosterone administration to elderly men have encountered worsening sleep apnea (Hoyos et al. 2012). In a large meta-analysis of placebo-controlled trials of testosterone administration to (elderly) men (Calof et al. 2005), the frequency of sleep apnea was not significantly different between men who received testosterone and placebo. But it is advisable to consider obstructive pulmonary disease in overweight persons or heavy smokers as a relative contraindication.

Conclusion

Aging is characterized by an accumulation of ailments such as osteoporosis, atherosclerosis, hypertension, cardiovascular disease, diabetes mellitus, lower urinary tract symptoms, and erectile dysfunction. Until a decade ago, these conditions were regarded as distinct diagnostic/therapeutic entities, but there is a growing recognition that these entities are not disparate but interdependent in their etiology and that they require an integral diagnostic and therapeutic approach. Testosterone deficiency is a common denominator. Measurement of testosterone should be a pivotal component in the diagnostic workup of men suffering from the above conditions. And, if warranted by clinical symptoms and laboratory findings, testosterone treatment should be given in addition to organ (system)-specific treatment. Traditionally, there has been a large degree of trepidation in administering testosterone to aging men for fear that testosterone treatment would worsen atherosclerosis resulting in cardiovascular disease, lower urinary tract symptoms, and malignant development of the prostate. These fears have not been substantiated in recent research.

Testosterone treatment of elderly men can be regarded as a responsible practice if certain guidelines phrased by professional scientific and clinical organizations are adhered to (Wang et al. 2008; Bhasin et al. 2010). This consensus is based on expert opinion and, therefore, must be periodically updated.

Supported by an unrestricted educational grant from BHC.

References

Arafa M, Zohdy W, Aboulsoud S, Shamloul R (2012) Prevalence of late-onset hypogonadism in men with type 2 diabetes mellitus. Andrologia 44(Suppl 1): 756–763

Aversa A, Isidori AM, Greco EA, Giannetta E, Gianfrilli D, Spera E, Fabbri A (2004) Hormonal supplementation and erectile dysfunction. Eur Urol 45(5):535–538

Aversa A, Bruzziches R, Francomano D, Rosano G, Isidori AM, Lenzi A, Spera G (2010a) Effects of testosterone undecanoate on cardiovascular risk factors and atherosclerosis in middle-aged men with late-onset hypogonadism and metabolic syndrome: results from a 24-month, randomized, double-blind, placebo-controlled study. J Sex Med 7(10):3495–3503

Aversa A, Bruzziches R, Francomano D, Spera G, Lenzi A (2010b) Efficacy and safety of two different testosterone undecanoate formulations in hypogonadal men with metabolic syndrome. J Endocrinol Invest 33(11): 776–783

Aversa A, Bruzziches R, Francomano D, Greco EA, Fornari R, Di Luigi L, Lenzi A, Migliaccio S (2012)

Effects of long-acting testosterone undecanoate on bone mineral density in middle-aged men with late-onset hypogonadism and metabolic syndrome: results from a 36 months controlled study. Aging Male 15(2): 96–102

Bagatell CJ, Heiman JR, Rivier JE, Bremner WJ (1994) Effects of endogenous testosterone and estradiol on sexual behavior in normal young men. J Clin Endocrinol Metab 78(3):711–716

Bancroft J (2005) The endocrinology of sexual arousal. J Endocrinol 186(3):411–427

Barrett-Connor E, Goodman-Gruen D, Patay B (1999a) Endogenous sex hormones and cognitive function in older men. J Clin Endocrinol Metab 84(10):3681–3685

Barrett-Connor E, Von Muhlen DG, Kritz-Silverstein D (1999b) Bioavailable testosterone and depressed mood in older men: the Rancho Bernardo study. J Clin Endocrinol Metab 84(2):573–577

Barrett-Connor E, Dam TT, Stone K, Harrison SL, Redline S, Orwoll E (2008) The association of testosterone levels with overall sleep quality, sleep architecture, and sleep-disordered breathing. J Clin Endocrinol Metab 93(7):2602–2609

Basaria S (2013) Reproductive aging in men. Endocrinol Metab Clin North Am 42(2):255–270

Basaria S, Coviello AD, Travison TG, Storer TW, Farwell WR, Jette AM, Eder R, Tennstedt S, Ulloor J, Zhang A, Choong K, Lakshman KM, Mazer NA, Miciek R, Krasnoff J, Elmi A, Knapp PE, Brooks B, Appleman E, Aggarwal S, Bhasin G, Hede-Brierley L, Bhatia A, Collins L, LeBrasseur N, Fiore LD, Bhasin S (2010) Adverse events associated with testosterone administration. N Engl J Med 363(2):109–122

Bassil N (2011) Late-onset hypogonadism. Med Clin North Am 95(3):507–523, x

Behre HM, Kliesch S, Leifke E, Link TM, Nieschlag E (1997) Long-term effect of testosterone therapy on bone mineral density in hypogonadal men. J Clin Endocrinol Metab 82(8):2386–2390

Behre HM, Christin-Maitre S, Morales AM, Tostain J (2012) Transversal European survey on testosterone deficiency diagnosis. Aging Male 15(2):69–77

Bhasin S (2003) Regulation of body composition by androgens. J Endocrinol Invest 26(9):814–822

Bhasin S, Buckwalter JG (2001) Testosterone supplementation in older men: a rational idea whose time has not yet come. J Androl 22(5):718–731

Bhasin S, Cunningham GR, Hayes FJ, Matsumoto AM, Snyder PJ, Swerdloff RS, Montori VM (2010) Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 95(6): 2536–2559

Black AM, Day AG, Morales A (2004) The reliability of clinical and biochemical assessment in symptomatic late-onset hypogonadism: can a case be made for a 3-month therapeutic trial? BJU Int 94(7):1066–1070

Borst SE, Yarrow JF, Conover CF, Nseyo U, Meuleman JR, Lipinska JA, Braith RW, Beck DT, Martin JS, Morrow M, Roessner S, Beggs LA, McCoy SC, Cannady DF, Shuster JJ (2014) Musculoskeletal and prostate effects of combined testosterone and finasteride administration in older hypogonadal men: a randomized, controlled trial. Am J Physiol Endocrinol Metab 306:E433–E442

Breuer B, Trungold S, Martucci C, Wallenstein S, Likourezos A, Libow LS, Zumoff B (2001) Relationships of sex hormone levels to dependence in activities of daily living in the frail elderly. Maturitas 39(2):147–159

Brock GB, McVary KT, Roehrborn CG, Watts S, Ni X, Viktrup L, Wong DG, Donatucci C (2014) Direct effects of tadalafil on lower urinary tract symptoms versus indirect effects mediated through erectile dysfunction symptom improvement: integrated data analyses from 4 placebo controlled clinical studies. J Urol 191(2):405–411

Buvat J, Montorsi F, Maggi M, Porst H, Kaipia A, Colson MH, Cuzin B, Moncada I, Martin-Morales A, Yassin A, Meuleman E, Eardley I, Dean JD, Shabsigh R (2011) Hypogonadal men nonresponders to the PDE5 inhibitor tadalafil benefit from normalization of testosterone levels with a 1 % hydroalcoholic testosterone gel in the treatment of erectile dysfunction (TADTEST study). J Sex Med 8(1):284–293

Calof OM, Singh AB, Lee ML, Kenny AM, Urban RJ, Tenover JL, Bhasin S (2005) Adverse events associated with testosterone replacement in middle-aged and older men: a meta-analysis of randomized, placebo-controlled trials. J Gerontol A Biol Sci Med Sci 60(11):1451–1457

Caminiti G, Volterrani M, Iellamo F, Marazzi G, Massaro R, Miceli M, Mammi C, Piepoli M, Fini M, Rosano GM (2009) Effect of long-acting testosterone treatment on functional exercise capacity, skeletal muscle performance, insulin resistance, and baroreflex sensitivity in elderly patients with chronic heart failure a double-blind, placebo-controlled, randomized study. J Am Coll Cardiol 54(10):919–927

Carson CC 3rd, Rosano G (2012) Exogenous testosterone, cardiovascular events, and cardiovascular risk factors in elderly men: a review of trial data. J Sex Med 9(1):54–67

Cattabiani C, Basaria S, Ceda GP, Luci M, Vignali A, Lauretani F, Valenti G, Volpi R, Maggio M (2012) Relationship between testosterone deficiency and cardiovascular risk and mortality in adult men. J Endocrinol Invest 35(1):104–120

Cooper LA, Page ST (2014) Androgens and prostate disease. Asian J Androl 16(2):248–255

Cornil CA, Ball GF, Balthazart J (2012) Rapid control of male typical behaviors by brain-derived estrogens. Front Neuroendocrinol 33(4):425–446

Corona G, Rastrelli G, Maggi M (2013a) Diagnosis and treatment of late-onset hypogonadism: systematic review and meta-analysis of TRT outcomes. Best Pract Res Clin Endocrinol Metab 27(4):557–579

Corona G, Vignozzi L, Sforza A, Maggi M (2013b) Risks and benefits of late onset hypogonadism treatment: an expert opinion. World J Mens Health 31(2): 103–125

Coviello AD, Kaplan B, Lakshman KM, Chen T, Singh AB, Bhasin S (2008) Effects of graded doses of

testosterone on erythropoiesis in healthy young and older men. J Clin Endocrinol Metab 93(3):914–919
De Sousa AG, Cercato C, Mancini MC, Halpern A (2008) Obesity and obstructive sleep apnea-hypopnea syndrome. Obes Rev 9(4):340–354
Feldman HA, Longcope C, Derby CA, Johannes CB, Araujo AB, Coviello AD, Bremner WJ, McKinlay JB (2002) Age trends in the level of serum testosterone and other hormones in middle-aged men: longitudinal results from the Massachusetts male aging study. J Clin Endocrinol Metab 87(2):589–598
Fernandez-Balsells MM, Murad MH, Lane M, Lampropulos JF, Albuquerque F, Mullan RJ, Agrwal N, Elamin MB, Gallegos-Orozco JF, Wang AT, Erwin PJ, Bhasin S, Montori VM (2010) Clinical review 1: adverse effects of testosterone therapy in adult men: a systematic review and meta-analysis. J Clin Endocrinol Metab 95(6):2560–2575
Ferrando AA, Sheffield-Moore M, Paddon-Jones D, Wolfe RR, Urban RJ (2003) Differential anabolic effects of testosterone and amino acid feeding in older men. J Clin Endocrinol Metab 88(1):358–362
Fillo J, Breza J, Levcikova M, Luha J, Vachulova A, Durdik S, Labas P (2012) Occurrence of erectile dysfunction, testosterone deficiency syndrome and metabolic syndrome in patients with abdominal obesity. Where is a sufficient level of testosterone? Int Urol Nephrol 44(4):1113–1120
Fink HA, Ewing SK, Ensrud KE, Barrett-Connor E, Taylor BC, Cauley JA, Orwoll ES (2006) Association of testosterone and estradiol deficiency with osteoporosis and rapid bone loss in older men. J Clin Endocrinol Metab 91(10):3908–3915
Francomano D, Ilacqua A, Bruzziches R, Lenzi A, Aversa A (2014) Effects of 5-year treatment with testosterone undecanoate on lower urinary tract symptoms in obese men with hypogonadism and metabolic syndrome. Urology 83(1):167–174
Frontera WR, Hughes VA, Fielding RA, Fiatarone MA, Evans WJ, Roubenoff R (2000) Aging of skeletal muscle: a 12-yr longitudinal study. J Appl Physiol 88(4):1321–1326
Garcia-Cruz E, Piqueras M, Huguet J, Perez-Marquez M, Gosalbez D, Peri L, Izquierdo L, Luque P, Ribal MJ, Alcaraz A (2012) Hypertension, dyslipidemia and overweight are related to lower testosterone levels in a cohort of men undergoing prostate biopsy. Int J Impot Res 24(3):110–113
Garcia-Cruz E, Leibar-Tamayo A, Romero J, Piqueras M, Luque P, Cardenosa O, Alcaraz A (2013) Metabolic syndrome in men with low testosterone levels: relationship with cardiovascular risk factors and comorbidities and with erectile dysfunction. J Sex Med 10(10):2529–2538
Giltay EJ, Tishova YA, Mskhalaya GJ, Gooren LJ, Saad F, Kalinchenko SY (2010) Effects of testosterone supplementation on depressive symptoms and sexual dysfunction in hypogonadal men with the metabolic syndrome. J Sex Med 7(7):2572–2582
Gooren LJ (1987) Androgen levels and sex functions in testosterone-treated hypogonadal men. Arch Sex Behav 16(6):463–473
Gray PB, Singh AB, Woodhouse LJ, Storer TW, Casaburi R, Dzekov J, Dzekov C, Sinha-Hikim I, Bhasin S (2005) Dose-dependent effects of testosterone on sexual function, mood, and visuospatial cognition in older men. J Clin Endocrinol Metab 90(7):3838–3846
Greco EA, Spera G, Aversa A (2006) Combining testosterone and PDE5 inhibitors in erectile dysfunction: basic rationale and clinical evidences. Eur Urol 50(5):940–947
Greenstein A, Mabjeesh NJ, Sofer M, Kaver I, Matzkin H, Chen J (2005) Does sildenafil combined with testosterone gel improve erectile dysfunction in hypogonadal men in whom testosterone supplement therapy alone failed? J Urol 173(2):530–532
Grossmann M (2014) Testosterone and glucose metabolism in men: current concepts and controversies. J Endocrinol 220:R37–R55
Grossmann M, Cheung AS, Zajac JD (2013) Androgens and prostate cancer; pathogenesis and deprivation therapy. Best Pract Res Clin Endocrinol Metab 27(4):603–616
Hackett G, Cole N, Bhartia M, Kennedy D, Raju J, Wilkinson P (2013) Testosterone replacement therapy with long-acting testosterone undecanoate improves sexual function and quality-of-life parameters vs. placebo in a population of men with type 2 diabetes. J Sex Med 10(6):1612–1627
Haddad RM, Kennedy CC, Caples SM, Tracz MJ, Bolona ER, Sideras K, Uraga MV, Erwin PJ, Montori VM (2007) Testosterone and cardiovascular risk in men: a systematic review and meta-analysis of randomized placebo-controlled trials. Mayo Clin Proc 82(1):29–39
Haider A, Gooren LJ, Padungtod P, Saad F (2009) Concurrent improvement of the metabolic syndrome and lower urinary tract symptoms upon normalisation of plasma testosterone levels in hypogonadal elderly men. Andrologia 41(1):7–13
Hajjar RR, Kaiser FE, Morley JE (1997) Outcomes of long-term testosterone replacement in older hypogonadal males: a retrospective analysis. J Clin Endocrinol Metab 82(11):3793–3796
Hamidi Madani A, Heidarzadeh A, Akbari Parsa N, Khosravi Darestani F, Hamidi Madani Z (2012) A survey on relative frequency of metabolic syndrome and testosterone deficiency in men with erectile dysfunction. Int Urol Nephrol 44(3):667–672
Harkonen K, Huhtaniemi I, Makinen J, Hubler D, Irjala K, Koskenvuo M, Oettel M, Raitakari O, Saad F, Pollanen P (2003) The polymorphic androgen receptor gene CAG repeat, pituitary-testicular function and andropausal symptoms in ageing men. Int J Androl 26(3):187–194
Harman SM, Blackman MR (2003) The effects of growth hormone and sex steroid on lean body mass, fat mass, muscle strength, cardiovascular endurance and adverse events in healthy elderly women and men. Horm Res 60(Suppl 1):121–124

Heufelder AE, Saad F, Bunck MC, Gooren L (2009) Fifty-two-week treatment with diet and exercise plus transdermal testosterone reverses the metabolic syndrome and improves glycemic control in men with newly diagnosed type 2 diabetes and subnormal plasma testosterone. J Androl 30(6):726–733

Hildreth KL, Barry DW, Moreau KL, Vande Griend J, Meacham RB, Nakamura T, Wolfe P, Kohrt WM, Ruscin JM, Kittelson J, Cress ME, Ballard R, Schwartz RS (2013) Effects of testosterone and progressive resistance exercise in healthy, highly functioning older men with low-normal testosterone levels. J Clin Endocrinol Metab 98(5):1891–1900

Ho CK, Beckett GJ (2011) Late-onset male hypogonadism: clinical and laboratory evaluation. J Clin Pathol 64(6):459–465

Hoekema A, Stel AL, Stegenga B, van der Hoeven JH, Wijkstra PJ, van Driel MF, de Bont LG (2007) Sexual function and obstructive sleep apnea-hypopnea: a randomized clinical trial evaluating the effects of oral-appliance and continuous positive airway pressure therapy. J Sex Med 4(4 Pt 2):1153–1162

Hoyos CM, Killick R, Yee BJ, Grunstein RR, Liu PY (2012) Effects of testosterone therapy on sleep and breathing in obese men with severe obstructive sleep apnoea: a randomized placebo-controlled trial. Clin Endocrinol (Oxf) 77(4):599–607

Huhtaniemi I (2014) Late-onset hypogonadism: Current concepts and controversies of pathogenesis, diagnosis and treatment. Asian J Androl 16:192–202

Huhtaniemi I, Forti G (2011) Male late-onset hypogonadism: pathogenesis, diagnosis and treatment. Nat Rev Urol 8(6):335–344

Ip FF, di Pierro I, Brown R, Cunningham I, Handelsman DJ, Liu PY (2010) Trough serum testosterone predicts the development of polycythemia in hypogonadal men treated for up to 21 years with subcutaneous testosterone pellets. Eur J Endocrinol 162(2):385–390

Isidori AM, Buvat J, Corona G, Goldstein I, Jannini EA, Lenzi A, Porst H, Salonia A, Traish AM, Maggi M (2014) A critical analysis of the role of testosterone in erectile function: from pathophysiology to treatment-a systematic review. Eur Urol 65(1):99–112

Jain P, Rademaker AW, McVary KT (2000) Testosterone supplementation for erectile dysfunction: results of a meta-analysis. J Urol 164(2):371–375

Johnson JM, Nachtigall LB, Stern TA (2013) The effect of testosterone levels on mood in men: a review. Psychosomatics 54(6):509–514

Karazindiyanoglu S, Cayan S (2008) The effect of testosterone therapy on lower urinary tract symptoms/bladder and sexual functions in men with symptomatic late-onset hypogonadism. Aging Male 11(3):146–149

Kelleher S, Conway AJ, Handelsman DJ (2004) Blood testosterone threshold for androgen deficiency symptoms. J Clin Endocrinol Metab 89(8):3813–3817

Khera M, Crawford D, Morales A, Salonia A, Morgentaler A (2014) A new era of testosterone and prostate cancer: from physiology to clinical implications. Eur Urol 65(1):115–123

Laurent M, Antonio L, Sinnesael M, Dubois V, Gielen E, Classens F, Vanderschueren D (2014) Androgens and estrogens in skeletal sexual dimorphism. Asian J Androl 16:213–222

Lin JW, Lee JK, Wu CK, Caffrey JL, Chang MH, Hwang JJ, Dowling N, Lin YS (2011) Metabolic syndrome, testosterone, and cardiovascular mortality in men. J Sex Med 8(8):2350–2360

Liu PY, Yee B, Wishart SM, Jimenez M, Jung DG, Grunstein RR, Handelsman DJ (2003) The short-term effects of high-dose testosterone on sleep, breathing, and function in older men. J Clin Endocrinol Metab 88(8):3605–3613

Lopez-Jimenez F, Sert Kuniyoshi FH, Gami A, Somers VK (2008) Obstructive sleep apnea: implications for cardiac and vascular disease. Chest 133(3):793–804

Lyngdorf P, Hemmingsen L (2004) Epidemiology of erectile dysfunction and its risk factors: a practice-based study in Denmark. Int J Impot Res 16(2):105–111

Meier C, Nguyen TV, Handelsman DJ, Schindler C, Kushnir MM, Rockwood AL, Meikle AW, Center JR, Eisman JA, Seibel MJ (2008) Endogenous sex hormones and incident fracture risk in older men: the Dubbo Osteoporosis Epidemiology Study. Arch Intern Med 168(1):47–54

Meikle AW, Arver S, Dobs A, Sanders SW, Mazer NA (1996) Androderm: a permeation-enhanced, nonscrotal testosterone transdermal system for the treatment of male hypogonadism. In: Bhasin S (ed) Pharmacology, biology, and clinical applications of androgens. Wiley Liss, Inc, New York, pp 449–457

Michael H, Harkonen PL, Vaananen HK, Hentunen TA (2005) Estrogen and testosterone use different cellular pathways to inhibit osteoclastogenesis and bone resorption. J Bone Miner Res 20(12):2224–2232

Morales A, Buvat J, Gooren LJ, Guay AT, Kaufman JM, Tan HM, Torres LO (2004) Endocrine aspects of sexual dysfunction in men. J Sex Med 1(1):69–81

Morales A, Schulman CC, Tostain J, Wu FC (2006) Testosterone Deficiency Syndrome (TDS) needs to be named appropriately–the importance of accurate terminology. Eur Urol 50(3):407–409

Morgentaler A (2007) Testosterone replacement therapy and prostate cancer. Urol Clin North Am 34(4):555–563

Morgentaler A (2009) Rapidly shifting concepts regarding androgens and prostate cancer. ScientificWorldJournal 9:685–690

Morgentaler A, Schulman C (2009) Testosterone and prostate safety. Front Horm Res 37:197–203

Morgentaler A, Lipshultz LI, Bennett R, Sweeney M, Avila D Jr, Khera M (2011) Testosterone therapy in men with untreated prostate cancer. J Urol 185(4):1256–1260

Morley JE, Perry HM 3rd, Kaiser FE, Kraenzle D, Jensen J, Houston K, Mattammal M, Perry HM Jr (1993) Effects of testosterone replacement therapy in old

hypogonadal males: a preliminary study. J Am Geriatr Soc 41(2):149–152
Nieschlag E, Behre HM, Bouchard P, Corrales JJ, Jones TH, Stalla GK, Webb SM, Wu FC (2004) Testosterone replacement therapy: current trends and future directions. Hum Reprod Update 10(5):409–419
O'Donnell AB, Araujo AB, McKinlay JB (2004) The health of normally aging men: the Massachusetts Male Aging Study (1987–2004). Exp Gerontol 39(7): 975–984
Page ST, Amory JK, Bowman FD, Anawalt BD, Matsumoto AM, Bremner WJ, Tenover JL (2005) Exogenous testosterone (T) alone or with finasteride increases physical performance, grip strength, and lean body mass in older men with low serum T. J Clin Endocrinol Metab 90(3):1502–1510
Perry HM 3rd, Miller DK, Patrick P, Morley JE (2000) Testosterone and leptin in older African-American men: relationship to age, strength, function, and season. Metabolism 49(8):1085–1091
Pitteloud N, Mootha VK, Dwyer AA, Hardin M, Lee H, Eriksson KF, Tripathy D, Yialamas M, Groop L, Elahi D, Hayes FJ (2005) Relationship between testosterone levels, insulin sensitivity, and mitochondrial function in men. Diabetes Care 28(7):1636–1642
Rao PM, Kelly DM, Jones TH (2013) Testosterone and insulin resistance in the metabolic syndrome and T2DM in men. Nat Rev Endocrinol 9(8):479–493
Reed RL, Pearlmutter L, Yochum K, Meredith KE, Mooradian AD (1991) The relationship between muscle mass and muscle strength in the elderly. J Am Geriatr Soc 39(6):555–561
Reyes-Vallejo L, Lazarou S, Morgentaler A (2007) Subjective sexual response to testosterone replacement therapy based on initial serum levels of total testosterone. J Sex Med 4(6):1757–1762
Rhoden EL, Morgentaler A (2004) Risks of testosterone-replacement therapy and recommendations for monitoring. N Engl J Med 350(5):482–492
Rochira V, Granata AR, Madeo B, Zirilli L, Rossi G, Carani C (2005) Estrogens in males: what have we learned in the last 10 years? Asian J Androl 7(1):3–20
Saad F, Aversa A, Isidori AM, Zafalon L, Zitzmann M, Gooren L (2011) Onset of effects of testosterone treatment and time span until maximum effects are achieved. Eur J Endocrinol 165(5):675–685
Saad F, Aversa A, Isidori AM, Gooren LJ (2012) Testosterone as potential effective therapy in treatment of obesity in men with testosterone deficiency: a review. Curr Diabetes Rev 8:131–143
Saggese G, Bertelloni S, Baroncelli GI (1997) Sex steroids and the acquisition of bone mass. Horm Res 48(Suppl 5):65–71
Schiavi RC, Rehman J (1995) Sexuality and aging. Urol Clin North Am 22(4):711–726
Schmidt PJ, Berlin KL, Danaceau MA, Neeren A, Haq NA, Roca CA, Rubinow DR (2004) The effects of pharmacologically induced hypogonadism on mood in healthy men. Arch Gen Psychiatry 61(10): 997–1004
Schooling CM (2013) Androgen activity, ischaemic heart disease and risk factors among men in NHANES III. Eur J Clin Invest 43(12):1273–1281
Seidman SN, Weiser M (2013) Testosterone and mood in aging men. Psychiatr Clin North Am 36(1):177–182
Selvin E, Burnett AL, Platz EA (2007) Prevalence and risk factors for erectile dysfunction in the US. Am J Med 120(2):151–157
Shabsigh R (1997) The effects of testosterone on the cavernous tissue and erectile function. World J Urol 15(1):21–26
Shabsigh R, Kaufman JM, Steidle C, Padma-Nathan H (2004) Randomized study of testosterone gel as adjunctive therapy to sildenafil in hypogonadal men with erectile dysfunction who do not respond to sildenafil alone. J Urol 172(2):658–663
Shabsigh R, Arver S, Channer KS, Eardley I, Fabbri A, Gooren L, Heufelder A, Jones H, Meryn S, Zitzmann M (2008) The triad of erectile dysfunction, hypogonadism and the metabolic syndrome. Int J Clin Pract 62(5):791–798
Shelton JB, Rajfer J (2012) Androgen deficiency in aging and metabolically challenged men. Urol Clin North Am 39(1):63–75
Sih R, Morley JE, Kaiser FE, Perry HM 3rd, Patrick P, Ross C (1997) Testosterone replacement in older hypogonadal men: a 12-month randomized controlled trial. J Clin Endocrinol Metab 82(6):1661–1667
Snyder PJ, Peachey H, Hannoush P, Berlin JA, Loh L, Holmes JH, Dlewati A, Staley J, Santanna J, Kapoor SC, Attie MF, Haddad JG Jr, Strom BL (1999) Effect of testosterone treatment on bone mineral density in men over 65 years of age. J Clin Endocrinol Metab 84(6):1966–1972
Spitzer M, Huang G, Basaria S, Travison TG, Bhasin S (2013) Risks and benefits of testosterone therapy in older men. Nat Rev Endocrinol 9(7):414–424
Spivak JL (2000) The blood in systemic disorders. Lancet 355(9216):1707–1712
Srinivas-Shankar U, Roberts SA, Connolly MJ, O'Connell MD, Adams JE, Oldham JA, Wu FC (2010) Effects of testosterone on muscle strength, physical function, body composition, and quality of life in intermediate-frail and frail elderly men: a randomized, double-blind, placebo-controlled study. J Clin Endocrinol Metab 95(2):639–650
Svartberg J, Agledahl I, Figenschau Y, Sildnes T, Waterloo K, Jorde R (2008) Testosterone treatment in elderly men with subnormal testosterone levels improves body composition and BMD in the hip. Int J Impot Res 20(4):378–387
Tajar A, Huhtaniemi IT, O'Neill TW, Finn JD, Pye SR, Lee DM, Bartfai G, Boonen S, Casanueva FF, Forti G, Giwercman A, Han TS, Kula K, Labrie F, Lean ME, Pendleton N, Punab M, Vanderschueren D, Wu FC (2012) Characteristics of androgen deficiency in late-onset hypogonadism: results from the European Male Aging Study (EMAS). J Clin Endocrinol Metab 97(5):1508–1516
Tan WS, Ng CJ, Khoo EM, Low WY, Tan HM (2011) The triad of erectile dysfunction, testosterone deficiency

syndrome and metabolic syndrome: findings from a multi-ethnic Asian men study (The Subang Men's Health Study). Aging Male 14(4):231–236

Tracz MJ, Sideras K, Bolona ER, Haddad RM, Kennedy CC, Uraga MV, Caples SM, Erwin PJ, Montori VM (2006) Testosterone use in men and its effects on bone health. A systematic review and meta-analysis of randomized placebo-controlled trials. J Clin Endocrinol Metab 91(6):2011–2016

Traish AM (2009) Androgens play a pivotal role in maintaining penile tissue architecture and erection: a review. J Androl 30(4):363–369

Traish AM, Kypreos KE (2011) Testosterone and cardiovascular disease: an old idea with modern clinical implications. Atherosclerosis 214(2):244–248

Traish AM, Saad F, Feeley RJ, Guay A (2009) The dark side of testosterone deficiency: III. Cardiovascular disease. J Androl 30(5):477–494

Traish AM, Miner MM, Morgentaler A, Zitzmann M (2011) Testosterone deficiency. Am J Med 124(7): 578–587

Traish AM, Haider A, Doros G, Saad F (2013) Long-term testosterone therapy in hypogonadal men ameliorates elements of the metabolic syndrome: an observational, long-term registry study. Int J Clin Pract. doi:10.1111/ijcp.12319

van den Beld AW, de Jong FH, Grobbee DE, Pols HA, Lamberts SW (2000) Measures of bioavailable serum testosterone and estradiol and their relationships with muscle strength, bone density, and body composition in elderly men. J Clin Endocrinol Metab 85(9):3276–3282

Wang C, Swerdloff RS, Iranmanesh A, Dobs A, Snyder PJ, Cunningham G, Matsumoto AM, Weber T, Berman N (2000) Transdermal testosterone gel improves sexual function, mood, muscle strength, and body composition parameters in hypogonadal men. J Clin Endocrinol Metab 85(8):2839–2853

Wang C, Nieschlag E, Swerdloff R, Behre HM, Hellstrom WJ, Gooren LJ, Kaufman JM, Legros JJ, Lunenfeld B, Morales A, Morley JE, Schulman C, Thompson IM, Weidner W, Wu FC (2008) Investigation, treatment and monitoring of late-onset hypogonadism in males: ISA, ISSAM, EAU, EAA and ASA recommendations. Eur J Endocrinol 159(5):507–514

Woodhouse LJ, Gupta N, Bhasin M, Singh AB, Ross R, Phillips J, Bhasin S (2004) Dose-dependent effects of testosterone on regional adipose tissue distribution in healthy young men. J Clin Endocrinol Metab 89(2): 718–726

Yaffe K, Lui LY, Zmuda J, Cauley J (2002) Sex hormones and cognitive function in older men. J Am Geriatr Soc 50(4):707–712

Yassin AA, Saad F (2006) Dramatic improvement of penile venous leakage upon testosterone administration. A case report and review of literature. Andrologia 38(1):34–37

Yeap BB (2014) Sex steroids and cardiovascular disease. Asian J Androl 16:239–247

Zitzmann M (2007) Mechanisms of disease: pharmacogenetics of testosterone therapy in hypogonadal men. Nat Clin Pract Urol 4(3):161–166

Zitzmann M, Nieschlag E (2007) Androgen receptor gene CAG repeat length and body mass index modulate the safety of long-term intramuscular testosterone undecanoate therapy in hypogonadal men. J Clin Endocrinol Metab 92:3844–3853

Zitzmann M, Faber S, Nieschlag E (2006) Association of specific symptoms and metabolic risks with serum testosterone in older men. J Clin Endocrinol Metab 91(11):4335–4343

Testosterone and Prostate Safety 11

Claude Schulman and Abraham Morgentaler

The great enemy of the truth is very often not the lie…. but the myth, persistent, persuasive and unrealistic John F. Kennedy

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11.1 Introduction

One of the major issues with testosterone (T) therapy (TTh) is the fear that raising serum T concentrations will result in an increased risk of prostate cancer (PCa) or will convert an occult cancer into a clinical one (Morgentaler 2006). This fear arises from the original work by Huggins and Hodges, who showed in 1941 that severe lowering of T by castration or estrogen therapy resulted in regression of advanced PCa and who reported also that T administration caused "enhanced growth" of PCa (Huggins and Hodges 1941). This work by Huggins established the androgen dependence of PCa and later earned him the Nobel Prize.

To this day, androgen deprivation therapy (ADT) remains a mainstay of treatment for men with advanced PCa, with rapid observable reductions in the serum marker, prostate specific antigen (PSA). In addition, it is well recognized that restoration of testosterone concentrations, such as by discontinuation of ADT during intermittent treatment (IADT), results in a rise in PSA in a substantial number of men. From these two current, clinical observations, it is easy to understand why clinicians would be concerned that T therapy might pose an increased risk of PCa. Curiously, clinical experience and scientific research fail to demonstrate an increased risk.

Nevertheless, most patients dying from metastatic PCa have castrate levels of T.

V. Mirone (ed.), *Clinical Uro-Andrology*,
DOI 10.1007/978-3-662-45018-5_11, © Springer-Verlag Berlin Heidelberg 2015

We will review the available evidence regarding the relationship of T and the prostate, with special attention to safety issues regarding PCa. Although there are as yet no large-scale, long-term controlled studies of T therapy to document its safety, there does exist a substantial literature examining this relationship and providing a rationale for why ADT causes PCa to regress, but T therapy does not appear to cause PCa to progress.

11.2 Testosterone Trials

In the absence of any single large study on T therapy, one must examine the results from smaller studies, many of which have examined PSA changes and PCa detection rates in trials of 12 months to 3.5 years.

One of these was a 12-month study of 371 men on T gel therapy (Dean et al. 2004). Over the course of 1 year, three cancers were detected, by a rise in PSA (<1 %). In this study the mean rise in PSA was 0.4 ng/ml. This increase was noted at 3 months, and PSA remained unchanged over the next 9 months.

Other studies have revealed a similar rate of cancer detection in T therapy trials. In a review of nine separate T therapy trials involving 579 men and ranging from 3–36 months, seven cancers were identified, representing a cancer detection rate of 1.2 % (Rhoden and Morgentaler 2006).

Wang et al. (2004) performed one of the longest T therapy trials. In this study, 163 men with a mean age of 51 years received T gel for 42 months. Over this time the mean PSA increased from 0.85 ng/ml at baseline to 1.1 ng/ml at 6 months and then did not change significantly over the next 3 years of the study. Three men were diagnosed with prostate cancer, representing a cancer rate of less than 1 % per year of treatment.

Finally, prostate cancer rates were investigated among men with and without the prostatic precancerous lesion represented by high-grade prostatic intraepithelial neoplasia (PIN). In this 12-month study, 75 men with hypogonadism received T therapy, including 55 men with benign pretreatment prostate biopsy and 20 men with biopsy revealing PIN (Rhoden and Morgentaler 2003). A similar 12-month increase in PSA of 0.3 ng/ml was seen in both groups, corresponding to a 15 % rise. A single cancer was detected, in the PIN group, representing an overall cancer rate of 1.3 %. The 5 % cancer rate among men with PIN compares to a 25 % risk over 3 years in this population, suggesting no significantly increased cancer risk.

One study that examined the effect of T therapy on PSA found that the overall change was mild, and the individual response varied considerably. Among 58 men who underwent T therapy for 1 year, the majority (32 men) demonstrated a mild PSA increase of 0.5 ng/ml or less (Rhoden and Morgentaler 2006). There were also 14 men with a PSA increase greater than 0.5 ng/ml but 12 men with a decline in PSA. No apparent differences in age, baseline T concentrations, or baseline PSA were noted between men with a PSA increase >0.5 ng/ml and men whose PSA declined.

To put these studies and their results in perspective, it is important to note that the observed PSA changes in multiple studies of approximately 15–20 % is not much greater than the 13 % increase noted over 1 year in 50–60-year-old men participating in the placebo arm of an unrelated study (D'Amico and Roehrborn 2007). In addition, the annual cancer rate of approximately 1 % that shows up repeatedly in T therapy trials compares favorably to cancer detection rates in men undergoing prostate cancer screening (Rhoden and Morgentaler 2004).

Perhaps most importantly, two studies involving more than 400 men in total have shown that hypogonadal men with PSA of 4.0 ng/ml or less have a biopsy-detectable cancer rate of approximately 15 % (Morgentaler et al. 1996; Morgentaler and Rhoden 2006). If one in seven men with low T has PCA, and if raising T truly caused PCa to grow more rapidly, logic would suggest that T therapy trials should be associated with a much higher rate of prostate cancer.

11.3 Longitudinal Studies

The relationship of T and other sex hormones to subsequent development of PCa has been extensively studied, in at least 16 population-based

longitudinal studies (Hsing 2001; Eaton et al. 1999; Stattin et al. 2004; Barrett-Connor et al. 1990; Parsons et al. 2005; Gann et al. 1996). In these studies, a health history is obtained, and blood samples at baseline are then frozen for the duration of the study, in some cases up to 20 years or longer. At the end of the study, men who have developed PCa are identified, and a matched set of men without PCa serve as controls.

A total of greater than 430,000 men have been included in these studies, including 1,400 men with PCa and 4,400 men identified as controls. Not one study has shown a direct correlation between total testosterone levels and PCa. Isolated associations have been reported with some measures and PCa: minor androgens in one (Barrett-Connor et al. 1990), calculated free testosterone in another (Parsons et al. 2005), and with quartile analysis of hormone ratios or controlling for multiple variables in a third (Gann et al. 1996). None of these positive associations have been supported by later studies. It is worth noting that the largest study of this type actually noted *reduced* PCa risk in men with higher T levels (Stattin et al. 2004).

The importance of these studies is that they provide a sophisticated method of investigation to determine the long-term effects of endogenous hormone levels, especially testosterone, on the subsequent risk of development of PCa. Although such studies cannot entirely replace the value of a prospective long-term controlled study of T therapy, they do address the question as to whether high levels of T (or other hormones) predispose men to a greater risk of later development of PCa. On this question these prospective longitudinal studies provide two uniform and convincing answers – first, that men who develop PCa do not have higher baseline T levels, and second, men with higher T levels are at no greater risk of developing PCa than men with lower T concentrations.

11.4 Resolving the Paradox

How is it possible that androgen deprivation and its discontinuation can have such a powerful effect on advanced prostate cancer growth, yet T therapy trials appear to have little impact on PCa risk or even PSA?

The answer is provided by a recent landmark study by Marks et al. (2006). In this randomized, placebo-controlled, double-blind trial, 40 men with hypogonadism underwent prostate biopsy and comprehensive evaluation at baseline and after 6 months of injections of T or placebo every 2 weeks. Despite large changes in serum T concentrations, the intraprostatic concentrations of both T and dihydrotestosterone (DHT) did not change significantly. Furthermore, no changes were noted in expression of androgen-related genes or genes associated with prostatic proliferation. These results indicate that substantial changes in serum androgens are not reflected within the prostate and do not appear to induce biological changes within prostate tissue.

This study provides scientific evidence supporting the concept of saturation of the prostate androgen receptors with regard to T, as proposed recently (Morgentaler 2007a). In this saturation model, at the extreme low end of T concentrations, there is a profound influence of T on prostate growth, yet at higher T concentrations this influence appears to be marginal, if present at all. Fowler and Whitmore lay the groundwork for this model in their 1981 report detailing the effect of T administration in men with metastatic PCa (Fowler and Whitmore 1981). They noted that T administration resulted in rapid and near-universal PCa progression in men who had undergone prior androgen ablation, but not in men without prior hormonal manipulation of metastatic PCa. The authors concluded that naturally occurring endogenous T concentrations may be sufficient to produce "near maximal stimulation" of PCa. This concept is supported by the study of Marks et al. (2006) and describes the essence of the saturation model.

11.5 Low T and Prostate Cancer

As clinicians have begun to let go of the old belief that raising T would necessarily increase PCa risk, there has been a coincidental recognition that low T may itself represent a risk factor

for PCa. There is now emerging data that testosterone deficiency is associated with greater risk of PCa, high Gleason scores, worse stage at presentation, and worse survival (Morgentaler 2007b).

A study of 345 men with hypogonadism and PSA levels of 4.0 ng/ml or less found that the group of men in the lowest tertile of total T had more than double the risk of cancer on biopsy compared with men in the highest tertile (OR, 2.15; 95 % CI, 1.01–4.55) (Morgentaler and Rhoden 2006). In another study of 326 men who underwent radical prostatectomy, pretreatment T concentrations correlated with the likelihood of organ-confined disease (Isom-Batz et al. 2005). In addition, there is now evidence correlating high Gleason scores with low T (Hoffman et al. 2000). What these findings mean is that there is growing evidence that men with low T diagnosed with prostate cancer are more likely to have positive margins in their prostate specimens and higher Gleason grades, and men with higher T were more likely to have negative margins and less aggressive disease.

11.6 Testosterone Therapy After Diagnosis of Prostate Cancer

The growing number of men who appear to be cured from PCa after definitive therapy has created pressure to consider T therapy in those men who are symptomatic from testosterone deficiency. Although this has been a long-standing taboo, clinical experience with T therapy together with the scientific evidence reviewed in this chapter suggests this may be far less risky than had previously been assumed. Results from several small studies suggest that T therapy may be used, with caution and in a carefully selected population, after PCa has been successfully treated.

The first of these was a small series of seven cases in which T therapy was provided to symptomatic hypogonadal men who had undergone radical prostatectomy and who had an undetectable postoperative PSA (Kaufman and Graydon 2004). No recurrences were noted in these men despite 1–12 years of T therapy in these men.

A second study reported similar reassuring results in ten men who had also undergone radical prostatectomy with undetectable PSA (Agarwal and Oefelein 2005). Mean total T increased from 197 ng/dl to 591 ng/dl, and symptoms of hypogonadism improved. Most importantly, no PCa recurrences were noted with a median follow-up of 19 months.

A third study reported results in 31 men who received T therapy after PCa treatment with brachytherapy (Sarosdy 2007). In this group the median duration of treatment was 4.5 years with a range of 0.5–8.5 years. Total T concentrations rose from a median of 188 to 498 ng/dL. No recurrences or PCa progression was noted, and all men remained with PSA less than 1.0 ng/ml at the end of the study.

The largest series to date of TTh in men after radical prostatectomy was reported by Pastuszak et al., who evaluated 103 hypogonadal men (77 low/intermediate risk and 26 high risk) who received TTh after RP and compared biochemical recurrences to 49 eugonadal controls (35 low/intermediate risk and 15 high risk) (Pastuszak et al. 2013a). High risk was defined as GL $\geq$8, positive margins, and positive lymph nodes. After a median of 27.5 months of follow-up, there were four biochemical recurrences (4 %) in the TTh group versus 8 (16 %) in the non-TTh group.

A number of reports have provided information regarding the outcomes of TTh in men with PCa after radiation treatment. Sarosdy et al. reported no biochemical recurrences among 31 men treated with TTh after brachytherapy, with a median duration of treatment of 4.5 years (25). Two published studies have reported results in which TTh was offered after external beam radiation for PCa. Morales et al. reported no biochemical recurrences in five men with up to 27 months follow-up (Morales et al. 2009). Pastuszak et al. reported no recurrences in 13 additional men with median follow-up of 29.7 months (Pastuszak et al. 2013b).

Perhaps most provocative of all is the use of TTh in men with untreated PCa, such as men undergoing active surveillance for low-risk PCa. Morgentaler et al. reported on TTh in 13 such men, with mean duration of treatment of 2.5 years.

All men underwent follow-up prostate biopsies, an average of two sets of biopsies per individual. No change with TTh was noted for mean serum PSA or prostate volume, and none of the men demonstrated cancer progression. Follow-up biopsies revealed no cancer in 54 % of cases.

These clinical series provide some reassurance to physicians who wish to relieve the symptoms of hypogonadal men with T therapy following definitive treatment of localized prostate cancer. However, determination of the true safety of this approach will require time and much larger studies (Isbarn et al. 2009).

11.7 Effects of Testosterone Therapy on the Benign Prostate

In addition to concerns regarding PCa, there have also been concerns that T therapy may cause exacerbation of lower urinary tract symptoms due to growth of the benign prostate, since the benign prostate is also under androgenic control. However, all available data indicates that any negative clinical impact on the benign prostate is minor and infrequent (Wang et al. 2004; Rhoden and Morgentaler 2004). Multiple studies have shown that T therapy is associated with only a mild increase in prostate volume as measured by transrectal ultrasound. In addition, studies consistently show no changes in uroflow rate, postvoid residual urine, and no changes in mean voiding symptoms as measured by the International Prostate Symptom Score (Wang et al. 2004; Rhoden and Morgentaler 2004).

Conclusion

Although we still lack a large-scale controlled study to definitively assess the safety of T therapy, it is becoming increasingly clear that this treatment poses little clinical risk of PCa in the short to midterm. The reasons for the historical concern that T therapy may cause PCa progression are easy to understand given the androgen dependence of PCa and the dramatic effect of ADT in advanced metastatic prostate cancer although most men dying from PCa have castrate levels of T, yet this concern is belied by clinical experience and scientific investigations. Specifically, T therapy trials of up to 42 months as well as more than a dozen longitudinal population-based studies have consistently shown no increased PCa risk associated with higher T levels.

The explanation for the lack of PCa progression with higher T appears to be that prostate tissue is saturated with regard to T at a relatively low serum T concentration, and additional T beyond this saturation point is not reflected by intraprostatic concentrations of androgens. Recent small studies suggest that T therapy may even be a reasonable treatment for men who have undergone definitive treatment for localized prostate cancer, a group for whom such treatment was considered taboo only a few years ago. The long-standing belief that higher serum androgen concentrations cause ever-increasing rates of PCa growth, termed the androgen hypothesis, can no longer be accepted in the face of large amounts of contradictory evidence. In its place, we see that PCa is indeed sensitive to changes in serum T at the very low end of the range of T concentrations and becomes indifferent to changes in serum T at higher concentrations (Morgentaler 2012).

On the other hand, there is now growing awareness that low T may itself be a risk for PCa and may portend worrisome consequences once PCa is diagnosed. It will be fascinating to see what other changes come to pass over the next few years in this rapidly changing field.

References

Agarwal PK, Oefelein MG (2005) Testosterone replacement therapy after primary treatment for prostate cancer. J Urol 173:533–536

Barrett-Connor E, Garland C, McPhillips JB, Khaw KT, Wingard DL (1990) A prospective, population-based study of androstenedione, estrogens, and prostatic cancer. Cancer Res 50:169–173

D'Amico AV, Roehrborn CG (2007) Effect of 1 mg/day finasteride on concentrations of serum prostate-specific antigen in men with androgenic alopecia: a randomised controlled trial. Lancet Oncol 8:21–25

Dean JD, Carnegie C, Rodzvilla J, Smith T (2004) Long-term effects of Testim 1 % testosterone gel in hypogonadal men. Rev Urol 6:S22–S29

Eaton NE, Reeves GK, Appleby PN, Key TJ (1999) Endogenous sex hormones and prostate cancer: a quantitative review of prospective studies. Br J Cancer 80:930–934

Fowler JE, Whitmore WF Jr (1981) The response of metastatic adenocarcinoma of the prostate to exogenous testosterone. J Urol 126:372–375

Gann PH, Hennekens CH, Ma J, Longcope C, Stampfer MJ (1996) Prospective study of sex hormone levels and risk of prostate cancer. J Natl Cancer Inst 88: 1118–1126

Hoffman MA, DeWolf WC, Morgentaler A (2000) Is low serum free testosterone a marker for high grade prostate cancer? J Urol 163(3):824–827

Hsing AW (2001) Hormones and prostate cancer: what's next? Epidemiol Rev 23:42–58

Huggins C, Hodges CV (1941) Studies on prostatic cancer: I. The effect of castration, of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. Cancer Res 1: 293–297

Isbarn H, Pinthus JH, Marks LS, Montorsi F, Morales A, Morgentaler A, Schulman C (2009) Testosterone and prostate cancer: revisiting old paradigms. Eur Urol 56:48–56

Isom-Batz G, Bianco FJ Jr, Kattan MW, Mulhall JP, Lilja H, Eastham JA (2005) Testosterone as a predictor of pathological stage in clinically localized prostate cancer. J Urol 173:1935–1937

Kaufman JM, Graydon RJ (2004) Androgen replacement after curative radical prostatectomy for prostate cancer in hypogonadal men. J Urol 172:920–922

Marks LS, Mazer NA, Mostaghel E et al (2006) Effect of testosterone replacement therapy on prostate tissue in men with late-onset hypogonadism: a randomized controlled trial. JAMA 296:2351–2361

Morales A, Black AM, Emerson LE (2009) Testosterone administration to men with testosterone deficiency syndrome after external beam radiotherapy for localized prostate cancer: preliminary observations. BJU Int 103:62–64

Morgentaler A (2006) Testosterone and prostate cancer: an historical perspective on a modern myth. Eur Urol 50:935–939

Morgentaler A (2007a) Testosterone replacement therapy and prostate cancer. Urol Clin N Am 34:555–563

Morgentaler A (2007b) Testosterone deficiency and prostate cancer: emerging recognition of an important and troubling relationship. Eur Urol 52:623–625

Morgentaler A (2012) Goodbye androgen hypothesis, hello saturation model. Eur Urol 62:765–767

Morgentaler A, Rhoden EL (2006) Prevalence of prostate cancer among hypogonadal men with prostate-specific antigen of 4.0 ng/ml or less. Urology 68:1263–1267

Morgentaler A, Bruning CO III, DeWolf WC (1996) Incidence of occult prostate cancer among men with low total or free serum testosterone. JAMA 276: 1904–1906

Parsons JK, Carter HB, Platz EA, Wright EJ, Landis P, Metter EJ (2005) Serum testosterone and the risk of prostate cancer: potential implications for testosterone therapy. Cancer Epidemiol Biomarkers Prev 14:2257–2260

Pastuszak AW, Pearlman AM, Lai WS et al (2013a) Testosterone replacement therapy in patients with prostate cancer after radical prostatectomy. J Urol 190: 639–644

Pastuszak AW, Pearlman AM, Godoy G et al (2013b) Testosterone replacement therapy in the setting of prostate cancer treated with radiation. Int J Impot Res 25:24–28

Rhoden EL, Morgentaler A (2003) Testosterone replacement therapy in hypogonadal men at high risk for prostate cancer: results of 1 year of treatment in men with prostatic intraepithelial neoplasia. J Urol 170: 2348–2351

Rhoden EL, Morgentaler A (2004) Risks of testosterone-replacement therapy and recommendations for monitoring. N Engl J Med 350:482–492

Rhoden EL, Morgentaler A (2006) Influence of demographic factors and biochemical characteristics on the prostate-specific antigen (PSA) response to testosterone replacement therapy. Int J Impot Res 18:201–205

Sarosdy MF (2007) Testosterone replacement for hypogonadism after treatment of early prostate cancer with brachytherapy. Cancer 109:536–541

Stattin P, Lumme S, Tenkanen L et al (2004) High levels of circulating testosterone are not associated with increased prostate cancer risk: a pooled prospective study. Int J Cancer 108:418–424

Wang C, Cunningham G, Dobs A et al (2004) Long-term testosterone gel (AndroGel) treatment maintains beneficial effects on sexual function and mood, lean and fat mass, and bone density in hypogonadal men. J Clin Endocrinol Metab 89:2085–2098

Male Factors in Couple's Infertility

12

G.R. Dohle

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12.1 Introduction: Aetiology and Prevalence

Infertility is defined as the absence of spontaneous pregnancy after 1 year of unprotected intercourse. About 15 % of couples with an active wish for children do not achieve a pregnancy within 1 year. Half of these couples will have a spontaneous pregnancy in the next year; eventually 4 % of couples will remain unwillingly childless (Rowe et al. 1993).

The main causes and associated factors of male infertility are listed in Table 12.1.

12.2 Testicular Insufficiency

The most common cause of male infertility is testicular dysfunction. This dysfunction can be of congenital origin or acquired later in life. Maldevelopment of the testes (dysgenesis) during early pregnancy can result in cryptorchidism, primary hypogonadism and impaired spermatogenesis later in life. These men also have an increased risk for testicular malignancies. Severe forms of testicular dysgenesis syndrome (TDS, Skakkebaek et al. 2001) may also be accompanied by other genital malformations, such as hypospadias and anogenital malformations. The cause of TDS is unknown: both genetic factors and environmental influences are suggested, especially elevated levels of (pseudo-) estrogens and antiandrogens in early pregnancy. Many genes

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V. Mirone (ed.), *Clinical Uro-Andrology*,
DOI 10.1007/978-3-662-45018-5_12, © Springer-Verlag Berlin Heidelberg 2015

Table 12.1 Main causes and associated factors of male infertility

Testicular insufficiency
Congenital
Testicular dysgenesis syndrome (TDS)
Acquired
(Viral) Orchitis/epididymo-orchitis
Testicular torsion
Cytotoxic therapy (chemotherapy)
Radiation therapy
Genetic abnormalities
Cyrogenetic abnormalities, Klinefelter's syndrome, Y-chromosomal deleties, CFTR gene mutaties
Endocrine abnormalities: *hypogonadotropic hypogonadism* (*low LH and FSH*)
Primary forms: Kallmann's syndrome, idiopathic congenital hypogonadotropic hypogonadism
Secondary forms: Pituitary dysfunction (adenoma, infection, haemochromatosis, drugs)
Anabolic steroids
Morbid obesity
Obstructions of the seminal pathway
Congenital bilateral absence of the vas deferens (CBAVD)
Midline prostatic cysts
Epididymal obstruction
Obstruction caused by previous scrotal and inguinal surgery
Urogenital infections/male accessory gland infection
Other causes
Sperm antibodies
Drugs
Chronic disease
Varicocele
Sexual problems
Ejaculatory dysfunction
Idiopathic male infertility (*30–40 %*)

are involved in gonadal development, including the sex region of the Y chromosome (SRY gene, Rey and Grinspon 2011). Polymorphisms of these genes may increase the chance of testicular dysgenesis.

Men with TDS present with small size testes, elevated FSH and LH, low testosterone and abnormal semen quality. On scrotal ultrasound examination testicular microcalcifications can be found and an inhomogeneous parenchyma of the testes. Severe forms of TDS are associated with testicular atrophy and non-obstructive azoospermia.

Acquired forms of testicular insufficiency are less common and can be the result of testicular torsion, testicular trauma, urogenital infections (epididymo-orchitis) and cancer treatment (chemotherapy and irradiation). Chronic diseases may influence spermatogenesis, either directly or by influencing the production of reproductive hormones.

12.3 Genetic Abnormalities

Male infertility can be the result of chromosomal defects, DNA mutations and deletions in genes involved in spermatogenesis. Cytogenetic abnormalities are present in 2–4 % of men with oligozoospermia and in 15 % of men with non-obstructive azoospermia. The most common example of a cytogenetic abnormality that causes male infertility is Klinefelter's syndrome (47, XXY karyotype, Rey and Grinspon 2011). This occurs in about 1:500 men. Klinefelter patients have atrophic testis and usually present with male infertility due to azoospermia. Mosaic Klinefelter patients (46, XY/47, XXY) may have severe oligozoospermia. It is suggested that the disturbance in spermatogenesis in men with Klinefelter's syndrome is progressive from puberty on. During adolescence spermatozoa may still be found in the testes; in older Klinefelter patients spermatogenesis is usually absent. Some Klinefelter patients have a typical eunuchoid body composition as a consequence of primary hypogonadism, including gynaecomastia and a tall stature. Klinefelter patients may need testosterone supplementation later in life.

Deletions of the azoospermic factor gene (AZF gene Reijo et al. 1995, Krausz 2009) on the long arm of the Y chromosome are associated with severe oligozoospermia and azoospermia. These are de novo deletion which will be passed on to the sons of these men, if a pregnancy can be obtained through intracytoplasmic sperm injection (ICSI). They are present in 2–4 % of men with less than five million spermatozoa per ml and in 13–15 % of men with non-obstructive azoospermia.

Mutations of the gene involved in cystic fibrosis (CFTR gene, De Braekeleer and Ferec 1996) can

result in maldevelopment of the epididymis, vas deferens and the seminal vesicles, resulting in obstructive azoospermia. These men present with bilateral absence of the vas deferens and have azoospermia with a low seminal volume (<1 ml) and a low seminal Ph (<7.0), due to the absence of fluid from the seminal vesicles. The gene defect can be passed on to the children of these men and may result in a child with some form of cystic fibrosis.

12.4 Hypogonadotropic Hypogonadism

A less common cause of male infertility is endocrine dysfunction. This also can be congenital and acquired. A congenital form of hypogonadotropic hypogonadism is Kallmann's syndrome with a prevalence of 1:10,000 men, characterised by the absence of gonadotropins (LH and FSH) (Behre et al. 2010). The testes of the men will not develop properly from puberty on (hypogonadism) due to the absence of LH and FSH. Spermatogenesis is absent. Delayed puberty and hypogonadism can be treated in these boys by weekly injections of gonadotropins (HCG/HMG or rFSH).

Acquired hypogonadotropic hypogonadism can be the result of pituitary dysfunction (adenoma, infection, haemochromatosis, drugs). Tumours of the pituitary (prolactinoma's, Bolyakov and Paduch 2011) should be ruled out in men with unexplained hypogonadotropic hypogonadism: a CT-scan or MRI of the pituitary (sella) region is recommended.

A suppression of reproductive hormones can occur in men taking testosterone, especially in a supraphysiological dose (anabolic steroids, Turek et al. 1995). This temporarily affects spermatogenesis and can result in infertility. It may take several months to more than 1 year before the hypothalamus and the pituitary resume their normal production of gonadotropins in these men, depending on the amount and duration of the testosterone abuse.

Obesity can also influence male infertility: the enzyme aromatase, abundantly present in fatty tissue, converts testosterone into estradiol. Estrogens suppress the production of LH and FSH. Normalisation of body weight next to eating healthy food is an important lifestyle advise for these men that can help them in improving their semen quality (Teerds et al. 2011).

12.5 Obstructions of the Seminal Pathway

Obstructions of the male genital tract occur in 10–15 % of infertile men. These men present with either severe oligozoospermia or azoospermia, normal size testes and normal gonadotropins. About 1 % of men with obstructive azoospermia have congenital bilateral absence of the vas deferens (CBAVD, Yu et al. 2012), a minor form of cystic fibrosis. Other congenital obstructions of the seminal path can occur in the epididymis and in the prostate (Practice Committee of American Society for Reproductive Medicine in collaboration with Society for Male Reproduction and Urology 2008). Obstructions of the ejaculatory ducts are characterised by low seminal volume and azoospermia. Transrectal ultrasound of the prostate and seminal vesicles is indicated in these men.

Acquired obstructions of the male genital tract are mainly due to previous scrotal and inguinal surgery and urogenital infection. Hernia repair, hydrocelectomy and vasectomy are common examples of this type of male infertility. Surgical repair with sperm harvesting and cryopreservation is advised as the primary management of these obstructions.

12.6 Urogenital Infections

Colonisation of the male genital tract is probably common and usually self-limiting. The male accessory sex glands often harbour microorganisms, like ureaplasma and chlamydia trachomatis, which may colonise the urogenital tract without obvious signs of infection (Purvis and Christiansen 1993). Occasionally, these microorganisms and other bacteria cause symptomatic urethritis, prostatovesiculitis and epididymitis, with deterioration of the semen quality and leucocytospermia.

A history of urogenital infection occurs in 1.6–10.3 % of men attending fertility clinics. Infection may have a detrimental effect on sperm quality by reducing forward motility and possibly affecting the number of morphological normal spermatozoa. In addition, infections may be the source of autoantibodies against spermatozoa, found in about 8 % of the infertile male population. Leucocytes may produce large amounts of reactive oxygen species and cytokines, directly effecting sperm motility and fertilising capacity.

Semen quality can be reduced mainly by the production of ROS from leucocytes, especially in the epididymis. ROS is known to produce DNA damage in spermatozoa (Zini and Dohle 2011). Exposure time of ROS, especially in the epididymis, is long enough to cause permanent damage to the spermatozoa and thus impair spontaneous conception rates. Some bacteria may cause a chronic infection of the prostate and the epididymis, resulting in (partial) obstruction of the ejaculatory ducts with low seminal volume and oligozoospermia (Dohle 2003). Treatment can eradicate bacteria in the accessory glands, but leucocytes and ROS production may continue to be produced and infertility will persist.

12.7 Varicoceles

Varicocele is a dilatation of the veins of the spermatic cord due to reflux of blood from the spermatic vein in an upright position. It is usually left sided but occurs bilaterally in about 15 % of cases (Dubin and Amelar 1977). Varicoceles are found in 11.7 % of men with normal semen but is more common in men with fertility problems, affecting 25.4 % of those with abnormal semen. Analysis of the WHO data of 3,468 men attending a fertility clinic indicated that varicocele is related to semen abnormalities, decreased testicular volume and a decline in Leydig cell function (WHO study- no authors listed 1992). The mechanism by which a varicocele influence male fertility is still unknown, but it is suggested that the impairment of semen in men with a varicocele is due to increased scrotal temperature, impaired blood drainage from the testis and reflux of metabolites, which all may cause a reduction in testicular growth and function. In some men the presence of varicocele is associated with progressive testicular damage from adolescence onwards and consequent reduction in fertility (Baazeem et al. 2011).

A recent meta-analysis of randomised controlled trials and observational studies showed that surgical varicocelectomy significantly improves semen parameters in men with abnormal semen but only in men with a clinical varicocele (Argawal et al. 2007). There is however an ongoing discussion on whether varicocele repair also results in an increased chance of natural conception. Recent meta-analysis of randomised controlled trials on varicocele repair indicates that varicocelectomy results in more spontaneous pregnancies compared to observation in young couples with a clinical varicocele, oligozoospermia and otherwise unexplained infertility (Kroese et al. 2012).

12.8 Cancer and Male Infertility

Cancer and cancer treatment can negatively influence male fertility. Common malignancies in patients of reproductive age are leukaemia, Hodgkin's lymphomas and testicular germ cell tumours.

Cytotoxic therapy influence spermatogenesis at least temporarily and in some cases permanently. The amount of damage inflicted by chemotherapy on spermatogenesis depends on the combination of chemotherapeutic drugs used and on the cumulative dose administered for cancer treatment. Alkylating agents, such as cyclophosphamide and procarbazine, are most detrimental to germ cells. Radiation therapy, especially whole body irradiation, is associated with a high risk of permanent sterility due to permanent DNA damage. Next to cancer treatment tumour type and pretreatment fertility is also of prognostic value for future fertility outcome in male cancer survivors (Dohle 2010).

Many men after cancer treatment need artificial reproductive techniques for achieving fatherhood: usually IVF or ICSI is indicated for

successful treatment. Treatment results with cryopreserved semen are generally good and comparable to general IVF and ICSI results. So far no studies have reported an increased rate of congenital abnormalities and malignancies in children born from fathers who had cancer treatment in the past, but close follow-up is warranted, especially in children born after IVF/ICSI (Wallace et al. 2005).

Cancer therapy has long-term consequences including reduced fertility and sometimes sterility. This should be discussed with the patient before chemotherapy and radiation therapy is started. Cryopreservation of spermatozoa is currently the only option with proven success. In some men sperm quality is already low before the start of cancer treatment, and cryopreservation is not always possible. In the near future harvesting testicular stem cells for in vitro maturation and xenografting may be a potential option for preserving fertility, especially in prepubertal boys with cancer (Tournaye et al. 2014).

References

Argawal A, Deepinder F, Cocuzza M, Argawal R, Short RA, Sabanegh E, Marmar JL (2007) Efficacy of varicocoelectomy in improving semen parqameters: new meta-analytical approach. Urology 70:532–538

Baazeem A, Belzile E, Ciampi A, Dohle G, Jarvi K, Salonia A, Weidner W, Zini A (2011) Varicocele and male factor infertility treatment: a new meta-analysis and review of the role of varicocele repair. Eur Urol 60(4):796–808

Behre HM, Nieschlag E, Partsch CJ et al (2010) Diseases of the hypothalamus and the pituitary gland. In: Nieschlag E, Behre HM, Nieschlag S (eds) Andrology – male reproductive health and dysfunction, 3rd edn. Springer, Berlin, pp 169–192

Bolyakov A, Paduch DA (2011) Prolactin in men's health and disease. Curr Opin Urol 21(6):527–534

De Braekeleer M, Ferec C (1996) Mutations in the cystic fibrosis gene in men with congenital bilateral absence of the vas deferens. Mol Hum Reprod 2(9):669–677

Dohle GR (2003) Inflammatory-associated obstructions of the male reproductive tract. Andrologia 35(5): 321–324

Dohle GR (2010) Male infertility in cancer patients: review of the literature. Int J Urol 17(4):327–331

Dubin L, Amelar RD (1977) Varicocoelectomy: 986 cases in a twelve-year study. Urology 10(5):446–449

Krausz C (2009) Genetic aspects of male infertility. Eur Urol Rev 3(2):93–96

Kroese AC, de Lange NM, Collins J, Evers JL (2012) Surgery or embolization for varicoceles in subfertile men. Cochrane Database Syst Rev 10:CD000479

Practice Committee of American Society for Reproductive Medicine in collaboration with Society for Male Reproduction and Urology (2008) The management of infertility due to obstructive azoospermia. Fertil Steril 90(5 Suppl):S121–S124

Purvis K, Christiansen E (1993) Infection of the male reproductive tract. Impact, diagnosis and treatment in relation to male infertility. Int J Androl 16:1–13

Reijo R, Lee T, Salo P (1995) Diverse spermatogenic defects in humans caused by Y chromosome deletions encompassing a novel RNA-binding protein gene. Nat Genet 10:383–393

Rey RA, Grinspon RP (2011) Normal male sexual differentiation and aetiology of disorders of sex development. Best Pract Res Clin Endocrinol Metab 25(2): 221–238

Rowe PJ, World Health Organization et al (1993) WHO manual for the standardized investigation and diagnosis of the infertile couple. Cambridge University Press, Cambridge/New York

Skakkebaek NS, Rajpert-De Meyts E, Main KM (2001) Testicular dysgenesis syndrome: an increasingly common developmental disorder with environmental aspects. Hum Reprod 16(5):972–978

Teerds KJ, de Rooij DG, Keijer J (2011) Functional relationship between obesity and male reproduction: from humans to animal models. Hum Reprod Update 17(5):667–683

Tournaye H, Dohle GR, Barratt CL (2014) Fertility preservation in men with cancer. Lancet 4;384(9950):1295–1301.

Turek PJ, Williamsl RH, Gilbaugh JH, Lipshultz LI (1995) The reversibility of anabolic steroid-induced azoospermia. J Urol 153(5):1628–1630

Wallace WH, Anderson RA, Irvine DS (2005) Fertility preservation for young patients with cancer: who is at risk and what can be offered? Lancet Oncol 6:209–218

WHO study- no authors listed (1992) The influence of varicocele on parameters of fertility in a large group of men presenting to infertility clinics. World Health Organization. Fertil Steril 57(6):1289–1293

Yu J, Chen Z, Ni Y, Li Z (2012) CFTR mutations in men with congenital bilateral absence of the vas deferens (CBAVD): a systemic review and meta-analysis. Hum Reprod 27(1):25–35

Zini A, Dohle G (2011) Are varicoceles associated with increased deoxyribonucleic acid fragmentation? Fertil Steril 96(6):1283–1287

Part V

Male Uro-genital Infections

Male Urogenital Infections

13

W. Weidner, Th. Diemer, and F. Wagenlehner

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13.1 Andrological Relevance of Male Urogenital Infections

Urogenital infections and inflammation are accepted causes of male infertility with 6.9 % (WHO 1987) to 8 % (Nieschlag 2002) of men. A recent analysis in our group provided hints for infection and inflammation in 155 of consecutive 1,834 men examined for infertility, meaning a percentage of 8.5 % (Weidner et al. 2010). Nevertheless, independent from these figures, there is an ongoing debate concerning the biological relevance of such findings for the individual infertile man (EAU Working Group on Male Infertility 2012).

First, the diverse contribution of the different accessory glands to the ejaculate as a whole in terms of volume and content as well as the different time spans during which germ cells or sperm can interact with microorganisms are changing biological factors. Second, cellular and humoral inflammatory components in the various parts of the seminal pathways needs to be taken into account, and third, although the majority of inflammatory disorders within the male genital tract is of infectious origin, also non-infectious causes of inflammation have to be considered (Chan and Schlegel 2002).

V. Mirone (ed.), *Clinical Uro-Andrology*,
DOI 10.1007/978-3-662-45018-5_13,

13.2 MAGI (Male Accessory Gland Infection) and CP/CPPS

This complex situation has been brought into an integrative system by the WHO (WHO 1993) defining 'male accessory gland infection (MAGI)' as an inflammatory and infectious entity without a localization of the contributing different organs, e.g. the prostate, seminal vesicles, epididymides and the testicles to the entity (Weidner et al. 2008). The current WHO definition is provided in Table 13.1.

The prostatitis syndrome is one of the most common entities encountered in urological practice. Classification of the prostatitis syndrome is based on the clinical presentation of the patient, the presence or absence of white blood cells in the expressed prostatic secretion (EPS) and the presence or absence of bacteria in the EPS (Schaeffer 1999). Depending upon the duration of symptoms, prostatitis is described as either acute or chronic, if symptoms are present for at least 3 months. Following various classification periods, the classification of the prostatitis syndrome suggested by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)/National Institutes of Health (NIH) from 1995 is currently applied in clinical routine as well as research (NIDDK Workshop Committee 1995; Krieger et al. 1999) (Table 13.2).

Unfortunately, although prostatic secretions and seminal vesicles fluid are the main parts of the ejaculate, published data comparing both classification systems concerning urogenital infections do not exist.

13.2.1 Bacteriospermia and Leukocytospermia

Bacteriospermia means evidence of common microorganisms in semen, e.g. *E. coli*, enterococci, proteus and others.

A prerequisite for the detection of a 'significant' bacteriospermia is to avoid a microbiological contamination from non-semen sources (WHO 2010). Cleaning of the foreskin and the

Table 13.2 Prostatitis NIH classification

I	Acute bacterial prostatitis
II	Chronic bacterial prostatitis
III	Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS)
	(a) Inflammatory
	(b) Noninflammatory
IV	Asymptomatic prostatitis

Table 13.1 Classification of MAGI according to WHO

MAGI - classification system

Group A	Group B	Group C
Typical history / physical signs	Urine after P-Massage	Ejaculate signs
e.g. UTI, Epididymitis, STD Epididymal swelling Abnormal prostate	Increased PML *C. trachomatis*	PPL Bacteriospermia *C. trachomatis* Biochemistry Inflammation

C. trachomatis PCR
PPL >1 Mill./ml
Bacteriospermia >10 m³ cfu/ml
Elastase >250 ng/ml

MAGI =
(a) 2 signs, each from a different group
(b) At least 2 ejaculate signs

glans penis reduces contamination, whilst the ejaculation into a sterile container – only after passing urine – is suggested by the WHO (WHO 2010). Unfortunately, ejaculate is usually contaminated by the flora of the anterior urethra (Weidner et al. 2010). It has been assumed that about 70 % of semen samples are contaminated with urethral commensals, so bacteriospermia does not inevitably mean infection (Cottell et al. 2000). Accepted pathogenic bacteria are *Escherichia* (*E.*) *coli* and *Enterococcus* (*E.*) *faecalis* (Lackner et al. 2006), which are typical pathogens in urinary tract infections (UTIs) and causative in up to 90 % of all men with chronic bacterial prostatitis (WHO 2010; Schaeffer et al, 2006). For the daily work, $\geq 10^3$ cfu/ml of common uropathogenic bacteria in the ejaculate has been suggested as 'significant' bacteriospermia (WHO 2010).

Traditionally, leukocytes in human semen are counted after a histochemical procedure that identifies the peroxidase enzyme (WHO 2010). The presence of $\geq 1 \times 10^6$ WBC/ml defines leukocytospermia (WHO 2010). Some authors consider this limit to be too high (Ludwig et al. 2003; Gdoura et al. 2008a, b), whereas others found leukocyte counts below the WHO threshold to be associated with deterioration of semen quality (Punab et al. 2003). The great majority of leukocytes are polymorphonuclear granulocytes identified by the specific staining of the peroxidase reaction (PPL = peroxidase-positive leukocytes).

Although most authors consider leukocytospermia to be a sign of bacterial induced inflammation, the condition is not necessarily associated with bacterial infections (Virecoulon et al. 2005). Notably, in proven bacterial prostatitis (Weidner et al. 2008), the concentration of PPL is very high. It is in accordance with earlier findings that elevated leukocyte numbers in semen do not inevitably result in male subfertility (Kopa and Berényi 2010). The impact of leukocytes depends upon the stages and sites at which WBCs enter the semen pathways (Kopa and Berényi 2010). There is also an obvious resolution of leukocytospermia after antibiotic therapy (Branigan and Muller 1994). We usually reconfirm leukocytospermia always by a second investigation. Then, in a case of a proven inflammatory situation, the subsequent exclusion of a bacterial infection of the prostate seems to be mandatory (Weidner et al. 2008). Until today, the role of macrophages in the ejaculate is not really identified although up to one third of all leukocytes are macrophages (overview in Rusz et al. 2012).

Table 13.3 Giessen cutpoints for EPS, urine after P.M. (VB3) and ejaculate/seminal plasma parameters indicative for inflammation

	Parameter	Cutpoint
EPS	Leukocytes	≥10–20/1,000×
VB3	Leukocytes	≥10/mm^3
Semen	PPL	$\geq 0.113 \times 10^6$/ml
Seminal plasma	Elastase	≥280 ng/ml
Seminal plasma	IL-8	>10,600 pg/ml

13.2.2 Other Characteristic Inflammatory Ejaculate Findings

Other markers in the ejaculate and the seminal plasma may be indicative for inflammation.

Seminal plasma elastase (polymorphonuclear elastase) measured in the seminal plasma by enzyme-linked immunosorbent assay also assists in the diagnosis of inflammation as elastase concentrations are correlating with the number of peroxidase-positive cells (Zorn et al. 2003; Kopa et al. 2005). Clinically, in our hands ≥280 ng/ml are indicative for further investigations (Wagenlehner et al. 2009) (Table 13.3).

Cytokines such as the interleukin (IL) family are inflammatory mediators secreted by activated leukocytes or other immunocompetent cells in semen. Levels and types of cytokines have a crucial effect on the initiation, progression, magnitude or resolution of an inflammatory response. For a range of pro-inflammatory cytokines including IL-1, IL-6, IL-8 and TNF-α, a close correlation with seminal leukocyte numbers has been reported (Kopa and Berényi 2010).

The relevance of *sperm antibodies* (*ASA*) in the seminal plasma antibodies, measured by the MAR or immunobead test (Marconi et al. 2009a, b) in genitourinary infections and inflammation

is still debatable. Some authors suggest an association between increased levels of sperm antibodies and prostatitis and epididymitis (Bates 1997; Hinting et al. 1996). Also an association to chlamydial infections has been described (Dimitrova et al. 2004). The prevalence of MAGI in patients with a positive mixed antiglobulin (MAR) test seems to be in the range of 20 %, whereby it is generally accepted that only antibodies bound to surface antigen of vital spermatozoa are clinically significant (Mazumdar and Levine 1998). Own data in chronic urethritis, epididymitis and prostatitis do not demonstrate any association between proven inflammatory/infectious diseases of the male reproductive tract and the presence of ASA (Marconi et al. 2009a, b).

Reactive oxygen species (*ROS*) interact theoretically with sperm abnormalities either by increased ROS production or depressed antioxidant mechanisms (Agarwal and Saleh 2002). The main sources of ROS in semen are the polymorphonuclear granulocytes (PMN) and the seminal macrophages in response to cytokine-stimulating factors, enhanced in the presence of cytokines and LPS. During infection/inflammation these antioxidant mechanisms may create a situation called 'oxidative stress' due to the elevated levels of ROS beyond the available total antioxidant capacity in the semen (Agarwal and Saleh 2002) resulting in sperm damage.

Table 13.3 summarizes inflammatory ejaculate findings indicative for MAGI and prostatitis.

13.2.3 Poor Semen Quality in MAGI and Prostatitis

In chronic urogenital inflammation, obstruction at the level of the veromontanum has been hypothesized as one cause of decreased ejaculate volume (Weidner et al. 1999). In chronic prostatitis (CBP, CP/CPPS Type A) a reduced ejaculate volume has not been found in general (Ludwig et al. 2002); in MAGI patients with significant bacteriospermia, a reduction of the sample volume has been detected (Marconi et al. 2009a, b). Decreased concentrations of prostatic secretory parameters, e.g. citric acid, phosphatase, zinc and alpha-glutamyl transferase, and reduced fructose levels as indicator of the seminal vesicles have been consented as signs for disturbed secretory function of the glands (overview in Weidner et al. 1999). Our own data reconfirm the detection of secretory damage of the prostate gland in inflammatory prostatitis (Ludwig et al. 2002) and in MAGI (Marconi et al. 2009a, b).

One key point in this context is the detection of reduced sperm counts and impaired sperm motility as a sequel of the different inflammatory entities. For prostatitis, a recent meta-analysis of our group demonstrated reduced sperm counts in 1 of 5 and reduced motility in 3 of 5 studies (Rusz et al. 2012). In proven chronic bacterial prostatitis, associated with significant bacteriospermia and leukocytospermia our group failed to show any differences compared to healthy controls (Weidner et al. 1991). Other data are not available.

Concerning morphology, in chronic inflammatory prostatitis, a deterioration of standard morphology seems not be proven (Weidner et al. 2008). Based on strict criteria for the definition of morphologically normal sperm, the group from Tygerberg has evaluated systematically the effect of male urogenital infections on sperm morphology and defined leukocytal activity as key point for hyperelongation and DNA damage of sperm (Menkveld 2010). Own data in inflammatory and noninflammatory chronic prostatitis/chronic pelvic pain syndrome demonstrate poorer sperm morphology (Menkveld et al. 2003) in inflammatory specimen associated with a reduced acrosomal inducibility (Henkel et al. 2006). Chronic epididymitis is of higher importance in this context (Haidl et al. 2008) with alterations of spermatozoa such as 'tapering' of sperm heads and differences in tail colouring (Menkveld et al. 2003; Haidl et al. 2008).

13.3 Role of Sexually Transmitted Microorganisms

13.3.1 HIV and Other Virus Infections

Investigations on viruses in the ejaculate are focused on hepatitis B (HBV), hepatitis C (HCV), human immunodeficiency virus type 1 (HIV) and

papilloma virus infections. One major problem for the clinical impact of HBV and HCV infections is the viral load, especially after sperm washing procedures (Garrido et al 2005). Changes of sperm density, motility and morphology have been reported in different grades depending upon the examined population and antiviral treatment (Vicari et al. 2006; Moretti et al. 2008; Lorusso et al. 2010). One mechanism behind debatable deleterious effects may be the different integration of these viruses into sperm chromosomes (Huang et al. 2002).

Concerning HIV infections, already in 1991, Krieger and co-workers investigated the impact of HIV on fertility in 21 HIV-positive men and compared the sperm characteristics with semen from 40 donors. Interestingly, no differences in sperm parameters were detected (Krieger et al. 1991). Several cross-sectional studies have focused on the effect of HIV infection on sperm parameters, and conflicting results have been published (overview in Rusz et al. 2012). The discrepancies in these reports may be due to the small numbers in some studies, methodological variations, differing stages of HIV disease in the study groups as well as considerable variation in the choice of control groups (overview in Rusz et al. 2012). Nevertheless, in most studies, HIV-infected men in early-stage disease had semen parameters consistent with fertility (Krieger et al. 1991; Dulioust et al. 2002). A long-term investigation of 55 men over 96 weeks confirmed these results and revealed no significant changes in semen parameters between the first and last investigation (van Leeuwen et al. 2008). However, with disease progression a detrimental effect on semen variables was noted (Dulioust et al. 2002; van Leeuwen et al. 2008).

Interestingly, in several studies at least one of the parameters ejaculate volume, sperm motility, sperm concentration or normal sperm morphology was significantly correlated with the number of CD4+ blood cells (van Leeuwen et al. 2008; Dondero et al. 1996). HPV virus infections have been shown in 25 % of the sperm heads of infected men with a decrease of sperm motility (Foresta et al. 2010a, b). These data have not been reconfirmed until today. The authors believe in the relevance of these findings for the transmission of this virus, especially for sperm donors (Punab et al. 2003).

13.3.2 *Chlamydia* (*C.*) *trachomatis*

Using nucleic acid amplification techniques, *C. trachomatis* has been detected in asymptomatic men in 2.5 % (Bezold et al. 2007). Depending upon the analyzed patient cohort, the prevalence of *C. trachomatis* infections in semen is between 1.6 and 10.9 % (Cunningham and Beagley 2008). Obviously, the possibility of a urethral infection reduces the significance of positive chlamydial findings in the ejaculate (Wagenlehner et al. 2006). Increased IL-8 levels and evidence of anti-chlamydial mucosal IgA in the seminal plasma are suggested to provide a clearer diagnosis (Mazzoli et al. 2007). There is no debate that *C. trachomatis* ascends the seminal pathways questionable up to the testicles, but a proven biological significance seems only to be accepted for acute epididymitis and consecutive azoospermia (Weidner et al. 2008; Rusz et al. 2012). Although the spread into the different accessory glands seems logical, until today proven prostatic infections have not been confirmed (Wagenlehner et al. 2006; Rusz et al. 2012). Normally, a leukocytal reaction of the ejaculate is associated with chlamydial infections (Hosseinzadeh et al. 2004; Kokab et al. 2010), partially including *C. trachomatis* inclusion inside the seminal leukocytes (Gallegos-Avila et al. 2009) and a cytokine response of IL-6 and IL-8 in the seminal plasma (Kokab et al. 2010). Direct effects on sperm may be caused by alive microorganisms but also by *C. trachomatis* LPS (Hosseinzadeh et al. 2003).

13.3.3 *Mycoplasma* Species

Already in the 1980s, *Mycoplasma* species (*M. hominis*, *M. genitalium*, *Ureaplasma* (*U.*) *urealyticum*) have been identified by culture in the ejaculate. Using a cut-off level of $\geq 10^3$ cfu/ml in 11.2 % of all genital specimens, mycoplasma has been detected (Weidner et al. 1985). More recent

systematic investigations are rare; the available data suggest a percentage of up to 25 % in semen samples of men attending infertility clinics (Wang et al. 2006; Agbakoba et al. 2007; Gdoura et al. 2008a, b).

To date, the impact of these bacteria for sperm parameters and the possible mechanism of interaction remain unclear. These conflicting results are surprising due to the fact that in vitro data demonstrate a direct binding of *M. hominis* and *M. genitalium* to the heads and tails of sperm with a probable negative effect on motility (Dieterle 2008). For ureaplasmas, besides these adhesion phenomena, changes of the microelement levels in the seminal fluid (Wang et al. 2006) and DNA damage of sperm (Reichart et al. 2000) have been discussed.

13.3.4 Gonococci and *Trichomonas* (*T.*) *vaginalis*

Today, infections of the ejaculate with *Neisseria* (*N.*) *gonorrhoeae* do not play any role in analyzing semen specimen in infertile populations (Weidner et al. 1999; Weidner et al. 2010) in Middle Europe. This statement may be much different in countries with a higher incidence of STD infections, especially when an inflammation in semen is obvious (Gdoura et al. 2008a, b). Interestingly, sperm motility in the presence of gonococci results in no decrease sperm motility measured by computerized sperm analysis (Liu et al. 2002).

Unfortunately, systematic investigations on the prevalence of *C. albicans* in the ejaculate are lacking. In vitro, a motility inhibitory effect was detectable with yeast concentrations of 20 Mill/ml (Huwe et al. 1998). A direct formation of sperm agglutination due to Candida particles (Huwe et al. 1998) has to be addressed. Today, such infections are uncommon in the ejaculate analysis of andrological patients (Weidner et al. 2010). Nevertheless, the parasite grows in the ejaculate and may reduce sperm motility depending upon concentrations (Daly et al. 1989). As mechanism behind this effect, soluble toxic factors have been postulated (Han et al. 2004).

13.4 Conclusions for Male Infertility

This chapter is focusing on available data demonstrating an interaction between urogenital infection and inflammation with disturbed ejaculate parameters. A potential negative influence on ejaculate parameters and sperm function seems to be obvious for many aspects. However, the severity of impairment differs according to the underlying infections and the involved urogenital compartments. Today, a significant improvement by antibiotic or antiphlogistic treatment is not proven.

References

Agarwal A, Saleh H (2002) Role of oxidants in male infertility: rationale, significance and treatment. Urol Clin North Am 29:817–827

Agbakoba NR, Adetosoye AI, Ikechebelu JI (2007) Genital mycoplasmas in semen samples of males attending a tertiary care hospital in Nigeria: any role in sperm count reduction? Niger J Clin Pract 10:169–173

Bates CA (1997) Antisperm antibodies and male subfertility. Br J Urol 80:691–697

Bezold G, Politch JA, Kiviat NB et al (2007) Prevalence of sexually transmissible pathogens in semen from asymptomatic male infertility patients with and without leukocytospermia. Fertil Steril 87:1087–1097

Branigan EF, Muller CHH (1994) Efficacy of treatment and recurrence rate of leukocytospermia in infertile men with prostatitis. Fertil Steril 62:580–584

Chan PT, Schlegel PN (2002) Inflammatory conditions of the male excurrent ductal system. Part I. J Androl 23:453–460

Cottell E, Harrison RF, McCaffrey M et al (2000) Are seminal fluid microorganisms of significance or merely contaminants? Fertil Steril 74:465–470

Cunningham KA, Beagley KW (2008) Male genital tract chlamydial infection: implications for pathology and infertility. Biol Reprod 79:180–189

Daly JJ, Sherman JK, Green L et al (1989) Survival of Trichomonas vaginalis in human semen. Genitourin Med 65:106–108

Dieterle S (2008) Urogenital infections in reproductive medicine. Andrologia 40:117–119

Dimitrova D, Kalaydjiev S, Hristov L et al (2004) Antichlamydial and antisperm antibodies in patients with chlamydial infections. Am J Reprod Immunol 52:330–336

Dondero F, Rossi T, D'Offizi G et al (1996) Semen analysis in HIV seropositive men and in subjects at high risk for HIV infection. Hum Reprod 11:765–768

Dulioust E, Du AL, Costagliola D et al (2002) Semen alterations in HIV-1 infected men. Hum Reprod 17:2112–2118

EAU Working Group on Male Infertility (2012) European Association of Urology guidelines on Male Infertility: the 2012 update. Eur Urol 62:324–332

Foresta C, Garolla A, Zuccarello D et al (2010a) Human papillomavirus found in sperm head of young adult males affects the progressive motility. Fertil Steril 93:802–806

Foresta C, Pizzol D, Moretti A et al (2010b) Clinical and prognostic significance of human papillomavirus DNA in the sperm or exfoliated cells of infertile patients and subject with risk factors. Fertil Steril 94:1723–1727

Gallegos-Avila G, Ortega-Martinez M, Ramos-Gonzalez B et al (2009) Ultrastructural findings in semen samples of infertile men infected with Chlamydia trachomatis and mycoplasmas. Fertil Steril 91:915–919

Garrido N, Meseguer M, Remohí J et al (2005) Semen characteristics in human immunodeficiency virus (HIV)- and hepatitis C (HCV)-seropositive males: predictors of the success of viral removal after sperm washing. Hum Reprod 20:1028–1034

Gdoura R, Kchaou W, Ammar-Keskes L et al (2008a) Assessment of Chlamydia trachomatis, Ureaplasma urealyticum, Ureaplasma parvum, Mycoplasma hominis, and Mycoplasma genitalium in semen and first voided urine specimens of asymptomatic male partners of infertile couples. J Androl 29:198–206

Gdoura R, Kchaou W, Znazen A et al (2008b) Screening for bacterial pathogens in semen samples from infertile men with and without leukocytospermia. Andrologia 40:209–218

Haidl G, Allam JP, Schuppe HC (2008) Chronic epididymitis – impact on semen parameters and therapeutic options. Andrologia 40:92–96

Han Q, Liu J, Wang T et al (2004) Influence of the metabolite produced by Trichomonas vaginalis on human sperm motility in vitro. Zhonghua Nan Ke Xue 10:272–274

Henkel R, Ludwig M, Schuppe HC et al (2006) Chronic pelvic pain syndrome/chronic prostatitis affect the acrosome reaction in human spermatozoa. World J Urol 24:39–44

Hinting A, Soebadi DM, Santoso RI (1996) Evaluation of the immunological cause of male infertility. Andrologia 28:123–126

Hosseinzadeh S, Pacey AA, Eley A (2003) Chlamydia trachomatis-induced death of human spermatozoa is caused primarily by lipopolysaccharide. J Med Microbiol 52: 193–200

Hosseinzadeh S, Eley A, Pacey AA (2004) Semen quality of men with asymptomatic chlamydial infection. J Androl 25:104–109

Huang JM, Huang TH, Qiu HY et al (2002) Studies on the integration of hepatitis B virus DNA sequence in human sperm chromosomes. Asian J Androl 4:209–212

Huwe P, Diemer T, Ludwig M et al (1998) Influence of different uropathogenic microorganisms on human sperm motility parameters in an in vitro experiment. Andrologia 30:55–59

Kokab A, Akhondi MM, Sadeghi MR et al (2010) Raised inflammatory markers in semen from men with asymptomatic chlamydial infection. J Androl 31:114–120

Kopa Z, Berényi M (2010) Inflammatory parameters of the ejaculate. In: Björndahl L, Giwercman A, Tournaye H, Weidner W (eds) Clinical andrology. Informa Healthcare, New York/London

Kopa Z, Wenzel J, Papp GK et al (2005) Role of granulocyte elastase and interleukin-6 in the diagnosis of male genital tract inflammation. Andrologia 37: 188–194

Krieger JN, Coombs RW, Collier AC et al (1991) Fertility parameters in men infected with human immunodeficiency virus. J Infect Dis 164:464–469

Krieger JN, Nyberg L Jr, Nickel JC (1999) NIH consensus definition and classification of prostatitis. JAMA 282:236–237

Lackner J, Schatzl G, Horvath S et al (2006) Value of counting white blood cells (WBC) in semen samples to predict the presence of bacteria. Eur Urol 49:148–152; discussion 152–153

Liu JH, Li HY, Cao ZG et al (2002) Influence of several uropathogenic microorganisms on human sperm motility parameters in vitro. Asian J Androl 4:179–182

Lorusso F, Palmisano M, Chironna M et al (2010) Impact of chronic viral diseases on semen parameters. Andrologia 42:121–126

Ludwig M, Vidal A, Diemer T et al (2002) Seminal secretory capacity of the male accessory sex glands in chronic pelvic pain syndrome (CPPS)/chronic prostatitis with special focus on the new prostatitis classification. Eur Urol 42:24–28

Ludwig M, Vidal A, Diemer T et al (2003) Chronic prostatitis/chronic pelvic pain syndrome: seminal markers of inflammation. World J Urol 21:82–85

Marconi M, Pilatz A, Wagenlehner F et al (2009a) Are antisperm antibodies really associated with proven inflammatory, infectious diseases of the male reproductive tract. Eur Urol 56:708–715

Marconi M, Pilatz A, Wagenlehner F et al (2009b) Impact of infection on the secretory capacity of the male accessory glands. Int Braz J Urol 35:299–309

Mazumdar S, Levine A (1998) Antisperm antibodies: etiology, pathogenesis, diagnosis and treatment. Fertil Steril 70:799–810

Mazzoli S, Lai T, Rupealta V et al (2007) Interleukin 8 and antichlamydia trachomatis mucosal Ig-A as urogenital immunological markers in patients with *C. trachomatis* prostatic infection. Eur Urol 51:1385–193

Menkveld R (2010) Sperm morphology in male urogenital infections. In: Björndahl L, Giwercman A, Tournaye H, Weidner W (eds) Clinical andrology. Informa Healthcare, New York/London

Menkveld R, Huwe P, Ludwig M et al (2003) Morphological sperm alterations in different types of prostatitis. Andrologia 35:288–293

Moretti E, Federico MG, Giannerini V et al (2008) Sperm ultrastructure and meiotic segregation in a group of

patients with chronic hepatitis B and C. Andrologia 40:286–291
NIDDK (1995) Workshop Committee of the National Institute of Diabetes and Digestive and Kidney Disease. Chronic Prostatitis Workshop, Bethesda
Nieschlag E (2002) Nosologie andrologischer Krankheitsbilder. In: Nieschlag E, Behre H (eds) Andrologie. Grundlagen und Klinik der reproduktiven Gesundheit des Mannes. Springer, Berlin
Punab M, Lõivukene K, Kermes K et al (2003) The limit of leucocytospermia from the microbiological viewpoint. Andrologia 35:271–278
Reichart M, Kahane I, Bartoov B (2000) In vivo and in vitro impairment of human and ram sperm nuclear chromatin integrity by sexually transmitted Ureaplasma urealyticum infection. Biol Reprod 63:1041–1048
Rusz A, Pilatz A, Wagenlehner F et al (2012) Influence of urogenital infections and inflammation on semen quality and male fertility. World J Urol 30:23–30
Schaeffer AJ (1999) Prostatitis: US perspective. Int J Antimicrob Agents 11:205–211; discussion 13–16
Schaeffer AJ, Anderson RU, Krieger JN et al (2006) The assessment and management of male pelvic pain syndrome including prostatitis. In: Mc Connel J, Abrams P, Denis L, Khoury S, Roehrborn C (eds) Male lower urinary tract dysfunction. Evaluation and management. 6th international consultation in Prostate Cancer and Prostate Diseases. Health Publications, Paris
van Leeuwen E, Wit FW, Prins JM et al (2008) Semen quality remains stable during 96 weeks of untreated human immunodeficiency virus-1 infection. Fertil Steril 90:636–641
Vicari E, Arcoria D, Di Mauro C et al (2006) Sperm output in patients with primary infertility and hepatitis B or C virus; negative influence of HBV infection during concomitant varicocele. Minerva Med 97:65–77
Virecoulon F, Wallet F, Fruchart-Flamenbaum A et al (2005) Bacterial flora of the low male genital tract in patients consulting for infertility. Andrologia 37:160–165
Wagenlehner FME, Naber KG, Weidner W (2006) Chlamydial infections and prostatitis in men. BJU Int 97:687–690
Wagenlehner FME, Naber KG, Bschleipfer T et al (2009) Diagnostik und Therapie der Prostatitis und des männlichen Beckenschmerzsyndroms. Dtsch Ärzteblatt 106:175–183
Wang Y, Liang CL, Wu JQ et al (2006) Do Ureaplasma urealyticum infections in the genital tract affect semen quality? Asian J Androl 8:562–568
Weidner W, Krause W, Schiefer HG et al (1985) Ureaplasmal infections of the male urogenital tract, in particular prostatitis, and semen quality. Urol Int 40: 5–9
Weidner W, Jantos C, Schiefer HG et al (1991) Semen parameters in men with and without proven chronic prostatitis. Arch Androl 26:173–183
Weidner W, Krause W, Ludwig M (1999) Relevance of male accessory gland infection for subsequent fertility with special focus on prostatitis. Hum Reprod Update 5:421–432
Weidner W, Wagenlehner FME, Marconi M et al (2008) Acute bacterial prostatitis and chronic prostatitis/chronic pelvic pain syndrome: andrological implications. Andrologia 40:105–112
Weidner W, Diemer T, Wagenlehner FME (2010) Male infertility in chronic urogenital infections and inflammation with special reference to ejaculate findings. In: Björndahl L, Giwercman A, Tournaye H, Weidner W (eds) Clinical andrology. Informa Healthcare, New York/London
WHO (1993) WHO manual for the standardized investigation and diagnosis of the infertile couple. Cambridge University Press, New York
WHO (2010) WHO laboratory manual for the examination and processing of human semen, 5th edn. WHO Press, Geneva
WHO Task Force on The Diagnosis and Treatment of Infertility (1987) Towards more objectivity in diagnosis and management of male infertility. Int J Androl Suppl 7:1–53
Zorn B, Sesek-Briski A, Osredkar J et al (2003) Semen polymorphonuclear neutrophil leukocyte elastase as a diagnostic and prognostic marker of genital tract inflammation – a review. Clin Chem Lab Med 41:2–12

HPV Infection in Male

14

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14.1 Epidemiology of HPV Infection

Human papillomavirus (HPV) infection is commonly recognized as the first cause of cervical cancer in women as well as other diseases in men and women (Garnock-Jones and Giuliano 2011). About 97 % of cervical cancers take its origin by a sexually transmitted viral infection that subsequently evolved to cancer transformation through the persistence of HPV into the cervical mucosa for long periods of time (till 20–30 years) (Tay 2012). Viral transmission normally occurs through sexual intercourse with commonly recognized infection distribution from man to woman or man to man where man is often considered as a disease healthy bearer. The viral passage from woman to man has been demonstrated and clarified in clinical practice only in the cases of anogenital warts in the sexual partner. In all these cases man represents the vector of HPV infection to sexual partners but he is rarely considered as a potential final target. HPV-related cancers in men are in fact found among selected people considered at risk for infection such as immunodeficiency patients (due to viruses such as HIV/AIDS or other non-viral causes) and/or homosexuals, overall in developed countries (Giuliano et al. 2007). About 32,000 cases of new cancers in men and women attributable to HPV infection such as cervix, vagina, vulva, penis, oral cavity, head or neck and canal anal, were found in the USA in 2009 (American Cancer Society 2009). HPV types that

V. Mirone (ed.), *Clinical Uro-Andrology*,
DOI 10.1007/978-3-662-45018-5_14, © Springer-Verlag Berlin Heidelberg 2015

infect the genital area are categorized in "high-risk" HPV (HR-HPV) and "low-risk" HPV (LR-HPV), and the World Health Organization (WHO) International Agency for Research on Cancer recognizes at least thirteen different types of HR-HPV. Types 16 and 18 are frequently associated with more than 70 % of cervical cancers worldwide, while types 6 and 11 are frequently involved in the majority of cases of anogenital warts (Albrow et al. 2012; Nyitray et al. 2010). The same genotypes responsible for anogenital cancers are often involved in the genesis of head and neck cancers (de Pokomandy et al. 2009). Genital infection is often asymptomatic in both genders although the evidence of sexual warts could be easily found in men than in women. In other rare cases the presence of plain condylomata has been identified through the preventive use of acetic acid solution (Wright 2003). On the other hand, periodical Pap test and subsequent HPV test investigations allow to exert cancer screening visits in women thus reducing the risk of developing cervical cancers and monitoring couples with stable sexual partners. The frequency of HPV infection in various groups of male subjects was analysed in a systematic review of the literature, which included 40 papers published from 1999 to 2006 (Giuliano et al. 2007). The prevalence of HPV in men ranged from 1.3 to 72.9 %, and it is at least 20 in 56 % of the analysed studies (Giuliano et al. 2010). Another review article by Partridge et al. describes a prevalence of HR-HPV infection ranging from 2.3 to 34.8 % of heterosexual males: in these subjects HPV infection has been found also in the anal area with a prevalence of 4.3–15 % independently from their heterosexual condition (Partridge and Koutsky 2006).

14.2 HPV Infection Natural History

14.2.1 Male HPV Infection Natural History

This is a critical point due to the limited information on HPV infection in men and the appropriate criteria of diagnosis to detect the presence of one or more HPV genotypes on the penis or in seminal fluids (Bartoletti et al. 2011). Risk factors could be represented by sexual behaviour, immunodeficiency or HIV co-infection and the evidence of HPV infection in a sexual partner. According to CDC guidelines, each male sexual partner of an infected woman should be accurately evaluated and treated if necessary at least for a period exceeding 3 months which is normally considered as the incubation period necessary to develop visible lesions. The persistence of visible lesion in the male partner could be considered as a determinant factor to induce a possible re-infection in subsequent sexual intercourse (Dunne et al. 2011). Kyo et al. described less prevalence of evident lesions in male partners of infected women but the presence of HPV-DNA in the semen of the same subjects (Kyo et al. 1994). Foresta et al. described HPV viral infection of spermatozoa with possible effects on fertility (Foresta et al. 2011). Penile condylomata represent the most frequent sign of infection in males. Local sense of burning, pain and bleeding are the most frequent subjective symptoms. HPV genotypes 6 and 11 are involved in at least 90 % of infection able to determine genital condylomata. Evident lesions should be adequately treated by N-YAG laser application, diathermo-coagulation, cryo-ablation or medical therapies such as imidazole derivative, podophyllotoxin or trichloroacetic acid (Dunne et al. 2006).

14.2.2 HPV Infection Spontaneous Clearance

The HPV infection prevalence is similar in all classes of age considered although the spontaneous time of infection clearance is usually short. Viral transmission from women to men is possible, but not all male sexual partners of infected women are positive for evident penile condylomata. A possible justification of this phenomenon could be the repeated infections that occurred during sexual activity persisting just for a period of time. Another justification could be represented by the presence of viral undetected infection in men. The mean time to the infection

clearance (as the time necessary to determine a complete regression in at least 50 % of infected subjects) has been estimated at 5.9 months (95 % CI 5.7–6.1), while the complete clearance of HPV-DNA in at least 75 % of infected subjects has been estimated at 12 months independently from the HPV genotype considered (Giuliano et al. 2011).

14.3 HPV-Associated Diseases in Men

14.3.1 Male HPV Infection–Related Cancers

HPV-DNA has been frequently found in several cancers in both genders. The cancer sites are strongly related with sexual activity; in particular penile, anal, oral, head and neck (tongue, pharynx, rhinopharynx, hypopharynx, larynx) cancers have been previously described. HPV-DNA has been also recently described in several cases of patients with superficial bladder tumours and benign prostate hyperplasia by Cai et al. (2011).

14.3.1.1 Penile Cancer

Penile cancer afflicts less than 0.5 % of all males with cancer diagnosis in western countries with a cumulative incidence close to 1 out 100,000 inhabitants. The incidence rises to 1.5–3.7 in some South American countries such as Brazil, Perù and Colombia, 2.8 in Uganda and 1.7 in Thailand and India. There is a direct relationship between cervical and penile cancer prevalence according to specific geographical areas. Moreover penile cancer seemed to be less frequent in countries with a large density of circumcised subjects such as Israel, USA, Japan and China (Johnson et al. 2010). HPV-DNA has been found in at least 40–50 % of all penile cancer pathological variants (intra-epithelial neoplasia, squamous–verrucous, basaloid–verrucous) with a prevalence of 16 and 18 genotypes. HPV-DNA has been also found in 75–80 % of penile basaloid intra-epithelial neoplasia (PIN) 1, 2 and 3, but 30–60 % of squamous penile carcinoma represents the most frequent penile cancer pathological variant (Chaux and Cubilla 2012).

14.3.1.2 Anal Cancer

Ninety nine thousand new cases of anal cancer have been estimated in 2002 all around the world. About 40 % of them have been found in men, and 65 % were squamous carcinomas developed from anal intra-epithelial tumours and often related with HPV infection (Cranston et al. 2012). In particular, both 16 and 18 genotypes seemed to be involved in the transformation process. An increased prevalence of 160 % in men and 78 % in women has been described in the USA from 1970 to 2000. This increase is particularly evident among homosexuals and HIV patients. The risk of developing HPV infection with subsequent anal cancer is also related to other factors such as cigarette smoking, anal sexual intercourse and the number of sexual partners (Gao et al. 2010).

14.3.1.3 Head and Neck Cancers

The definition includes all cancers with squamous pathological variant involving the oral cavity, oropharynx, hypopharynx and larynx. 405,000 new cases have been described in 2002 all around the world with 211,000 deaths disease related. The male/female ratio ranged from 2:1 to 15:1. The association with HPV infection is very frequent although some other risk factors such as cigarette or cigar smoking, alcohol consumption or their combination should be considered in each patient. HPV infection prevalence among these cancers is about 60 % in oro-pharynx cancers and 20 % in other head/neck tumours, while the prevalent genotype was HPV 16 (60–80 %). There is a strong relationship between HPV oral infection and oral sex practice (Bisht and Bist 2011).

14.3.1.4 Bladder Cancer

The relationship between HPV infection and bladder cancer has been previously found by different authors. Li and co-workers, in a meta-analysis study, confirmed a high HPV-DNA prevalence in 16.8 % (95 % CI 15.5–18.3 %) of patients with bladder cancer showing a determinant role of HPV 16 and high-risk genotypes in carcinogenesis mechanisms (Li et al. 2011). Moonen et al. confirmed these data but underlined the potential role of all HPV genotypes in the determination of bladder malignancies (virus

presence in 15.2 % of cases) (Moonen et al. 2007). At last Cai and co-workers found the presence of HPV-DNA in patients with bladder cancer but also in the control group of patients who have undergone trans-urethral resection for benign prostate hyperplasia (Cai et al. 2011). This could demonstrate the potential role of HPV infection in the genesis and/or progression of several urological diseases although the relationship between HPV and cellular transformation to cancer has still to be demonstrated (Cai et al. 2011).

14.3.2 HPV Infection and Fertility

The presence of HPV in the semen has been previously demonstrated by different authors although none of them supposed the relationship with male infertility. A recent paper by Foresta and co-workers demonstrated that in couples with HPV-infected male partners, the abort rate was significantly higher (66.7 %) when compared to normal couples (15 %). This phenomenon could be justified by the viral bodies' adhesion to spermatozoa with subsequent motility reduction. Six months thereafter at least 54 % of positive subjects become spontaneously negative to HPV infection without medical treatments, while 84 % become negative after 12 months (Foresta et al. 2010). Moreover, an important aspect to highlight is the impact of HPV and *Chlamydia trachomatis* co-infections on male fertility. Recent observational studies showed HPV and *Chlamydia trachomatis* co-infection in 13 % and 66.8 % respectively in patients attending the sexually transmitted disease clinics and the infertility centre (Görander et al. 2008; Cai et al. 2014).

14.4 Diagnosis of HPV-Related Diseases in Men

The diagnosis of HPV infection in man is strictly related with the presence of genital warts that could be easily retrieved on the glans penis and shaft by optical evaluation with or without the help of a colposcopy system. The penis could be tamponed with acetic acid to reveal "plain" warts. Once removed surgically, genital warts could be analysed and genotyped. Serum blood analysis related to the presence of HPV infection seemed to be more specific (>90 %) but less sensitive (50–60 %) when compared to the direct evidence of infection. Moreover, in women, naturally induced anti-HPV serum antibodies are a likely marker of host immune protection against subsequent HPV acquisition and progression to precancerous lesions and cancers. However, it is unclear whether the same is the case in men. Recently, Lu et al. demonstrated that prevalent serum antibodies induced by prior infection may not be a suitable marker for subsequent immune protection against genital HPV16 acquisition in men (Lu et al. 2012).

14.5 Clinical Follow-Up of Male Patients with HPV Infection

Clinical follow-up is strongly related to the presence and type of HPV-related diseases. The diagnosis of HPV-related cancer already includes a pre-determined follow-up programme. In all other cases some recommendations should be considered:

- Previously excised benign lesions should be monitored by penoscopy/anoscopy and HPV test every 4 months for the first year.
- HPV test every 4–6 months for subjects "at risk" with previous HPV-related cancers.
- HPV test every 8–12 months for subjects "at risk" without significant HPV lesions (immunodeficiency, HIV, homosexuals).
- HPV test after 8–12 months for asymptomatic subjects with previous diagnosis of HPV infection in order to test the viral spontaneous clearance (McGinley et al. 2011; CDC 2010).

14.6 Prevention of HPV Infection

14.6.1 Primary Prevention and Vaccination Programmes

Two different types of HPV vaccines are currently available: the bivalent vaccine against genotypes 16–18, indicated for the primary prevention of

cervical cancers in women from 10 to 25 years, and the quadrivalent vaccine against 6, 11, 16 and 18 HPV genotypes, indicated for cervical and genital wart prevention in women between 9 and 45 and men from 9 to 15 years. In 2009 the Food and Drug Administration (FDA) approved the extension to prevention with quadrivalent vaccine in men till 26 years (Anderson 2012). Vaccination in males could reduce both the prevalence of cervical cancers and the evidence of HPV-related cancers/genital warts. Albero et al. recently demonstrated the efficacy of vaccination programmes in men between 16 and 26 years compared to placebo, by reducing the prevalence of genital warts and HPV-related cancers in 90.4 % of treated subjects (95 % CI 69–98) (Albero et al. 2012).

14.6.2 Secondary Prevention

Secondary prevention is usually structured for women (cervical cancer screening and PAP test) but not for men. Data confirmed that the evidence of genital warts could not be considered as the only one clinical expression of HPV infection. Moreover insufficient data confirmed the role of useful methods for HPV infection diagnosis except penoscopy/anoscopy or the evidence of HPV-DNA in the semen. Due to these reasons HPV infection screening programmes in males have not yet been structured and organized. The use of condoms and circumcision has been thus considered as alternative methods for HPV infection secondary prevention. The efficacy of condom has been previously tested by different authors. Baldwin demonstrated that the permanent use of condoms for sexual intercourse significantly reduces the risk of infection from every type of HPV (Baldwin et al. 2004). Similar results have been confirmed by several authors although the risk of infection transmission through the hand to genital or inanimate objects to genital remains high. Moreover the infection clearance seemed to be significantly influenced by the permanent use of condoms (23 % of clearance compared to 4 % in non-users) (Larke et al. 2011). Circumcision is protective towards sexual infection transmission due to both the reduction of keratinized epithelium tissue surface and the reduction of vaginal secretion during sexual intercourse. Its role has been recently evaluated in studies of prevalence with a significant reduction of the risk of infection from 20 to 48 % in circumcised subjects.

References

Albero G, Castellsagué X, Giuliano AR, Bosch FX (2012) Male circumcision and genital human papillomavirus: a systematic review and meta-analysis. Sex Transm Dis 39(2):104–113

Albrow R, Kitchener H, Gupta N, Desai M (2012) Cervical screening in England: the past, present, and future. Cancer Cytopathol 120(2):87–96

American Cancer Society (2009) Cancer facts and figures. ACS, Atlanta

Anderson LA (2012) Prophylactic human papillomavirus vaccines: past, present and future. Pathology 44(1): 1–6

Baldwin SB, Wallace DR, Papenfuss MR, Abrahamsen M, Vaught LC, Giuliano AR (2004) Condom use and other factors affecting penile human papillomavirus detection in men attending a sexually transmitted disease clinic. Sex Transm Dis 31(10):601–607

Bartoletti R, Zizzo G, Cai T, Mirone V (2011) Genital condylomata are not the human papilloma virus male infection burden. Eur Urol 60(2):268–269

Bisht M, Bist SS (2011) Human papilloma virus: a new risk factor in a subset of head and neck cancers. J Cancer Res Ther 7(3):251–255

Cai T, Mazzoli S, Meacci F, Nesi G, Geppetti P, Malossini G, Bartoletti R (2011) Human papillomavirus and non-muscle invasive urothelial bladder cancer: potential relationship from a pilot study. Oncol Rep 25(2): 485–489

Cai T, Wagenlehner FM, Mondaini N, D'Elia C, Meacci F, Migno S, Malossini G, Mazzoli S, Bartoletti R (2014) Effect of human papillomavirus and Chlamydia trachomatis co-infection on sperm quality in young heterosexual men with chronic prostatitis-related symptoms. BJU Int 113(2):281–287

Chaux A, Cubilla AL (2012) The role of human papillomavirus infection in the pathogenesis of penile squamous cell carcinomas. Semin Diagn Pathol 29(2): 67–71

Cranston RD, Murphy R, Weiss RE, Da Costa M, Palefsky J, Shoptaw S, Gorbach PM (2012) Anal human papillomavirus infection in a street-based sample of drug using HIV-positive men. Int J STD AIDS 23(3): 195–200

de Pokomandy A, Rouleau D, Ghattas G, Vézina S, Coté P, Macleod J, Allaire G, Franco EL, Coutlée F for the HIPVIRG Study Group (2009) Prevalence, clearance, and incidence of anal human Papillomavirus infection

in HIV-infected men: the HIPVIRG cohort study. J Infect Dis 199:965–973

Dunne EF, Nielson CM, Stone KM, Markowitz LE, Giuliano AR (2006) Prevalence of HPV infection among men: a systematic review of the literature. J Infect Dis 194(8):1044–1057

Dunne EF, Friedman A, Datta SD, Markowitz LE, Workowski KA (2011) Updates on human papillomavirus and genital warts and counseling messages from the 2010 Sexually Transmitted Diseases Treatment Guidelines. Clin Infect Dis 53(Suppl 3):S143–152

Foresta C, Pizzol D, Moretti A, Barzon L, Palù G, Garolla A (2010) Clinical and prognostic significance of human papillomavirus DNA in the sperm or exfoliated cells of infertile patients and subjects with risk factors. Fertil Steril 94(5):1723–1727

Foresta C, Ferlin A, Bertoldo A, Patassini C, Zuccarello D, Garolla A (2011) Human Papillomavirus in the sperm cryobank: an emerging problem? Int J Androl 34(3):242–246

Gao L, Zhou F, Li X, Yang Y, Ruan Y, Jin Q (2010) Anal HPV infection in HIV-positive men who have sex with men from China. PLoS One 5(12):e15256

Garnock-Jones KP, Giuliano AR (2011) Quadrivalent human papillomavirus (HPV) types 6, 11, 16, 18 vaccine: for the prevention of genital warts in males. Drugs 71(5):591–602

Giuliano AR, Nielson CM, Flores R, Dunne EF, Abrahamsen M, Papenfuss MR et al (2007) The optimal anatomic sites for sampling heterosexual men for human Papillomavirus (HPV) detection: the HPV detection in men study. J Infect Dis 196(8): 1146–1152

Giuliano AR, Anic G, Nyitray AG (2010) Epidemiology and pathology of HPV disease in males. Gynecol Oncol 117(2 Suppl):S15–S19

Giuliano AR, Lee JH, Fulp W, Villa LL, Lazcano E, Papenfuss MR, Abrahamsen M, Salmeron J, Anic GM, Rollison DE, Smith D (2011) Incidence and clearance of genital human papillomavirus infection in men (HIM): a cohort study. Lancet 377(9769):932–940

Görander S, Lagergård T, Romanik M, Viscidi RP, Martirosian G, Liljeqvist JA (2008) Seroprevalences of herpes simplex virus type 2, five oncogenic human papillomaviruses, and Chlamydia trachomatis in Katowice, Poland. Clin Vaccine Immunol 15(4): 675–680

Johnson TV, Hsiao W, Delman KA, Jani AB, Brawley OW, Master VA (2010) Extensive inguinal lymphadenectomy improves overall 5-year survival in penile cancer patients: results from the Surveillance, Epidemiology, and End Results program. Cancer 116(12):2960–2966

Kyo S, Inoue M, Koyama M, Fujita M, Tanizawa O, Hakura A (1994) Detection of high-risk human papillomavirus in the cervix and semen of sex partners. J Infect Dis 170(3):682–685

Larke N, Thomas SL, Dos Santos Silva I, Weiss HA (2011) Male circumcision and human papillomavirus infection in men: a systematic review and meta-analysis. J Infect Dis 204(9):1375–1390

Li N, Yang L, Zhang Y, Zhao P, Zheng T, Dai M (2011) Human papillomavirus infection and bladder cancer risk: a meta-analysis. J Infect Dis 204(2):217–223

Lu B, Viscidi RP, Wu Y, Lee JH, Nyitray AG, Villa LL, Lazcano-Ponce E, da Silva RJ, Baggio ML, Quiterio M, Salmeron J, Smith DC, Abrahamsen ME, Papenfuss MR, Stockwell HG, Giuliano AR (2012) Prevalent serum antibody is not a marker of immune protection against acquisition of oncogenic HPV16 in men. Cancer Res 72(3):676–685

McGinley KF, Hey W, Sussman DO, Brown GA (2011) Human papillomavirus testing in men. J Am Osteopath Assoc 111(3 Suppl 2):S26–S28

Moonen PM, Bakkers JM, Kiemeney LA, Schalken JA, Melchers WJ, Witjes JA (2007) Human papilloma virus DNA and p53 mutation analysis on bladder washes in relation to clinical outcome of bladder cancer. Eur Urol 52(2):464–468

Nyitray AG, Smith D, Villa L et al (2010) Prevalence of and risk factors for anal human papillomavirus infection in men who have sex with women: a cross-national study. J Infect Dis 201(10):1498–1508

Partridge JM, Koutsky LA (2006) Genital human papillomavirus infection in men. Lancet Infect Dis 6(1):21–31

Tay SK (2012) Cervical cancer in the human papillomavirus vaccination era. Curr Opin Obstet Gynecol 24(1):3–7

Wright TC Jr (2003) Chapter 10: cervical cancer screening using visualization techniques. J Natl Cancer Inst Monogr 31:66–71

Part VI

Uro-genital Cancer

Testicular Cancer

15

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Testicular cancer includes diverse groups of tumors, 95 % of which are germ cell tumors (GCTs). GCTs are generally categorized as seminoma and nonseminoma (NSGCT) due to differences in natural history and treatment.

GCTs are moderately rare malignancies, accounting for 1–2 % of cancers among men in the United States, with an incidence in the order of five cases per 100,000. Approximately 90 % of GCTs take place in the testis and 2–5 % are extragonadal (the retroperitoneum and mediastinum are the most common sites). With the advancement of cisplatin-based chemotherapy and the combination with surgery, GCTs have become a model of a curable neoplasm and supply as a paradigm for the multidisciplinary management of cancer (Einhorn 1981). Prior to the introduction of treatment with cisplatin, the cure rate for patients with advanced GCT was 5–10 %. At present the long-term survival for men with metastatic GCT is 80–90 %. Mortality from GCT is due to resistance to platin chemotherapy and to the not successful eradication of residual disease elements in the early course of therapy. Non-GCTs of the testis are rare and include sex cord/stromal tumors, lymphoid and hematopoietic tumors, tumors of the collecting duct and rete testis, and tumors of the testicular adnexa.

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V. Mirone (ed.), *Clinical Uro-Andrology*,
DOI 10.1007/978-3-662-45018-5_15,

15.1 Germ Cell Tumors

15.1.1 Epidemiology

In the United States, it was estimated that 8,400 men developed a testicular cancer in United States, and 380 would die of this disease (Jemal et al. 2010).

Testicular cancer is the most frequent tumor among men aged 20–40 years and the second most frequent cancer after leukemia among males aged 15–19 years (Horner et al. 2009). Testicular tumors are distributed in three peaks: infancy, ages 30–34 years, and approximately age 60. The incidence of bilateral GCT is approximately 2 % (Fossa et al. 2005).

Testicular lymphoma is less frequent than GCT but represents the greater part of testicular tumors in men older than 50 years and is more likely to have a synchronous bilateral presentation. The incidence of testicular cancer varies drastically according to geographic region: rates are highest in Scandinavia, Germany, Switzerland, and New Zealand; intermediate in the United States and Great Britain; and lowest in Africa and Asia. The incidence of testicular tumor in the United States in non-Hispanic whites is five times higher than the incidence in African-Americans, four times higher than the incidence in Asians, and 78 % higher than in Hispanics (Horner et al. 2009).

The incidence of GCT is increased worldwide (McKiernan et al. 1999; McGlynn et al. 2005; Purdue et al. 2005). In the United States, the age-adjusted incidence rate for males aged 15–49 years increased from 2.9 per 100,000 in 1975 to 5.1 per 100,000 in 2004 (Holmes et al. 2008). Over this time period incidence rates have increased substantially more for seminoma than NSGCT (McGlynn et al. 2005; Powles et al. 2005). A change of GCT stage has been viewed in several countries owing, in part, to augmented attentiveness and earlier diagnosis. The percentage of tumors diagnosed at a localized stage increased from 55 to 73 %, between 1973 and 2001 among white males. The stage distribution for African-American males remained stable during this time (McGlynn et al. 2005). Only 10–30 % of men will present with distant metastatic disease.

In the United Kingdom the change in stage distribution over time is largely restricted to an increase in localized seminoma and a decrease in metastatic NSGCT; rates of localized NSGCT and metastatic seminoma are largely unchanged (McGlynn et al. 2005). Currently, localized seminoma is the most common presentation of GCT, representing approximately 50 % of all men with GCT (Powles et al. 2005). Thus, contemporary testicular germ cell tumors have more favorable prognostic features on average compared with those diagnosed in the 1970s and 1980s.

15.1.2 Risk Factors

There are four well-known risk factors for testicular tumor: cryptorchidism, family history of testicular cancer, a personal history of testicular cancer, and intratubular germ cell neoplasia (ITGCN). Infertility also is a cause of a higher incidence of testicular cancer. Numerous studies have showed that current increases in the incidence of testicular cancer can be mostly attributed to birth cohort effects, according to whom diet and other environmental factors have a key role in GCT carcinogenesis (Liu et al. 1999; Huyghe et al. 2003; McGlynn et al. 2003; Richiardi et al. 2004; Bray et al. 2006; Verhoeven et al. 2008).

Males with cryptorchidism are four to six times more likely to be diagnosed with testicular cancer, but the relative risk (RR) falls to 2.0–3.0 if orchidopexy is performed before puberty (Dieckmann and Pichlmeier 2004; Wood and Elder 2009). A lot of studies support the thesis that most of the increased risk reflects an increased risk of cancer in the undescended testis, but a recent meta-analysis of cryptorchidism studies reported that the contralateral descended testis is at slightly increased risk (RR 1.74 [95 % CI, 1.01–2.98]) (Akre et al. 2009).

Men with a relative with testicular cancer have a considerably increased risk, and the median age at diagnosis in these men is 2–3 years younger than in the general population (Mai et al. 2009). An individual's RR for testicular cancer is 8.0–12.0 with an affected brother compared with

2.0–4.0 in those with an affected father (Westergaard et al. 1996; Sonneveld et al. 1999; Hemminki and Chen 2006).

Men with a history of testicular cancer are at a 12-fold increased risk of developing GCT in the contralateral testis, but the 15-year cumulative incidence is only 2 %. The risk is higher in patients who are younger when testicular cancer is diagnosed and in men whose initial GCT is seminoma (Theodore et al. 2004; Fossa et al. 2005). A study showed that a man younger than the age of 30 with a testicular seminoma has a 3.1 % risk of developing a contralateral testicular cancer (Fossa et al. 2005) and reported also that the 10-year overall survival after diagnosis with a second primary (i.e., contralateral) testicular cancer was 93 %. Most GCTs arise from a precursor lesion called intratubular germ cell neoplasia (ITGCN) (which is also referred to as carcinoma in situ). There is a significantly increased risk of developing invasive GCT in men with ITGCN. Different studies have demonstrated that ITGCN is present in adjacent testicular parenchyma in 80–90 % cases of invasive GCT and is associated with a 50 % risk of GCT within 5 years and a 70 % risk within 7 years (Skakkebaek et al. 1982; Dieckmann and Skakkebaek 1999; Montironi 2002).

Other studies showed that from 5 to 9 % patients with GCT, there is ITGCN within the unaffected contralateral testis, and the incidence of contralateral ITGCN increases to about 36 % in men with testicular atrophy or cryptorchidism (Dieckmann and Loy 1996; Dieckmann and Skakkebaek 1999).

With a gene expression profile analysis, it has been found that ITGCN develops before birth from an arrested gonocyte (Hussain et al. 2008; Sonne et al. 2009). In men with a history of GCT, the finding of testicular microlithiasis on ultrasound evaluation of the contralateral testis is associated with an increased risk of ITGCN (Karellas et al. 2007). Though the meaning of microlithiasis in the general population is not completely clear, a study of 1,500 army volunteers found a 5.6 % prevalence of microlithiasis, yet fewer than 2 % of those with microlithiasis developed cancer within the subsequent 5 years (DeCastro et al. 2008).

15.1.3 Pathophysiology

There are a lot of steps to make clear the carcinogenesis of GCTs. As described before, a precursor lesion, ITGCN, is necessary to testicular GCT development. ITGCN probably develops from arrested primordial germ cells or gonocytes that failed to differentiate into prespermatogonia (Rajpert-de Meyts and Hoei-Hansen 2007; Hussain et al. 2008). These cells are thought to lie dormant until after puberty when they are stimulated by augmented testosterone levels. The augmented incidence of testicular cancer, initiated in the first half of the twentieth century, has been gone together with an increased incidence of other male reproductive disorders, such as hypospadias, cryptorchidism, and subfertility (Rajpert-de Meyts and Hoei-Hansen 2007; Sonne et al. 2008). Testicular cancer and these other disorders are all consequences of a testicular dysgenesis syndrome, which in turn resulted from environmental and/or lifestyle factors and genetic susceptibility. The specific environmental or lifestyle factors have not been defined.

The first hypothesis about the risk factors referred to prenatal estrogen exposure, but this is controversial (Martin et al. 2008). Meanwhile there are stronger evidences that testicular dysgenesis syndrome can be caused by reduction in androgen activity. At same time this deficiency might be the cause also of cryptorchidism, hypospadias, and impaired spermatogenesis, but a direct link between reduced androgen signaling and ITGCN or GCTs remains hypothetical (Sonne et al. 2008; Hu et al. 2009). Another evidence for the contribution given by the environmental and lifestyle factors to testicular cancer includes the rapid increase in its incidence as well as findings that the risk in second-generation immigrants is similar to that in their country of birth. Some studies founded that mothers of children with testicular cancer (but not the testicular cancer patients themselves) have been found to have higher blood levels of certain organic pollutants compared with other mothers (Sonne et al. 2008).

Also the genetic factors have been evaluated, and the evidences include the clustering of testicular cancer in some families, the big disparity

in the rate of testicular cancer in black and white Americans, and the finding of susceptibility loci on chromosomes 5, 6, and 12 in case-control studies (Mai et al. 2009). Furthermore, specific polymorphisms of certain genes, including the gene encoding c-KIT ligand, have been associated with an increased risk of testicular cancer (Blomberg Jensen et al. 2008; Kanetsky et al. 2009). Gonocytes depend on c-KIT ligand for survival, and the gene for this protein is located on the short arm of chromosome 12. Approximately 70 % of GCTs have an extra copy of chromosome 12 in the form of an isochromosome 12p (i[12p]) (Bosl et al. 1989). Thus, a connection between mutations or polymorphisms in this gene and GCT has biologic plausibility.

The most important characteristic of GCTs is their sensitivity to cisplatin-based chemotherapy, which allows cure in almost all of patients with widely metastatic disease. The specific biologic basis of this acute vulnerability to chemotherapy is still not completely clear, but probably it derives from the low threshold for undergoing apoptosis in response to DNA damage due to the close relationship between GCTs and embryonal stem cells and gonocytes (Mayer et al. 2003; Schmelz et al. 2010).

GCTs have elevated intrinsic levels of wild-type TP53 protein (acting a role in cell cycle arrest and apoptosis), and TP53 mutations in GCTs are uncommon, yet differences have not been consistently found in TP53 status when comparing chemosensitive and chemoresistant germ cell tumors (Burger et al. 1998; Houldsworth et al. 1998). Likewise, in germ cell tumors, the expression of the antiapoptotic protein BCL2 is low, but BCL2 levels do not discriminate chemosensitive and chemoresistant cell lines (Mayer et al. 2003).

With gene expression analysis has been demonstrated an upregulation of numerous genes that facilitate apoptosis, including FASLG, TNFSF10, and BAX, whereas BCL2 is downregulated (Schmelz et al. 2010). Expression patterns of genes controlling the G1/S-phase checkpoint in GCTs seem to promote induction of apoptosis (Schmelz et al. 2010). Furthermore, GCTs do not have transporters to export cisplatin from the cell and have a diminished capability to repair cisplatin-induced DNA damage (Mayer et al. 2003).

Nevertheless, a few of GCTs are resistant to chemotherapy, and the origin of that resistance remains obscure, although DNA mismatch repair deficiency, microsatellite instability, and BRAF mutations have been associated with treatment failure (Honecker et al. 2009).

Up to 10 % of GCTs are extragonadal developing in midline anatomic locations. There are proposed two main theories concerning the pathogenesis of extragonadal GCTs. The first one proposes that the extragonadal GCTs originate from germ cells that had an unusual migration along the genital ridge and were able to survive in an extragonadal environment. The second hypothesis sustains a reverse migration from the testis to extragonadal locations (Chaganti and Houldsworth 2000). Primary mediastinal NSGCTs differ in numerous ways from those originating in the testis or retroperitoneum. Primarily they are less sensitive to chemotherapy and have a poor prognosis with a 5-year overall survival of about 45 % (Bokemeyer et al. 2002b). In mediastinal NSGCTs, there are often yolk sac tumor components; for this there is a correlation with elevations in serum α-fetoprotein (AFP) (Kesler et al. 2008). They are also associated with Klinefelter syndrome and with hematologic malignancies that carry extra copies of the short arm of chromosome 12, as seen in adult GCTs (Bokemeyer et al. 2002a; McKenney et al. 2007). In contrast, mediastinal seminomas carry a similar prognosis to testicular seminomas. Primary retroperitoneal GCTs are impossible to differentiate biologically from testicular GCTs and have the same prognosis.

15.1.4 Histopathology

GCTs are generally cataloged as seminoma and NSGCT, and the relative distribution of each is 52–56 % and 44–48 %, respectively (McGlynn et al. 2005; Powles et al. 2005). NSGCTs comprise embryonal carcinoma (EC), yolk sac tumor, teratoma, and choriocarcinoma subtypes, either alone as pure forms or in combination as mixed

GCT with or without seminoma (Ulbright 2005). Most NSGCTs are mixed tumors formed by two or more GCT subtypes. GCTs that contain both NSGCT subtypes and seminoma are classified as NSGCT.

Intratubular Germ Cell Neoplasia

Except the spermatocytic seminoma, all invasive GCTs developed by the adult arise from ITGCN. ITGCN is made of undifferentiated germ cells that seem like seminoma, located basally within the seminiferous tubules. In the tubule typically there is absent or decreased spermatogenesis, and normal cells are replaced by ITGCN. When a specimen obtained performing orchiectomy in men with testicular cancer shows presence of ITGCN, there is not any prognostic implications about risk of relapse of the cancer (von Eyben et al. 2004).

Seminoma

Seminoma is the most frequent category of GCT. Normally, seminomas arise at an older average age than NSGCTs, and the diagnosis is most common during the fourth or fifth decade of life (Rayson et al. 1998). The seminoma is a soft tan to white diffuse or multinodular mass. Necrosis could be present but is frequently focal and not prominent. Seminomas are a sheetlike collection of cells with polygonal nuclei and clear cytoplasm, with the cells that are collected into nests by fibrovascular septa containing lymphocytes (Ulbright 2005). Syncytiotrophoblasts, which are positive for human chorionic gonadotropin (hCG) marker, can be recognized in about 15 % of cases of pure seminoma, but there is not any clear prognostic significance (Cheville 1999). Lymphocytic infiltrates and granulomas are often seen and seminomas seem to be related with an increased incidence of sarcoidosis (Rayson et al. 1998; Tjan-Heijnen et al. 1998). Seminomas could be mystified with solid-pattern EC, yolk sac tumor, or Sertoli cell tumors (Ulbright and Young 2008). Even if immunohistochemical staining has no big role in the diagnosis of GCTs, seminomas are typically negative for CD30, positive for CD117, and strongly positive for placental alkaline phosphatase (PLAP). Anaplastic seminoma was a previously recognized subtype of seminoma, but this difference is of no clear biologic or clinical meaning and is no longer documented. Seminoma occurs from ITGCN and is believed to be the common precursor for the other NSGCT subtypes (Ulbright 2004). This aptitude of seminoma to transform into NSGCT elements has significant therapeutic implications for the managing of seminoma (Ulbright 2004).

Spermatocytic Seminoma

Spermatocytic seminoma represents less than 1 % of GCTs. It is a distinct clinicopathologic entity from other GCTs, but it is classified as a variant of seminoma. Spermatocytic seminoma does not develop from ITGCN, is not connected with cryptorchidism or bilaterality, does not arise as part of mixed GCTs, and does not express PLAP or i(12p) (Ulbright 2005). Histopathologically, it varies from seminoma in that the nuclei are round, it has minimal lymphocytic infiltration, and three distinct cell types are present, including small lymphocyte-like cells, medium-sized cells with dense eosinophilic cytoplasm and a round nucleus, and large mononucleated or multinucleated cells (Aggarwal and Parwani 2009). The sixth decade of life is the most involved (Eble 1994; Chung et al. 2004a). It is a benign tumor (only one documented case having metastasized) and is almost always cured with orchiectomy (Chung et al. 2004a).

Embryonal Carcinoma

EC shows undifferentiated malignant cells similar to primitive epithelial cells from early-stage embryos with packed pleomorphic nuclei (Ulbright 2005). Grossly, EC is a tan to yellow neoplasm that often displays large areas of hemorrhage and necrosis. At microscopic observation, these tumors appear significantly different, and they may grow in solid sheets or in papillary, glandular alveolar, or tubular patterns. At times, syncytiotrophoblasts can be recognized. EC is related with a high rate of metastasis, frequently in patients with regular serum tumor markers. EC is the most undifferentiated cell type of NSGCT and has a totipotential capacity to differentiate to

other NSGCT cell types (including teratoma) both within the primary tumor or metastases . EC typically stains for AE1/AE3, PLAP, and OCT3/4 and does not stain for c-KIT.

Choriocarcinoma

Choriocarcinoma is an aggressive tumor that classically shows with high serum hCG levels and disseminated disease. It is rare and usually spreads by hematogenous routes, and common sites of metastases comprise the lungs and brain, but eye and skin metastases have also been reported (Tinkle et al. 2001; Osada et al. 2004). Microscopically the tumor is composed of syncytiotrophoblasts and cytotrophoblasts, and specimen stains positively for hCG (Cheville 1999). Seminoma and EC may also contain syncytiotrophoblasts. Usually there are huge areas of necrosis and hemorrhage, so testicular choriocarcinoma is prone to serious hemorrhage, and such bleeding can be catastrophic, predominantly when it happens in the lungs or brain (Motzer et al. 1987).

Yolk Sac Tumor

Yolk sac tumors (also called endodermal sinus tumors) are only a small part of adult-type GCTs but are more common in mediastinal and pediatric GCTs. In mixed GCTs frequently some component of yolk sac tumor can be included, which consists of a reticular network of medium-sized cuboidal cells with cytoplasmic and extracytoplasmic eosinophilic, hyaline-like globules (Epstein 2010). Hyaline globules are a typical characteristic and are present in up to 84 % of cases. Yolk sac tumors can grow in a glandular, papillary, or microcystic pattern. The Schiller-Duval body is a distinctive feature, which looks a lot like endodermal sinuses, and is seen in approximately half of cases. Yolk sac tumors almost always produce AFP but not hCG. Among men with CS I NSGCT with standard serum tumor markers, the presence of a yolk sac tumor is related with a minor risk of relapse, but this can merely be a result of serum tumor markers (i.e., AFP) having a higher sensitivity to identify micrometastatic disease in this type of GCT (Read et al. 1992).

Teratoma

Teratoma in the ancient Greek means "monster tumor." Teratomas include well-differentiated or moderately differentiated elements of at least two of the three germ cell layers of endoderm, mesoderm, and ectoderm. Normally all components are intermixed. Well-differentiated tumors are marked as mature teratomas, and the partially differentiated are called immature teratomas. Mature teratomas may contain elements of mature bone, cartilage, teeth, hair, and squamous epithelium. Their form may depend on the elements within it, with most tumors having solid and cystic areas. Generally this tumor is related with usual serum markers, but mildly elevated serum AFP levels are often reported. Pure teratomas are uncommon but roughly 47 % of adult mixed GCTs contain teratoma (Epstein 2010). In adults, teratomas are histologically benign but are frequently found at metastatic sites in patients with advanced NSGCT. A hypothesis is that nonteratomatous elements (mostly EC) are able to mature into teratoma and that the metastases derive from these elements before their differentiation. Teratoma is resistant to chemotherapy. The intrinsic chemoresistance of teratoma reduces the possible treatment approaches for NSGCT that utilize chemotherapy alone. Sometimes teratomas present genetic abnormalities recurrently found in malignant GCT elements, including aneuploidy, i(12p), and widely variable proliferative capacity (Castedo et al. 1989; Sella et al. 1991). Different studies demonstrated that cystic fluid from teratoma often contains hCG and AFP, corroborating the malignant potential of teratoma (Sella et al. 1991; Beck et al. 2004). The genetic instability of teratoma has significant clinical implications. Teratomas may develop uncontrollably, invade adjacent structures, and become unresectable (growing teratoma syndrome) (Logothetis et al. 1982). Infrequently teratoma may transform into a somatic malignancy such as rhabdomyosarcoma, adenocarcinoma, or primitive neuroectodermal tumor (Little et al. 1994; Comiter et al. 1998; Motzer et al. 1998). In these cases, the literature uses the appellatives "teratoma with somatic-type malignancy" or "teratoma

with malignant transformation." Frequently abnormalities of chromosome 12 or i(12p) are shown, preserving their origin from GCT. These kinds of teratomas are highly aggressive, resistant to conventional chemotherapy, and associated with a poor prognosis. Last but not least, unresected teratoma in patients with advanced NSGCT may result in late relapse (Sheinfeld 2003).

15.1.5 Clinical Presentation

In most cases the presentation of testicular cancer is a painless testicular mass. A less common presentation is represented by acute testicular pain, due to a rapid expansion of the testis caused by intratumor hemorrhage or infarction depending on tumor growth.

Pain is usually associated with NSGCT, because these tumors are inclined to be more vascular and show more fast growth compared with seminomas. Patients commonly report a history of testicular trauma, although incidental trauma is likely responsible of an increased attention of the patients on his testis for the first time. A vague scrotal discomfort or a heaviness can be complained by patients. Regional or distant metastasis at diagnosis is present in about two thirds of NSGCTs and 15 % of pure seminomas, and symptoms related to metastatic disease are the presenting complaint in 10–20 % of patients. Sometimes a palpable mass can be caused by bulky retroperitoneal metastasis, associated with abdominal pain, flank pain due to ureteral obstruction, back pain due to involvement of the psoas muscle or nerve roots, lower extremity swelling due to compression of the inferior vena cava, or gastrointestinal symptoms. If there is pulmonary metastasis, they may cause dyspnea, chest pain, cough, or hemoptysis.

Metastasis to supraclavicular lymph nodes can arise as a neck mass. About 2 % of men have gynecomastia, and this is caused by the combination of different factors as high serum hCG levels, decreased androgen production, or augmented estrogen levels (frequently seen in men with Leydig cell tumors). About two thirds of men with GCT have diminished fertility, but it is not a common initial presentation.

15.1.6 Clinical Examination

A correct physical examination requires cautious inspection of both the affected and the normal contralateral testes, investigating their size and uniformity and palpating for any testicular or extratesticular masses. Atrophy of the involved or contralateral testis is common, predominantly in patients with a history of cryptorchidism. Any solid area within the testis should suggest further investigations cause is indicative of a possible malignancy. Sometimes there is a hydrocele along with testicular cancer and can falsify the physician's examination of the testis. In this case, to improve the diagnostic capability, a scrotal ultrasonography is warranted. The evaluation of the patient should be carried out for any evidence of palpable abdominal mass or tenderness, inguinal lymphadenopathy (predominantly if he had inguinal or scrotal surgery), gynecomastia, and supraclavicular lymphadenopathy, and the research for intrathoracic disease should be done with the auscultation of the chest.

15.1.7 Differential Diagnosis

There are a lot of diseases that we must consider in the differential diagnosis of testicular mass, including epididymo-orchitis, testicular torsion, hematoma, or paratesticular neoplasm (benign or malignant). Other possible similar diseases which can be distinguished from a testicular mass by physical examination comprise hernia, varicocele, or spermatocele. A solid intratesticular mass should be considered cancer until proved otherwise and it is mandatory investigate this mass with scrotal ultrasonography. In patients which received a diagnosis of epididymo-orchitis, a second evaluation is compulsory within 2–4 weeks of treatment with a proper oral antibiotics administration. If there is a persistent mass or continuous pain, they should be investigated further with scrotal ultrasonography.

15.1.8 Diagnosis: Importance of Timing

Testicular cancer is the tumor most frequent in young adult males and is also famous for the diagnostic delay due to patient and physician's delay. Patients affected by testicular cancer are usually young and are often less prone to medical examination for symptoms due to denial, ignorance, or limited access. In other cases the delay is due to misunderstanding by physician in the diagnosis. Studies show that more than one third of testicular tumors are diagnosed as epididymitis or hydrocele at first (Bosl et al. 1981). Rarely, in patients with signs or symptoms from metastatic GCT, the physician could focus his/her attention only on the symptomatic metastasis failing to diagnose GCT. These patients may undergo inappropriate treatment, diagnostic tests, and superfluous surgery with consequent delays in best therapy. In the literature, there are reported cases describing patient which underwent exploratory laparotomy, neck dissection, or mastectomy for unsuspected metastatic GCT. The absence of an early diagnosis is associated with advanced clinical stage, suboptimal response to chemotherapy, and reduced survival. Moul and colleagues (1990) described a decrease in survival in GCT patients cured from 1970 to 1987 with a diagnostic delay greater than 16 weeks, even though an important survival difference was not detected among patients treated in the cisplatin era.

In the literature, a higher number of men requiring intensive chemotherapy (multiple regimens, high dose, and salvage chemotherapy) are reported among those with a treatment delay greater than 30 days due to avoidable exploratory laparotomy (Stephenson et al. 2004).

The improvement of physician's education and patient's compliance can reduce the diagnostic delay. Any male 15–50 years old with a solid testicular mass, midline retroperitoneal mass, or mass in the left supraclavicular fossa should be investigated for the diagnosis of GCT. A methodical physical examination with proper radiologic (testicular ultrasonography) and serologic evaluations (serum AFP, hCG, lactate dehydrogenase [LDH]) is the correct way to obtain a correct diagnosis.

15.1.9 Disease Determination, Diagnostic, and First Management

15.1.9.1 Scrotal Ultrasonography

Scrotal ultrasonography is a technique capable of differentiating intratesticular masses from extratesticular lesions with high-frequency transducers (5–10 MHz). It is often used because it is widespread, cheap, and noninvasive. Scrotal ultrasonography must be performed, after the physical examination, in patients who show testicular mass, hydrocele, or other unknown scrotal symptoms or signs.

Ultrasonography can distinguish GCT from NSGCT. In fact GCT appears as multiple discrete hypoechoic lesions. Heterogeneous echostructure is typically associated with NSGCT, because seminomas typically have a homogeneous echostructure. The increase of vascularization within the lesion on color Doppler ultrasonography is indicative of malignancy; however, its absence does not exclude GCT. Testicular microlithiasis can be recognized by ultrasonography, but its presence does not require further investigation because the association with GCT has not been well defined (DeCastro et al. 2008). Although the incidence (2 %) and diagnosis (0.5 % of all GCTs) of bilateral tumors are low, both testes should be evaluated ultrasonographically, while metachronous presentation is more frequent (Fossa et al. 2005). In men with advanced GCT and a normal testicular examination, scrotal ultrasonography should be executed to rule out the presence of a small, impalpable scar or calcification, indicating a "burned-out" primary testicular tumor. The diagnosis of small (<10 mm), impalpable intratesticular lesions in the absence of disseminated GCT or elevated serum tumor markers is very difficult because they could be benign (testicular cysts, small infarcts, Leydig cell nodules, or small Leydig cell or Sertoli cell tumors) or even malignant (usually seminoma) (Hindley et al. 2003; Connolly et al. 2006; Muller et al. 2006).

Management options include inguinal orchiectomy, which should be performed when there are signs of malignancy (in fact the risk increases

with the size of the lesion) (Carmignani et al. 2005); inguinal exploration with intraoperative ultrasonography which can be useful to locate the lesion; excision (with frozen section analysis to rule out GCT); and observation with frequent ultrasonographic evaluation (with exploration of growing lesions).

15.1.9.2 Serum Tumor Markers

High levels of serum tumor markers (LDH, AFP, and hCG) can be found in testicular tumor, especially in NSGT. They are necessary in its diagnosis, prognosis, evaluation of treatment, and monitoring for risks of relapse through evaluation of enzymes before and after orchiectomy. But the serum tumor marker test should not be used to evaluate the use of orchiectomy.

At diagnosis, AFP levels are elevated in 50–70 % of low-stage (CS I, IIA, IIB) NSGCT and 60–80 % of advanced (CS IIC, III) NSGCT. EC and yolk sac tumors secrete AFP. Choriocarcinomas and seminomas do not secrete AFP. The half-life of AFP is 5–7 days. AFP levels are not specific because they also can be found in hepatocellular carcinoma and cancers of the stomach, pancreas, biliary tract, and lung, or in nonmalignant liver disease (autoimmune, drug induced, infectious, alcohol induced), ataxic telangiectasia, and hereditary tyrosinemia.

hCG levels are elevated in 20–40 % of low-stage NSGCT and 40–60 % of advanced NSGCT. About 15 % of seminomas secrete hCG. Also choriocarcinoma and EC secrete hCG. Levels greater than 5,000 IU/L are frequently associated with NSGCT. The half-life of hCG is 24–36 h. hCG levels may be elevated in cancers of the liver, breast, pancreas, stomach, biliary tract, kidney, and bladder.

False positive can be given by cross-reactivity of the hCG assay with luteinizing hormone in patients with primary hypogonadism or by marijuana use. Elevated serum hCG results caused by hypogonadism will normalize within 48–72 h after the administration of testosterone, and this can be done to distinguish between true- and false-positive hCG results.

LDH levels are increased about 20 % of low-stage GCTs and 20–60 % of advanced GCTs. A nonspecific marker for GCT in fact is expressed in tissues such as smooth, cardiac, and skeletal muscles or in diseases like a lymphoma. LDH-1 is commonly the isoenzyme most elevated in GCT. LDH-1 levels are correlated with the chromosome arm 12p copy number, which is frequently amplified in GCT. High levels of LDH are correlated with the mass of disease. The serum half-life of LDH is 24 h.

In rare patients who present a testicular, retroperitoneal, or mediastinal primary tumor and conditions in which the patients require urgent treatment, elevated serum AFP and/or hCG levels may be considered sufficient for diagnosis of GCT. For rare patients with medically unstable disease, treatment must not be delayed until histology results permit a tissue diagnosis. However, these patients should have radical orchiectomy after the completion of chemotherapy, because the testis is a sanctuary site for malignant GCT owing to the blood–testis barrier and because the testis frequently contains residual invasive GCT, teratoma, and/or ITGCN (Geldart et al. 2002).

15.1.9.3 Radical Inguinal Orchiectomy

A removal of the tumor-bearing testis and spermatic cord to the level of the internal inguinal ring should be performed in patients with a suspect testicular neoplasm. A transscrotal orchiectomy or biopsy is contraindicated because it amplifies the risk of local recurrence and pelvic or inguinal lymph node metastasis. Because of the rapid growth of GCT, orchiectomy should be performed quickly, avoiding an unjustified delay. Radical orchiectomy has different important roles: it defines the histologic diagnosis and primary T stage, gives important prognostic information from the tumor histology, and is curative in 80–85 % and 70–80 % of CS I seminoma and CS I NSGCT, respectively. The histopathologic examination of the testis helps to define the histologic type of the tumor, the tumor size, multifocality, local tumor invasion (rete testis, tunica albuginea, tunica vaginalis, epididymis, spermatic cord, scrotum), primary T stage (Sobin and Wittekind 2002; Greene et al. 2002), presence of ITGCN, invasion of blood or lymphatic vessels (termed lymphovascular invasion [LVI]), and the surgical margin status

(Sobin and Wittekind 2002). Mixed GCTs have to be evaluated by each individual tumor subtype and its relative proportion. A review of primary tumor specimens by experienced pathologists is necessary, because the treatment of GCT is based on the histopathologic diagnosis.

15.1.9.4 Testis-Sparing Surgery

Patient suspected of having a testicular neoplasm with a normal contralateral testis should not undergo a testis-sparing surgery. However, it may be indicated for organ-confined tumors of less than 2 cm in patients with synchronous bilateral tumors or tumor in a solitary testis with sufficient testicular androgen production. If serum AFP, hCG, and LDH values are normal, suspected benign tumor or indeterminate lesion can be treated with a testis-sparing surgery. This procedure is frequently unsuitable for larger tumors (>2 cm) because a complete excision frequently leaves insufficient residual testicular parenchyma for preservation. When this kind of surgery is performed, biopsies of the adjacent testicular parenchyma should be executed to verify an eventual ITGCN, which is present in adjacent testicular parenchyma in 80–90 % cases of GCT and is associated with a 50 % risk of GCT within 5 years and 70 % within 7 years (Skakkebaek et al. 1982; Dieckmann and Skakkebaek 1999; Montironi 2002). Adjuvant radiotherapy to the residual testis using doses of 20 Gy or greater is usually sufficient to prevent the development of a GCT.

15.1.9.5 Biopsy of the Contralateral Testis

In normal patients with GCT, the risk of ITGCN in the contralateral testis is between 5 and 9 % (Dieckmann and Skakkebaek 1999), while it rises to 36 % in patients with an atrophic testis, history of cryptorchidism, or younger than 40 years (Dieckmann and Loy 1996). In the latter category of patients, an open inguinal biopsy of the contralateral testis may be considered (Motzer et al. 2006).

15.1.9.6 Supposed Extragonadal GCT

Extragonadal GCTs are 2–5 % of GCT (Bokemeyer et al. 2002b). One third of the patients with metastatic GCT without a testicular mass definitively have a primary extragonadal GCT (Scholz et al. 2002). GCT should be considered in any young male with a midline mass. For the diagnosis of GCT, elevated serum AFP and/or hCG and a normal testicular evaluation are enough, while histologic confirmation by biopsy is not necessary before starting therapy. If serum tumor markers are regular, the diagnosis of GCT can be confirmed only by the biopsy of the mass. A biopsy specimen presenting poorly mature carcinoma represents a diagnostic dilemma if a primary tumor site cannot be confirmed. Inguinal orchiectomy is indicated in patients with probable retroperitoneal extragonadal GCT at some point during their treatment course if the pattern of metastasis is consistent with a right- or left-sided testicular primary tumor or if there is ultrasonographic evidence of a "burned-out" primary tumor.

15.1.10 Clinical Staging

The prognosis of GCT and the treatment choices are led by the clinical stage; this is an estimation of how much cancer is based on histopathologic exam results and the pathologic stage of primary tumor, the levels of tumor markers in serum of patients with orchiectomy, and on any metastases and their extension evaluated with imaging techniques. Only in 1997 an international classification of GCT was established by the American Joint Committee on Cancer (AJCC) and Union Internationale Contre le Cancer (UICC); this staging system is unique for the reason that serum tumor marker group(s) centered on postorchiectomy AFP, hCG, and LDH levels is used to improve the prognostic grades as determined by body extension of pathological process.

Nowadays the CS is divided in three stages: the first one is clinically defined as testis-confined disease, the second one by the extension to the retroperitoneal lymph node metastasis, and the third one by the involvement of non-regional lymph node and/or organ metastasis.

15.1.10.1 Staging Imaging Studies

The expectable pattern of metastatic diffusion of GCT has facilitated the successful treatment.

Excluding the only choriocarcinoma that spreads via hematogenous vessels, the most important way of cancer diffusion is through lymphatic vessels, from the principal tumor mass to the retroperitoneal lymph nodes (that represents the first metastatic site in 70–80 % of patients), and then to the farthest sites. A series of studies on retroperitoneal lymph node dissection (RPLND) have increased the knowledge of the testicular lymphatic drainage, and they revealed the common sites of metastatic spread (Sheinfeld 1994). The interaortocaval lymph nodes inferior to the renal vessels represent for right testicular tumors the primary drainage site, followed by the paracaval and para-aortic nodes; instead for left testicular tumors, the first "landing zone" is the para-aortic lymph nodes, followed by the interaortocaval nodes (Donohue et al. 1982). Moreover, in the retroperitoneum, the pattern of lymphatic drainage is from right to left; therefore, contralateral dissemination is commonly seen from the primary metastatic site with right-side tumors but is unusual for the left-side one and generally is associated with bulky disease. More caudal "landing zone" of metastatic disease typically reproduces retrograde spread to distal iliac and inguinal lymph nodes, subordinate to seriousness of disease, and very seldom aberrant testicular lymphatic drainage. Retroperitoneal lymphatic vessels drain into the cisterna chyli behind the right renal artery and right crus of the diaphragm, thus making it possible to see, in patients with retroperitoneal disease, the metastasis of retrocrural lymph node that via the thoracic duct spreads to the posterior mediastinum and left supraclavicular fossa.

Staging imaging studies of the abdomen and pelvis are fundamental for patients with GCT; the most operative and noninvasive technique is the computed tomography (CT) after administration of intravenous or oral contrast agents. Moreover, CT procures a more specific anatomic evaluation of the retroperitoneum to detect pathologic anomalies that may complicate successive RPLND, such as a circumaortic or retroaortic left renal vein, lower pole renal artery, or retrocaval right ureter. Lymphangiography has no role where transaxial imaging is available. Inflamed retroperitoneal lymph nodes are found on CT in 10–20 % of seminomas and 60–70 % of NSGCT. The retroperitoneum represents the most difficult area to stage clinically; in fact otherwise the progresses in CT over the past four decades, also in the presence of a "normal" CT scan about 25–35 % pathological retroperitoneal lymph nodes has been reported for CS I NSGCT (Fernandez et al. 1994). There is not unanimous consensus about universal size criteria for retroperitoneal lymph nodes that establish a "normal" CT scan; a size of 10 mm is detected as cutoff for identifying enlarged lymph nodes, but false-negative rates up to 63 % have been described when this size criterion is used. Among patients with CS IIA and IIB disease, clinical overrating by CT (i.e., pathologically negative lymph nodes at RPLND despite enlarged lymph nodes on CT) is reported in 12–40 % of patients.

The knowledge of the primary drainage sites for left- and right-side tumors has led the studies to increase the sensitivity of abdominopelvic CT by reducing the size criteria for clinically positive lymph nodes in the primary "landing zone," and a size criterion smaller of 4 mm has been proposed. Leibovitch and colleagues (1995) showed that a size cutoff of 4 mm in the primary landing zone and 10 mm outside this region was correlated with a sensitivity and specificity for pathologic stage II disease of 91 and 50 %, respectively. In a similar study, Hilton and associates (1997) described a sensitivity and specificity of 93 and 58 %, respectively, using a cutoff of 4 mm for lymph nodes in the primary "landing zone" that were anterior to a horizontal line bisecting the aorta. Based on this information, retroperitoneal lymph nodes greater than 5–9 mm in the primary "landing zone," particularly if they are anterior to the great vessels on transaxial CT images, should be viewed with misgiving for regional lymph node metastasis. Due to the rapid growth of GCT, it is suitable to base the management decision on CT studies executed within 4 weeks of the start of treatment. Malignant GCT gathers fluorodeoxyglucose (FDG), and several researches have studied FDG-labeled positron emission tomography (FDG-PET) in the staging of GCT at diagnosis and assessing response after chemotherapy.

Numerous small pilot studies proposed that FDG-PET can recognize retroperitoneal metastasis in low-stage seminoma and NSGCT with more accuracy than CT (Albers et al. 1999). In a prospective trial, FDG-PET studies in 111 contemporary patients with CS I NSGCT on surveillance were reviewed; relapse was detected in 33 of 87 patients who were PET negative, with a valued relapse-free rate of 63 % (Huddart et al. 2007). The researcher established that FDG-PET is not sufficiently sensitive to accurately stage CS I NSGCT. De Wit and associates (2008) also recounted that FDG-PET yielded only rather better results than CT as a primary staging technique for low-stage NSGCT. Nowadays there is no part for FDG-PET in the routine valuation of NSGCT and seminoma at the time of diagnosis. CS II disease is categorized into three groups—IIA (enlarged retroperitoneal lymph nodes ≤2 cm), IIB (enlarged retroperitoneal lymph nodes >2 cm but ≤5 cm), and IIC (enlarged lymph nodes >5 cm)—which are based on the size of regional lymph node(s) as determined by abdominopelvic imaging.

15.1.10.2 Chest Imaging

A chest imaging is required before any treatment decisions are taken for every patients with GCT. It is very rare, especially for seminoma, to observe thorax metastasis in the lack of retroperitoneal one and/or high serum tumor markers. Hence, routine chest CT may be correlated with an elevated amount of false-positive findings, which may complicate successive therapy (Horan et al. 2007). Thus, it is suggested to achieve a chest RX at the time of diagnosis as a first imaging technique, and then a CT should be executed only in patients with raised postorchiectomy levels of serum tumor markers, evidence of metastatic disease by physical examination or abdominopelvic CT, and atypical or ambiguous findings on thorax radiography. It could be sensible to effect chest CT in patients with CS I NSGCT with evidence of LVI or EC predominance because some works have reported an important rate of hematogenous metastasis to the lung in the context of a negative CT for retroperitoneal metastasis (Hermans et al. 2000; Sweeney et al. 2000). Mediastinal or hilar lymphadenopathy without retroperitoneal disease suggests a suspicion of non-GCT etiology such as lymphoma or sarcoidosis, and histologic confirmation of GCT by mediastinoscopy and biopsy should be performed before initiating systemic therapy (Hunt et al. 2009). In non-attendance of symptoms or other clinical signs of disease, it is unusual in GCT observing visceral metastasis to bone or brain; for this reason, there is no evidence to execute a bone scintigraphy or brain CT at the time of diagnosis. An exception to this is brain CT for patients with a very high hCG value (>10,000 IU/L) because these levels are often joined with metastatic choriocarcinoma, which has a propensity for brain metastases.

15.1.11 Prognosis in Advanced GCT

An international, retrospective pooled analysis of 5,202 patients with advanced NSGCT treated between 1975 and 1990 with platin-containing chemotherapy regimens (cisplatin or carboplatin) identified AFP, hCG, and LDH levels at the initiation of chemotherapy, the presence of non-pulmonary visceral metastasis, and primary mediastinal NSGCT as significant and independent prognostic factors for progression and survival. In 660 patients with advanced seminoma, only the presence of non-pulmonary visceral metastasis was an important predictor of progression and survival (International Germ Cell Consensus Classification 1997). Based on these evidences, the International Germ Cell Consensus Classification Group (IGCCCG) risk classification for advanced GCT was settled. The IGCCCG risk group should be defined for each patient with metastatic GCT, and this could be led treatment decision making on the selection of chemotherapy (discussed later). This systematization involves only patients with advanced GCT at the time of diagnosis, but not patients with relapsed GCT. The classification is also based on the postorchiectomy serum tumor marker levels at the beginning of chemotherapy, not the preorchiectomy levels. 56, 28, and 16 % of patients with advanced NSGCT are categorized as good, intermediate,

and poor risk, respectively, by the IGCCCG criteria, and the 5-year progression-free and overall survival rates for these patients are 89 % and 92 %, 75 % and 80 %, and 41 % and 48 %, respectively. There is no poor-risk category for seminoma. Approximately 90 and 10 % of patients with advanced seminoma are classified as good and intermediate risk, respectively, by the IGCCCG criteria, and the 5-year progression-free and overall survival rates for these patients are 82 % and 86 % and 67 % and 72 %, respectively. Van Dijk and coworkers (2006) published a meta-analysis of ten studies of 1775 NSGCT patients treated after 1989 and reported pooled 5-year survival estimates of 94, 83 and 71 % for good-, intermediate-, and poor-risk patients by the IGCCCG criteria. From these data, the survival results significantly improved, especially if they are compared with those of the original study (particularly for those classified as poor risk), and are ascribed to more efficient treatment strategies and more understanding in treating NSGCT patients. The TNM system does incorporate marker levels (S0-3) and non-pulmonary visceral metastasis in the staging of testicular cancer. However, this system does not recognize the differences in prognosis between seminomas and NSGCT with non-pulmonary visceral metastasis. In the TNM system, these would both be classified as CSIII, but IGCCCG would classify the former as intermediate risk and the latter as poor risk. As such, the IGCCCG system is preferentially used for prognostic assessment and the selection of chemotherapy.

15.1.12 Treatment

To avoid evitable deaths or pain, a rapid diagnosis and an appropriate treatment for GCT are necessary. After orchiectomy, staging imaging studies, serum tumor marker status, and treatment plans should be performed rapidly. *Considering that the cure is possible even in the presence of metastasis*, *an aggressive chemotherapeutic and postchemotherapeutic approach* (*postchemotherapeutic surgery*) *has been developed*. Chemotherapy is generally administered regardless of low white blood cell counts or thrombocytopenia, and nephrotoxic chemotherapy (cisplatin) is often administered even in the presence of moderate-to-severe renal insufficiency (Williams et al. 1987a; Einhorn et al. 1989; Bajorin et al. 1993; Loehrer et al. 1995; Bokemeyer et al. 1996b; Nichols et al. 1998; de Wit et al. 2001). After chemotherapy for NSGCT, an aggressive surgical approach is taken to resect all sites of residual disease, even if this involves multiple anatomic sites. The young age and generally good health of GCT patients permit an aggressive treatment approach if needed. Serum tumor markers strongly influence the management of GCTs, particularly NSGCT. *An initial approach with chemotherapy is indicated in patients with elevated serum AFP or HCG after orchiectomy*: *in fact the elevation of these markers in the blood indicates the presence of metastatic disease*. For patients receiving chemotherapy, rising serum tumor marker levels during or after therapy generally indicate refractory or relapsed disease, respectively. As discussed, serum AFP, hCG, and LDH levels at the beginning of chemotherapy are important prognostic factors and define the type and duration of chemotherapy regimens (International Germ Cell Consensus Classification 1997). Testicular cancer is a relatively rare disease; the treatment algorithms are relatively complex (Donohue et al. 1993, 1995; Heidenreich et al. 2003; Stephenson et al. 2005b; Williams et al. 2009b). If the treatment is provided at a high-volume institution, the survival rate improves (Aass et al. 1991; Harding et al. 1993; Feuer et al. 1994; Collette et al. 1999; Joudi and Konety 2005; Suzumura et al. 2008). Therefore, whenever possible, GCT patients should be treated at a high-volume centers and RPLND should be performed by experienced surgeons.

15.1.12.1 Differences Between Seminoma and NSGCT

It is very important to distinguish between seminoma and NSGCT for treatment purposes. In comparison with NSGCT, seminoma has a more favorable natural history. In fact seminoma is less aggressive, is usually diagnosed at an earlier stage,

and spreads predictably along lymphatic channels to the retroperitoneum before spreading hematogenously to the lungs or other organs. *At diagnosis the proportion of patients with CS I, II, and III disease is 85, 10, and 5%, respectively, for seminoma and approximately 33, 33, and 33% for NSGCT* (Powles et al. 2005). The proportion of patients with CS I are 85 % for seminoma while that of patients with CS I for NSGCT are just 33 %. Occult metastasis occurs less frequently in patients with CS I for seminoma. *Seminoma also has a lower risk of systemic relapse after treatment of the retroperitoneum (1–4% after radiotherapy for seminoma vs. 10% after RPLND for NSGCT*). Serum tumor markers do not reach high levels in seminoma and are not used in the evaluation of risk in the IGCCCG risk classification. Compared with NSGCT, *seminoma is exquisitely sensitive to radiation therapy and platin-based chemotherapy*. Regarding the former aspect, substantially lower radiation doses are required to eradicate seminoma compared with other solid tumors. As such, *radiation therapy is a standard treatment option for CS I and IIA-B seminoma but has no role in NSGCT*, with the exception of treatment for brain metastases. Seminoma is sensitive to lower radiation doses, while radiation therapy does not have a role in NSGCT. Seminoma is also very sensitive to platin-based chemotherapy. *It is very important to consider the potentiality of seminoma to transform into NSGCT after a failure of chemotherapy or a radiation therapy*. This eventuality influences the management of the treatment. In fact, an eventual NSGCT at metastatic sites can require both chemotherapy and surgery. It is widely accepted that the successful integration of systemic therapy and PCS is a major contributing factor to the improved cure rates for metastatic GCT seen over the past several decades. Although minimizing unnecessary treatment is an important goal, chemotherapy, radiation therapy, and CT imaging are associated with an increased lifetime risk of secondary malignant neoplasms and/or cardiovascular disease (Meinardi et al. 2000; Zagars et al. 2004; Hinz et al. 2008; van den Belt-Dusebout et al. 2007; Tarin et al. 2009). In contrast, RPLND is associated with a substantially more favorable long-term toxicity profile when performed by experienced surgeons.

15.1.12.2 NSGCT

Clinical Stage I NSGCT

Approximately 33 % of NSGCT patients have CS I with normal postorchiectomy levels of serum tumor markers. Although the controversy about the optimal management of these patients, surveillance is the preferred approach in select centers because it is not associated with morbidity such as RPLND and primary chemotherapy approach after orchiectomy. In fact, occult metastasis occurs in only 20–30 % of patients overall so radiotherapy or chemotherapy represents overtreatment in most cases.

Risk Assessment

For occult metastasis, LVI and a predominant component of EC are commonly identified as histopathologic risk factors (Heidenreich et al. 1998; Sogani et al. 1998; Hermans et al. 2000; Sweeney et al. 2000; Alexandre et al. 2001; Roeleveld et al. 2001; Vergouwe et al. 2003; Nicolai et al. 2004; Stephenson et al. 2005a; de Wit et al. 2008). *The risk of occult metastasis is less than 20% if these two risk factors are absent*. Other identified risk factors include advanced pT stage, absence of mature teratoma, absence of yolk sac tumor, presence of EC (regardless of the percent composition), percentage of MIB-1 staining, tumor size, and patient age. In a pooled analysis of 23 studies assessing predictors of occult metastasis in CS I NSGCT, LVI (odds ratio [OR] 5.2), MIB-1 staining greater than 70 % (OR 4.7), and EC predominance (OR 2.8) were identified as the strongest predictors. Moreover, the results of abdominopelvic CT should be considered when defining treatment recommendations because a size cutoff of 1 cm is associated with a high false-negative rate. Retroperitoneal lymph nodes greater than 5–9 mm in the primary "landing zone" should be viewed with suspicion of regional lymph node metastasis (Freedman et al. 1987; Read et al. 1992; Heidenreich et al. 1998; Sogani et al. 1998; Hermans et al. 2000; Alexandre et al. 2001; Albers et al. 2003; Nicolai et al. 2004; Stephenson et al. 2005a). Three recent prospective studies suggest that LVI and EC predominance may be associated with a lower

risk of metastasis, in particular between 35 and 45 %, not 50–70 % as has been reported in most older studies.

Surveillance

Surveillance cures 70–80 % of patients with CS I NSGCT after orchiectomy with identical survival rates of RPLND and primary chemotherapy (International Germ Cell Consensus Classification 1997). As a result, initial surveillance is regarded as a standard treatment option for CS I NSGCT. On the other hand, surveillance is associated with the highest risk of relapse and the potential for secondary malignant neoplasm due to the number of CT (Brenner and Hall 2007; Tarin et al. 2009). *Published surveillance series have reported results on more than 2,500 men, with a mean relapse risk of 28 % and a 1.2 % cancer-specific mortality. More than 90 % of relapses occur within the first 2 years, but late relapses (>5 years) are found in up to 1 % of patients (as many as 5 % in some reports)* (Daugaard et al. 2003). Induction chemotherapy is indicated as the common treatment in patients with bulky (>3 cm) retroperitoneal lymphadenopathy, elevated serum tumor marker levels, or distant metastasis, while RPLND is commonly indicated if the lymphadenopathy is not bulky and the serum markers are normal (Stephenson et al. 2007). The surveillance schedule employed in published series is highly variable and no schedule has been demonstrated to be superior to another in terms of survival. Surveillance imaging and testing is intense in years 0–2, with less frequent testing in years 3–5 because the relapses occur more frequently within the first 2 years. The risk of late relapse mandates surveillance beyond 5 years.

Retroperitoneal Lymph Node Dissection

The rationale for RPLND for CS I NSGCT is based on several factors: (1) the retroperitoneum is the most common site of occult metastatic disease and the risk of associated systemic disease is low; (2) 15–25 % incidence of retroperitoneal teratoma (which is resistant to chemotherapy) in those with occult metastasis; (3) low risk of abdominopelvic recurrence after full, bilateral template RPLND thereby obviating the need for routine surveillance CT; (4) high cure rates after RPLND alone for patients with low-volume (pN1) retroperitoneal malignancy and teratoma (pN1-3); (5) avoidance of chemotherapy in more than 75 % or more of patients if adjuvant chemotherapy is restricted to those with extensive retroperitoneal malignancy (pN2-3); (6) high salvage rate of relapses with good-risk induction chemotherapy; and (7) low short- and long-term morbidity when a nerve-sparing RPLND is performed by experienced surgeons. *In low-stage NSGCT the therapeutic focus is the retroperitoneum, for which RPLND provides most the effective control with the lowest rates of serious long-term morbidity. The disadvantages of RPLND are that all patients undergo major abdominal surgery, it requires the availability of experienced surgeons and thus may not be deliverable to all patients, and it is associated with the highest rate of double therapy*. The rate of pathologic stage II in these series ranges from 19 to 28 %, and an estimated 66–81 % of these patients were cured after RPLND alone (where adjuvant chemotherapy was not dictated by protocol) (Donohue et al. 1993; Hermans et al. 2000; Sweeney et al. 2000; Rabbani et al. 2001; Nicolai et al. 2004; Stephenson et al. 2005b). *The long-term cancer-specific survival with RPLND (±adjuvant chemotherapy) approaches 100 %, and the risk of late relapse is negligible. Most RPLND series have reported retroperitoneal recurrences in less than 2 % of patients, demonstrating its efficacy for control of the retroperitoneum* (Donohue et al. 1993; Hermans et al. 2000; Stephenson et al. 2005b). *A full, bilateral template dissection is associated with the lowest risk of abdominopelvic recurrence (<2 %) and the highest rate of antegrade ejaculation (>90 %) when nerve-sparing techniques are employed* (Jewett 1990; Donohue et al. 1998; Stephenson et al. 2005b; Eggener et al. 2007b; Subramanian et al. 2010). For this reason it is now considered by many to be the standard of care for primary RPLND (Risk et al. 2011). *Thus, patients who opt for RPLND should have this procedure performed by an experienced surgeon with a full, bilateral template dissection. Otherwise, patients*

should go on surveillance or receive primary chemotherapy. RPLND is a curative procedure in 60–90 % of patients with pN1 disease and up to 100 % of patients with teratoma only (regardless of the extent of lymph node involvement) (Pizzocaro and Monfardini 1984; Williams et al. 1987b; Richie and Kantoff 1991; Rabbani et al. 2001; Sheinfeld et al. 2003; Stephenson et al. 2005b). The risk of relapse in patients with pN2-3 disease is greater than 50 % (Vogelzang et al. 1983; Williams et al. 1987b; Socinski et al. 1988; Stephenson et al. 2005b). With two cycles of adjuvant chemotherapy (most commonly BEP 2 or EP 2), relapses are reduced to 1 % or less (Behnia et al. 2000; Albers et al. 2003; Kondagunta et al. 2004). *A randomized trial of adjuvant chemotherapy versus observation after RPLND for pathologic stage II showed a significant reduction in the risk of relapse* (*6 % vs. 49 %*) *but no difference in overall survival* (Williams et al. 1987b). Adjuvant chemotherapy and observation are acceptable treatment options for patients with pathologic stage II disease, and patients should be informed of the risk of relapse after RPLND and the potential benefits and risks of these approaches.

Primary Chemotherapy

In distinction to adjuvant chemotherapy given for pathologic stage II disease after RPLND, primary chemotherapy refers to treatment administered to men with CS I NSGCT after orchiectomy. The goal of primary chemotherapy is to minimize the risk of relapse and to allow men to avoid RPLND and induction chemotherapy (for those who experience relapse on surveillance). The rationale for primary chemotherapy is based on the efficacy of two cycles of chemotherapy to eradicate micrometastatic disease when given as adjuvant therapy after RPLND and the 20–25 % need for chemotherapy despite RPLND (either as adjuvant or for treatment of relapse) (Donohue et al. 1993; Hermans et al. 2000; Nicolai et al. 2004; Stephenson et al. 2005a). *Primary chemotherapy offers patients the greatest chance of being relapse-free with any single treatment modality, and it can be delivered at community-based institutions* (Tandstad et al. 2009). *The disadvantages of primary chemotherapy are that* (*1*) *it does not treat retroperitoneal teratoma and thus exposes patients to the potential for chemoresistant and/or late relapse* (*see later*), (*2*) *long-term surveillance CT of the retroperitoneum is required, and* (*3*) *all patients are exposed to chemotherapy and the potential risk of late toxicity* (*cardiovascular disease and secondary malignant neoplasms among others*). The risk of late toxicity from two cycles of chemotherapy is poorly defined, although there appears to be no safe lower limit. Primary chemotherapy has been investigated in 11 published series, the majority of which have used BEP 2 (Abratt et al. 1994; Cullen et al. 1996; Pont et al. 1996; Ondrus et al. 1998; Bohlen et al. 1999; Amato et al. 2004; Chevreau et al. 2004; Oliver et al. 2004; Dearnaley et al. 2005; Albers et al. 2008; Tandstad et al. 2009). In men with LVI and/or EC predominance, it is possible to reduce the recurrence rate to 2–3 % with BEP 2 chemotherapy. In 7 of the 11 series, no deaths from GCT have been observed over an average median follow-up of 5 years. In the other four studies totaling 406 patients, 13 relapses (3 %) have been observed and 6 (46 %) of these relapsing patients have died of GCT. *Thus, although primary chemotherapy is associated with the lowest risk of relapse, these relapses are less amenable to salvage therapy because they are chemoresistant. In contrast, patients who experience relapse after RPLND or on surveillance are chemotherapy naïve and are cured with chemotherapy in virtually all cases*. Although relapses are uncommon with primary chemotherapy, virtually all occur in the retroperitoneum. This mandates the use of surveillance abdominopelvic CT in the follow-up of these patients. Many European institutions prefer BEP 2 to RPLND, because the RPLND is primarily used as a staging procedure and performed without curative intent (Krege et al. 2008a; Schmoll et al. 2009a). A recent randomized trial and a population-based study have investigated the use of BEP 1 as primary chemotherapy for CS I NSGCT (Albers et al. 2008; Tandstad et al. 2009). Over a median follow-up of less than 5 years in both studies, the risk of relapse after BEP 1 ranged from 1 to 3 % and the cancer-specific survival approached 100 % in both studies. BEP 1 needs to be compared

with BEP 2 in a randomized trial to verify its safety and efficacy.

Treatment Selection for Clinical Stage I NSGCT

There are no randomized trials that compare the standard treatment approaches for CS I NSGCT. A recent phase III, randomized trial compared BEP 1 versus unilateral, modified-template RPLND (with BEP 2 for patients with pathologic stage II disease) (Albers et al. 2008). Although a statistically significantly reduced risk of relapse was reported with BEP 1, no cancer-specific deaths were reported in either arm. This trial has been criticized because it compared two nonstandard treatment approaches for CS I NSGCT (Sheinfeld and Motzer 2008). Given the excellent long-term survival with surveillance, RPLND, and primary chemotherapy, it is inappropriate to recommend any specific treatment option because there are relative advantages and disadvantages of each approach in terms of treatment-related toxicity, the need for subsequent treatment, and intensity of surveillance testing and imaging. Likewise, patient preferences may vary and should be considered. *Several clinical practice guidelines for CS I NSGCT have been published, and surveillance is generally recommended to low-risk patients and either surveillance, RPLND, or primary chemotherapy to those at high risk* (Albers et al. 2005; Motzer et al. 2006; Hotte et al. 2008; Krege et al. 2008a; Schmoll et al. 2009a; Stephenson et al. 2011).

Clinical Stage IS NSGCT

CS IS is defined as the presence of elevated postorchiectomy serum tumor markers without clinical or radiographic evidence of metastatic disease. Studies of primary RPLND for CS IS NSGCT have reported that 37–100 % of patients subsequently required chemotherapy for retroperitoneal metastasis, persistently elevated serum tumor markers, or relapse (Davis et al. 1994; Saxman et al. 1996). *There is consensus that these patients should be treated similar to those with CS IIC-III and receive induction chemotherapy*. The cancer-specific survival after chemotherapy for CS IS is greater than 90 % (Culine et al. 1996; International Germ Cell Consensus Classification 1997). Slightly elevated and stable serum tumor marker levels after orchiectomy in patients without clinical evidence of disease should be interpreted cautiously because they may represent false-positive results for disseminated NSGCT.

Clinical Stage IIA and IIB NSGCT

The optimal management of CS IIA-B NSGCT is controversial. *RPLND* (± *adjuvant chemotherapy*) *and induction chemotherapy* (± *postchemotherapy RPLND*) *are accepted treatment options, with survival rates exceeding* 95 %. There are no randomized trials comparing these treatment approaches. In a prospective, multicenter, nonrandomized trial of RPLND and two cycles of adjuvant chemotherapy versus induction chemotherapy, no significant differences in recurrence (7 % for RPLND vs. 11 % for chemotherapy) or overall survival were observed (Weissbach et al. 2000). A single institution, nonrandomized, retrospective comparison of RPLND (and two cycles of adjuvant chemotherapy for pathologic stage II) and induction chemotherapy reported a significant reduction in the risk of recurrence with induction chemotherapy (98 % vs. 79 %), but cancer-specific survival approached 100 % with both modalities (100 % vs. 98 %), RPLND patients received fewer cycles of chemotherapy (mean 4.2 vs. 1.4), and 51 % of RPLND patients avoided chemotherapy (Stephenson et al. 2007). *The arguments in favor of RPLND for CS IIA-B are that* (1) 13–35 % of patients have pathologically negative lymph nodes and thus avoid chemotherapy (Pizzocaro 1987; Donohue et al. 1995; Weissbach et al. 2000; Stephenson et al. 2007); (2) approximately 30 % have retroperitoneal teratoma that is resistant to chemotherapy (Foster et al. 1996; Stephenson et al. 2007); (3) long-term cancer-specific survival is 98–100 % with RPLND adjuvant chemotherapy (Pizzocaro 1987; Donohue et al. 1995; Weissbach et al. 2000; Stephenson et al. 2007); (4) 10–52 % avoid any chemotherapy (Pizzocaro 1987; Donohue et al. 1995; Weissbach et al. 2000; Stephenson et al. 2007); and (5) ejaculatory function is preserved in 70–90 % of patients (Richie and Kantoff 1991; Donohue et al. 1995; Weissbach et al.

2000). *The disadvantages of RPLND are that* (1) additional therapy is required in 48 % or more of patients, (2) 13–15 % have persistence of disease after RPLND and require a full induction chemotherapy regimen, and (3) high-quality RPLND may not be deliverable at all institutions (Weissbach et al. 2000; Stephenson et al. 2007). *The arguments in favor of induction chemotherapy are that* (1) 60–78 % of patients achieve a complete response and avoid PCS, (2) treatment can be delivered at community-based institutions, and (3) cancer-specific survival is 96–100 % (Peckham and Hendry 1985; Logothetis et al. 1987; Socinski et al. 1988; Ondrus et al. 1992; Horwich et al. 1994; Lerner et al. 1995; Culine et al. 1997; Debono et al. 1997; Weissbach et al. 2000; Stephenson et al. 2007). *The disadvantages of chemotherapy are that* (1) all patients are exposed to the risk of long-term toxicity of chemotherapy and (2) those who do not undergo postchemotherapy RPNLD are at risk of relapse with chemorefractory GCT. Given that 13–35 % of patients with CS IIA NSGCT have pathologically negative lymph nodes (thus, a false-positive CT result), patients with indeterminate lesions on staging abdominopelvic CT who are at otherwise low risk for metastatic disease may be observed closely initially to clarify subsequent treatment decisions. *Treatment considerations for CS IIA-B NSGCT include the risk of occult systemic disease*, *risk of retroperitoneal teratoma*, *short- and long-term treatment-related morbidity*, *and need for double therapy*. As with CS IS NSGCT, the presence of elevated postorchiectomy AFP and hCG is associated with an increased risk of systemic relapse after RPLND. Rabbani and associates (2001) reported relapses after RPLND in four of five patients (80 %) with elevated postorchiectomy AFP or hCG compared with 7 of 45 (16 %) patients with normal serum tumor markers. Stephenson and coworkers (2005b) identified the presence of elevated serum tumor markers (hazard ratio [HR] 5.6, $P < .001$) and retroperitoneal lymphadenopathy greater than 3 cm (hazard ratio [HR] 12.3, $P < .001$) as significant predictors of systemic relapse after RPLND in multivariable analysis adjusting for treatment year and the use of adjuvant chemotherapy. *Thus, there is consensus that CS IIA-B NSGCT patients with elevated AFP or hCG or bulky lymph nodes* (*>3 cm*) *should receive induction chemotherapy*.

Clinical Stage IIC and III NSGCT

Induction chemotherapy with cisplatin-based multiagent regimens is the initial approach used for the treatment of CS IIC and CS III NSGCT. As discussed previously, induction chemotherapy is also the preferred approach for CS IS and CS IIA-B with elevated postorchiectomy AFP and hCG. The specific regimen and number of cycles are based on the IGCCCG risk stratification (International Germ Cell Consensus Classification 1997). The development of cisplatin-based chemotherapy represents the most important advancement in the treatment of GCT. Before the identification of cisplatin, complete responses to chemotherapy were achieved in 10–20 % of patients and the cure rate was only 5–10 % (Einhorn 1990). Long-term cure is now anticipated in 80–90 % of patients with metastatic GCT. Randomized trials have evaluated the efficacy and safety of various drug combinations to determine the optimal regimen based on the IGCCCG risk (International Germ Cell Consensus Classification 1997). The initial landmark study was conducted at Indiana University using cisplatin–vinblastine–bleomycin (PVB 4) in the 1970s and reported complete responses in 74 % of patients and over 70 % long-term survivors (Einhorn 1990). When it was demonstrated that etoposide could cure some patients with relapse after PVB chemotherapy, PVB 4 was compared with bleomycin–etoposide–cisplatin (BEP 4) in a multicenter randomized trial. No significant difference in overall survival was seen between the two regimens (2-year survival 80 %, $P = .11$), but BEP 4 was associated with less neuromuscular toxicity and was subsequently adopted as the standard regimen (Williams et al. 1987a).

Relapsing NSGCT

The treatment of relapsing NSGCTs depends on what treatment the patient has previously received and, in certain cases, the location of the relapse. Patients who have never received chemotherapy

have a much more favorable prognosis than patients who have already been treated with chemotherapy for disseminated disease.

15.1.12.3 Seminoma

Clinical Stage I Seminoma

Generally, testicular cancer in the 80 % of patients with seminoma could be classified as CS I disease. *During the last two decades, the treatment of these patients has changed a lot, and as regards surveillance, in particular radiotherapy and chemotherapy with single-agent carboplatin are now accepted among treatment options*.

New studies have tried to reduce the burden's therapy. *Platin-based chemotherapy and infradiaphragmatic radiotherapy are connected to an increased danger of late cardiovascular toxicity and secondary malignant neoplasms* (Zagars et al. 2004; Travis et al. 2005; van den Belt-Dusebout et al. 2007). Reducing target volume and dose has been investigated to decrease the toxicity of radiotherapy. Carboplatin is less neurotoxic, ototoxic, and nephrotoxic matched with cisplatin, but the risks of cardiovascular disease and secondary malignant neoplasms are widely unknown. In many cases, the short-term efficacy and safety of these approaches have been authenticated by randomized tests. *With each of these modalities, the long-term cancer check approaches 100 %*.

Primary Radiotherapy

Until a short time ago, the pivot of therapy for CS I seminoma in the last 40 years had been primary radiotherapy to the retroperitoneum and ipsilateral pelvis, called *dog-leg configuration*. Published. *The optimal radiation dose has not been determined, and most centers use 25–35 Gy in 15–20 daily fractions* (Fossa et al. 1989a, 1999b; Warde et al. 1995). Long-term cancer-specific survival approaches 100 %, and progression-free chance between 95 and 97 % is reported (Fossa et al. 1989a, 1999b; Warde et al. 1995, 2005). *In-field recurrence after dog-leg radiotherapy is less than 1 %*, solving the need for daily/routine monitoring abdominopelvic CT imaging. Inguinal metastases are unusual in those without prior inguinal or scrotal surgery. *The most usual/ordinary sites of recurrence are the thorax and left supraclavicular fossa. Practically all recurrences are cured with first-line chemotherapy.* Select patients with isolated inguinal relapse may be saved with radiotherapy or surgical resection. *The surveillance of patients after dog-leg radiotherapy is characterized by standard clinical assessment, chest radiography, and serum tumor markers*. Most patients show some acute side effects with adjuvant radiotherapy, which generally include transient nausea, vomiting, and diarrhea that are regularly mild and self-limited. Acute grade II–IV hematologic toxicity happens in 5–15 % (Fossa et al. 1999b). Moderate and severe late gastrointestinal toxicity (usually chronic dyspepsia or peptic ulcer disease) is announced/indicated in 5 % and less than 2 % of patients, respectively. The testicular germinal epithelium is highly sensitive to ionizing radiation, and scatter dose to the contralateral testis may be very significative in spite of protective shielding. After dog-leg radiotherapy, persistent oligospermia is reported in 8 % (Fossa et al. 1999b). Given the long anticipated life expectance, the problem of late cardiac toxicity and secondary malignant neoplasms as regards these patients is principally germane. *The actuarial risk of developing secondary malignant neoplasms is estimated to be 18 % at 25 years after radiotherapy for seminoma* (Travis et al. 2005). The small but at the same time very important risk of pelvic recurrence requires the use of routine surveillance pelvic CT with the associated increased cost and radiation exposure (Brenner and Hall 2007). The MRC and the European Organisation for the Research and Treatment of Cancer (EORTC) also conducted a randomized test of 20-Gy versus 30-Gy PA radiotherapy for CS I seminoma (Jones et al. 2005). The 5-year relapse-free survival (96 % vs. 97 %) and total survival (99.6 % vs. 100 %) were alike, but patients receiving 20 Gy experienced less acute gastrointestinal toxicity, leukopenia, and lethargy (though outcomes were similar at 12 weeks). Further follow-up is necessary to estimate the durability/reliability of these results.

Surveillance

Given the potential for late toxicity with dog-leg radiotherapy, the 80–85 % cure rate after orchiectomy, and the more than 90 % cure rates achieved

with platin-based chemotherapy for advanced seminoma, surveillance has been evaluated at several centers. *In comparison with NSGCT, surveillance for CS I seminoma is much more difficult because of the inadequate role of serum tumor markers to identify relapse and the need for long-term surveillance CT because 10–20 % of relapses occur 4 years or more after diagnosis* (Chung et al. 2002). *The 5-year relapse-free survival ranges from 80 to 86 %, and cancer-specific survival approaches 100 %. Eighty-four to 100 % of patients experience relapse in the retroperitoneum, and 18–24 % of patients have bulky retroperitoneal disease and/or distant metastases at the time of recurrence* (Horwich et al. 1992; von der Maase et al. 1993; Warde et al. 1995; Aparicio et al. 2003). Dog-leg radiotherapy is used for cure of relapse in 73–88 % of patients, and cure rates of 70–90 % are announced. Basically all patients who feel/test relapse of disease outside the retroperitoneum are cured with first-line chemotherapy. *To locate and cure recurrences, in the initial phase patients on surveillance should be followed with clinical assessment, chest radiography, serum tumor marker evaluation, and abdominopelvic CT. Surveillance schedules employ rating every 2–4 months in years 1–3, every 6 months in years 4–7, and then annually therefore*. The required frequency of CT is poorly defined, and centers perform this every 4–6 months in years 1–3, every 6 months in years 4–7, and then annually therefore. A recent MRC trial proposed that the frequency of surveillance CT in low-risk CS I NSGCT in years 0–2 may be safely decreased from 5 to 2 without affecting survival or burden of treatment (Rustin et al. 2007). It is not clear if these results can be safely enforced to surveillance for seminoma. Long-term follow-up is obligatory given the higher incidence of relapse after 5 years compared with NSGCT (Chung et al. 2002). *In a pooled analysis of three large surveillance series from the 1980s, tumor size greater than 4 cm and invasion of the rete testis were significant predictors of relapse in multivariable analysis* (Warde et al. 2002). *Otherwise in NSGCT, LVI has not been acknowledged as a very important predictor of relapse for CS I seminoma*. The 5-year relapse rate for patients with 0, 1, and 2 risk factors was 12, 16, and 32 %, respectively.

Primary Chemotherapy with Single-Agent Carboplatin

Primary chemotherapy with one to two cycles of single-agent carboplatin has also been studied as a different choice in place of radiotherapy to decrease collateral effects. A study with only carboplatin showed a 65–90 % complete reaction rates noted among advanced stage seminoma patients (Horwich et al. 2000) and its moderate toxicity compared with cisplatin. Oliver et al. (1994) first described 78 patients treated with one to two cycles of carboplatin and there were just two relapses and zero deaths. The MRC and EORTC reported a randomized, phase III clinical trial of one cycle of carboplatin versus 20- to 30-Gy para-aortic radiotherapy in 1,477 patients with CS I seminoma (Oliver et al. 2005), and there were 96 % vs. 95 % of patients with 3-year relapse-free survival and just one death with radiotherapy. After a median follow-up of 6.5 years, the 5-year relapse-free survival (95 %) was the same in both arms of the trial (Oliver et al. 2008). The examination was planned as a noninferiority trial to rule out a risk of relapse higher than 3 % with carboplatin, but the trial just can eliminate a risk of relapse with 95 % confidence higher than 3.6 %; so the primary end point was not scoped. A problem with one cycle of carboplatin is the potential insufficient dose, resulting in increased danger of relapse. A phase 2 study demonstrating an upper relapse rate with one versus two cycles was reported, and a higher risk of relapse was reported among patients receiving an insufficient dose of carboplatin in the MRC/EORTC trial (Dieckmann et al. 2000; Oliver et al. 2008). The best dose of carboplatin is calculated with the formula 7 (glomerular filtration rate [GFR, mL/min] 25) mg (Calvert and Egorin 2002). To obtain GFR the serum creatinine level may be used but may underestimate the true GFR, leading to inadequate dosing of carboplatin. *Carboplatin dosing should not be based on estimated GFR. Thus, it is recommended to base one cycle of carboplatin dosing on the results of radioisotope renal scans or administer two cycles of therapy*. The equivalence of carboplatin to dog-leg radiotherapy has yet to be definitively proven, and several concerns about carboplatin approach limit its acceptance.

Carboplatin is inferior to cisplatin in advanced GCT, and there is little evidence that micrometastases will be more sensitive to carboplatin. This notion is based on the higher risk of relapse after carboplatin for CS I seminoma (3–5 % in most studies) in parallel with the 1 % or less risk of relapse after two cycles of cisplatin pt II NSGCT after RPLND (a cohort with a substantially higher risk of relapse). At this time there are not dates to understand the long-term efficacy. It is also unclear whether carboplatin is associated with a substantially reduced risk of late toxicity compared with radiotherapy. Lastly, the pattern of recurrence after carboplatin is the same as that for surveillance, with the retroperitoneum being the most common (and often solitary) site of relapse (Mead et al. 2008). Thus, patients need to be followed with routine abdominopelvic CT. *Given the low overall risk of relapse with CS I seminoma, the lack of prospectively validated markers to identify a high-risk population, and the potential for late toxicity with radiotherapy and carboplatin, many clinical practice guidelines now recommend surveillance as the preferred approach* (Krege et al. 2008a; Schmoll et al. 2009b). Surveillance enables 80–85 % of patients to avoid treatment-related toxicity, and relapses are effectively salvaged with dog-leg radiotherapy in most cases. However, surveillance must be continued for more than 5 years and frequent CT imaging is required. *For noncompliant patients or those unwilling to accept surveillance, primary radiotherapy is recommended given the long-term efficacy and simplified follow-up*. The early results of single-agent carboplatin are encouraging but insufficient at this time to demonstrate equivalence with radiotherapy.

Clinical Stage IIA and IIB Seminoma

Fifteen to 20 % of seminoma patients have CS II disease, 70 % of whom have CS IIA-B. Dog-leg radiotherapy using 25–30 Gy (including a 5- to 10-Gy boost to involved areas) is employed at most centers. The higher radiation doses administered to CS IIA-B patients are generally well tolerated, with acute grade III–IV gastrointestinal toxicity reported in 8–10 % (Classen et al. 2003b). Prophylactic radiation to the left supraclavicular fossa is no longer practiced because fewer than 3 % of patients are likely to benefit (Zagars and Pollack 2001; Chung et al. 2003). Long-term disease-free survival rates of 92–100 % for CS IIA and 87–90 % for CS IIB have been reported, with in-field recurrences reported in 0–2 % and 0–7 % of cases, respectively (Zagars and Pollack 2001; Classen et al. 2003b; Chung et al. 2004b). *Relapses are cured in virtually all cases with first-line chemotherapy, and disease-specific survival approaches 100%. Routine surveillance CT is not necessary after complete resolution of disease*. The Royal Marsden Hospital reported relapses in 15 and 30 % of CS IIA and IIB patients, respectively, with dog-leg radiotherapy alone, 87 % of which occurred at distant sites (Patterson et al. 2001). To reduce the risk of relapse, the combination of single-agent carboplatin and 30-Gy dog-leg radiotherapy was investigated in 33 patients, and only two relapses (6 %) were observed over a median follow-up of 48 months (Patterson et al. 2001). These early results are promising, but further data are required to assess the utility of this approach. Induction chemotherapy using first-line regimens (BEP 3 or EP 4) is an accepted alternative to dog-leg radiotherapy. The Spanish Germ Cell Cancer Study Group recently reported on the use of BEP 3 or EP 4 in 72 patients with CS IIA-B seminoma (Garcia del Muro et al. 2008). Overall, 83 % of patients achieved a serologic and radiographic complete response and only 1 (1.3 %) had residual mass greater than 3 cm, and the two patients who underwent PCS for residual masses had necrosis only in the resected specimens. Overall, the 5-year relapse-free and overall survival was 90 and 95 %, respectively. The rationale for chemotherapy in CS IIA-B seminoma is based on the risk of late toxicity due to dog-leg radiotherapy and the lower risk of relapse in patients with bulky retroperitoneal disease. *Induction chemotherapy is preferentially given to patients with bulky (>3 cm) and/or multiple retroperitoneal masses because the risk of relapse is lower than with dog-leg radiotherapy* (Patterson et al. 2001; Chung et al. 2004b; Garcia del Muro et al. 2008).

Clinical Stage IIC and III Seminoma

As with NSGCT, patients with CS IIC and III seminoma are subjected to induction chemotherapy, and the regimen and number of cycles depend

on the IGCCCG risk. Ninety percent of patients with advanced seminoma are ranked as good risk and should be given either BEP×3 or EP×4 chemotherapy. Complete radiographic results are reported in 70–90 % of patients, and the 5-year total survival is 91 % (Loehrer et al. 1987; Mencel et al. 1994; International Germ Cell Consensus Classification 1997; Gholam et al. 2003). Only a small percentage of advanced seminomas, exactly 10 %, have non-pulmonary visceral metastasis (this data represent an intermediate risk for IGCCCG criteria). With BEP 4 chemotherapy, the 5-year total and progression-free survival is 79 and 75 %, respectively (International Germ Cell Consensus Classification 1997). Single-factor carboplatin in advanced seminoma is associated with inferior survival compared with standard first-line regimens (Bokemeyer et al. 2004).

Management of Postchemotherapy Residual Masses

After the first phase of chemotherapy, *in 58–80 % of patients, residual masses can be detected* (Motzer et al. 1987; Puc et al. 1996; Duchesne et al. 1997; Fossa et al. 1997; Herr et al. 1997; Flechon et al. 2002; De Santis et al. 2004). *Spontaneous resolution of these masses is reported in 50–60 % of cases, and the average time to resolution is 13–18 months* (Flechon et al. 2002; De Santis et al. 2004). *The histology of residual masses is necrosis and viable malignancy in 90 and 10 % of cases, respectively* (Puc et al. 1996; Herr et al. 1997; Ravi et al. 1999; Flechon et al. 2002; De Santis et al. 2004). From the technical point of view, *PCS for seminoma is difficult* (*and it is rarely used*) *due to the desmoplastic reaction that triggers after chemotherapy with subsequent perioperative morbidity* (Mosharafa et al. 2003). Surgical complete removal in postchemotherapy seminoma is reported in only 58–74 % of patients (compared with 85 % or more after first-line chemotherapy for NSGCT) (Puc et al. 1996; Herr et al. 1997; Ravi et al. 1999; Flechon et al. 2002; De Santis et al. 2004). *Teratoma and malignant transformation are much less of a concern with advanced seminoma*. As such, the management of postchemotherapy residual masses differs substantially for seminoma compared with NSGCT. Noting that in almost all postchemotherapy residual masses there is necrosis, investigators have strived to justify PCS. *Postchemotherapy radiotherapy is not needed in the management of residual masses* (Duchesne et al. 1997). *The dimension of residual masses is an important symptom of viable malignancy*; *27–38 % of discrete residual masses larger than 3 cm carry viable malignancy compared with 0–4 % for masses less than 3 cm* (Puc et al. 1996; Herr et al. 1997; Flechon et al. 2002; De Santis et al. 2004). *Newly*, *FDG-PET has been considered to be useful*, *combined with CT to identify patients for PCS* (De Santis et al. 2004). FDG-PET does not unroll any action in the assessment of residual masses in NSGCT due to the scarce absorption of FDG by teratoma; this applies less to advanced seminoma. The particularity and sensitivity of a positive FDG-PET estimation for masses greater than 3 cm were 100 and 80 %, respectively. *Thus, patients with discrete residual masses greater than 3 cm should be submitted to a further analysis with FDG-PET and those who are PET positive should be subjected to PCS. PET-negative residual masses greater than 3 cm and masses less than 3 cm should be monitored.*

15.1.12.4 Metastases

About 1 % of men with scattered GCT are more likely predisposed to contract brain metastases detected before initiating chemotherapy, and between 0.4 and 3 % will develop brain metastases after the first cycle of chemotherapy (Raina et al. 1993; International Germ Cell Consensus Classification 1997; Fossa et al. 1999a). *Brain metastases are related to choriocarcinoma and any patient with a very high serum hCG level could be affected* (Fossa et al. 1999a; Kollmannsberger et al. 2000; Gremmer et al. 2008). *Choriocarcinomas are strongly vascular and turn to hemorrhage during chemotherapy*, *and death rates of 4–10 % owing to intracranial hemorrhage have been found* (Kollmannsberger et al. 2000; Nonomura et al. 2009). This risk must be considered in the care of this patient, and neurologic changes should be quickly evaluated. The 5-year global survival in patients with brain metastases is 33 and 57 % for those with scattered NSGCT and seminoma, respectively (International Germ Cell Consensus Classification 1997). *Men who have a setback in the brain after getting a complete response to chemotherapy seem to have a worse prognosis than those with brain implication at diagnosis*, with global survival rates

of 39–44 % for detached brain metastases and 2–26 % for those with brain metastases together with other sites of disease (Fossa et al. 1999a; Kollmannsberger et al. 2000; Hartmann et al. 2003; Salvati et al. 2006; Gremmer et al. 2008; Nonomura et al. 2009). Case studies and pooled analyses of GCT patients with brain metastases have showed results with distinct treatment approaches, but there are no randomized trials to clearly define optimal management (Spears et al. 1992; Fossa et al. 1999a; Kollmannsberger et al. 2000; Hartmann et al. 2003; Salvati et al. 2006; Gremmer et al. 2008; Nonomura et al. 2009). Treatment approaches have included chemotherapy, surgical removal, whole-brain radiation therapy, and stereotactic radiosurgery, with most patients receiving multiple treatment. *Patients with brain metastases at diagnosis should be subjected to BEP×4 chemotherapy followed by removal of residual masses*. The advantage offered by radiation treatment in this format is not so evident (Fossa et al. 1999a; Kollmannsberger et al. 2000; Hartmann et al. 2003). At the authors' institution, radiation treatment is only adopted for patients who have residual lesions that cannot be removed and are not treatable with stereotactic radiosurgery due to the fact that radiation causes neurotoxicity (Doyle and Einhorn 2008). *Patients, whose residual lesions are not removed after first cycle of chemotherapy, should be submitted to second phase chemotherapy followed by removal and/or radiation treatment* (Fossa et al. 1999a; Hartmann et al. 2003). For men who experience setback in the brain and at other areas of the body, the prognosis is particularly harsh, over all if it is not the first case of setback.

15.1.13 Treatment-Related Adverse Events

Testicular cancer treatment consequence can be splitted into late and early complications. Complications from orchiectomy and RPLND are explained in Chapter 32 and will not be seen again here except to note that the main problems after RPLND are midline scar, ejaculatory dysfunction, small bowel obstruction, and perioperative complications. It is also important to observe that there is a grown occurrence of hypogonadism after orchiectomy for GCT.

15.1.13.1 Early Toxicity

Cisplatin-based chemotherapy is related to several early complications and local effects, including fatigue, myelosuppression, infection, peripheral neuropathy, hearing loss, diminished renal function, and death. The toxic death rate is between 0 and 2.4 % during chemotherapy for good-risk illness and from 3.0 to 4.4 % during standard first cycle of chemotherapy for intermediate- and scarce-risk illness (Nichols et al. 1998; de Wit et al. 2001, 2008; Toner et al. 2001; Culine et al. 2007, 2008). The effect of chemotherapy and radiation therapy on spermatogenesis has been talked about previously. Most men can still procreate after therapy for GCT, but paternity rates are lower for men treated with radiation treatment and/or chemotherapy (Huyghe et al. 2004; Brydoy et al. 2005). Early complications of radiation therapy are represented by fatigue, nausea and vomiting, leukopenia, and dyspepsia (Fossa et al. 1999b; Jones et al. 2005; Oliver et al. 2005).

15.1.13.2 Late Toxicity

Numerous long-term sequelae have been reported in GCT survivors, including peripheral neuropathy, Raynaud phenomenon, hearing loss, hypogonadism, infertility, secondary malignant neoplasms, and cardiovascular disease (Brydoy et al. 2005, 2009; Rossen et al. 2009). Symptoms of Raynaud phenomenon and peripheral neuropathy have been reported in 20–45 % and 14–43 % of patients, respectively, and the risk appears to increase with increasing cumulative doses of cisplatin (Brydoy et al. 2009; Rossen et al. 2009). Significant hearing loss and/or tinnitus after cisplatin-based chemotherapy is reported in 20–40 % of patients and can be documented via audiometry in 30–75 %. Hypogonadism has been documented in 10–20 % of patients treated with orchiectomy alone, 15 % of patients treated with radiation therapy, and 20–25 % of men treated with first-line chemotherapy regimens (Nord et al. 2003; Lackner et al. 2009). Large population-based studies of GCT survivors have reported an increased risk of death from gastrointestinal and cardiovascular diseases after radiation therapy and an increased risk of death from infections and cardiovascular and pulmonary diseases after chemotherapy (Fossa et al. 2007). Patients treated with both radiation and chemotherapy have the

highest risk of death from nonmalignant causes. The increased incidence and mortality of cardiovascular disease in GCT survivors are particularly well documented (van den Belt-Dusebout et al. 2007; Meinardi et al. 2000; Huddart et al. 2003; Fossa et al. 2007, 2009). The causes of these cardiovascular complications are not well understood, but putative contributing factors are radiation- or chemotherapy-induced vascular injury, as well as chemotherapy-induced cardiac injury and metabolic syndrome (Nuver et al. 2005; Altena et al. 2009). *The risk of second malignant neoplasms is a particular concern. The incidence of non-germ cell malignancies is 60–100 % higher in GCT survivors treated with cisplatin-based chemotherapy or radiation therapy compared with the general population and 200 % higher in patients who received both radiation and chemotherapy* (Travis et al. 2005; Richiardi et al. 2007). The risk of death from non-germ cell malignancies in GCT survivors treated with radiation or chemotherapy is less well defined but appears to be doubled compared with the general population (Fossa et al. 2004). The frequent use of body CT in the surveillance of patients after therapy is another source of radiation that may increase the risk of secondary malignant neoplasms (Brenner and Hall 2007; Chamie et al. 2008; Tarin et al. 2009).

15.2 Non-germ Cell Tumors Sex Cord/Stromal Tumors

Sex cord/stromal tumors comprise 4 % of testicular neoplasms and they include Leydig cells, Sertoli cells, granulosa cells, or thecal cells.

15.2.1 Leydig Cell Tumors

Leydig cell tumors are the most frequent of the sex cord/stromal tumors, particularly in adult males between age 20 and 60 years. Cryptorchidism is not a risk factor. Most of them (90 %) are benign, and 10 % are malignant. Benign lesions are frequently small, well demarcated, and without areas of necrosis and of hemorrhage. Usually they contain Reinke crystals in 25–40 % of cases and appear as densely eosinophilic needle-like or rhomboid structures within the cytoplasm. Necrosis, nuclear atypia, and increased mitotic activity may suggest malignant Leydig cell tumor, but the only criterion for making diagnosis of malignancy is the presence of metastasis, localized frequently in the lung and in the retroperitoneum. The risk of developing cancer generally increases with age. Mainly symptoms in adult are testicular pain, frequently with feminizing characteristics, including gynecomastia, impotence, and decreased libido. Abdominopelvic CT and chest radiography are used to confirm the presence of disease and to make cancer staging. Inguinal orchiectomy is the standard treatment for suspected testicular carcinoma. RPLND is reasonable in select cases with adverse prognosis. Metastatic Leydig cell tumors are resistant to chemotherapy and radiation therapy. Mitotane (Lysodren), a potent inhibitor of steroidogenesis, may produce partial responses in metastatic patients with excess androgen production, but cure is not possible (Schwarzman et al. 1989).

15.2.2 Sertoli Cell Tumor

These tumors represent 1 % of testicular neoplasms. They can affect people of all ages, including infants. There is no association with cryptorchidism. They usually are benign (90 %). The tumors are well circumscribed with uniform consistency. Large size and necrosis are worrisome features for malignancy, but the presence of metastasis is the only criterion to make diagnosis of malignant tumors. Patients present with a testicular mass, and estrogen production by the tumor can result in gynecomastia and impotence. Treatment is radical inguinal orchiectomy. In cases of malignancy, RPLND is indicated. They do not respond to chemotherapy and radiation therapy.

15.2.3 Granulosa Cell Tumors

Granulosa cell tumors of the testis, similar to the typical granulosa cell tumors of the ovary, are rare in the testis. Often they have been associated

with gynecomastia. Large size, invasive growth pattern, lymphatic or vascular invasion, nuclear atypicality, high mitotic rate, and necrosis suggest a malignant behavior. These tumors have limited metastatic potential, so radical inguinal orchiectomy is therapeutic.

15.2.4 Gonadoblastoma

Gonadoblastoma is a rare benign tumor, usually occurring in patients with gonadal dysgenesis. It contains all gonadal elements and is frequently associated with an abnormal chromosomal karyotype. Moreover, it can affect a subset of patients with an intersex disorder or disorder of sex development. Eighty percent of affected individuals are phenotypic females, usually presenting with primary amenorrhea. The remainder of patients are phenotypic males, usually presenting in childhood or early adolescence with feminizing symptoms, including gynecomastia, cryptorchidism (with the dysgenic gonad in the inguinal or abdominal location), hypospadias, and some form of female internal genitalia. One third of cases are bilateral (Scully 1970). These tumors should be considered an in situ form of malignant GCT, because approximately 50 % will develop an invasive GCT (usually seminoma) (Ulbright 2004). Gonadoblastomas do not metastasize, but the malignant GCT elements may. Bilateral orchiectomy is required because of the risk of bilateral tumors.

15.3 Miscellaneous Testicular Neoplasms

15.3.1 Epidermoid Cyst

This is a rare benign tumor of the germ cell, typically present in mid-adulthood (2nd to 4th decades). It is often bilateral and associated with cryptorchidism (Younger et al. 2003). Patients typically present with a painless testicular mass between 1 and 3 cm in diameter. These lesions are benign with no malignant potential . The treatment consists in enucleation or partial orchiectomy.

15.3.2 Adenocarcinoma of the Rete Testis

Adenocarcinoma of the rete testis is a rare tumor, but highly malignant neoplasm. Most patients present with testicular pain and an associated hydrocele. The prognosis generally is poor and lymphatic metastasis to the retroperitoneum is the most common mode of spread. RPLND may be curative in patients with restricted retroperitoneal lymph node metastasis. Chemotherapy and radiation therapy are unsuccessful.

15.4 Secondary Tumors of the Testis

15.4.1 Lymphoma

Primary testicular non-Hodgkin lymphoma is a rare tumor and represents only 1–2 % of all cases of lymphoma. Most frequently, lymphoma involves the testis through dissemination from extratesticular sites (Ulbright 2004). Eighty-five percent of cases occur in men older than age 60. The most common type is diffuse large B-cell lymphoma. The common symptom is the enlargement of one of the two testes. There is usually little or no pain associated with this. About 25 % of men have systemic symptoms (fever, night sweats, weight loss). Central nervous system involvement at diagnosis is reported in 10 % of men. Testicular lymphomas have a high rate of recurrence and act aggressively. In the early stages (I and II), the treatment consists of orchidectomy, followed by chemotherapy and prophylactic scrotal radiotherapy. In the advanced stages (III and IV), chemotherapy is the treatment of choice.

15.4.2 Leukemic Infiltration

The testis is a common site of relapse in boys with acute lymphocytic leukemia. Bilateral involvement may be present in one half of cases. Testis biopsy is the diagnostic procedure of choice. Radiation with low-dose radiotherapy (20 Gy) is the preferred method of treatment.

Generally the prognosis is poor because most patients have associated systemic disease.

15.4.3 Metastases

Metastases to the testis are rare and usually associated with diffuse metastatic disease. These lesions are typically incidental findings at autopsy. Bilateral involvement occurs in 15 % of patients. The most common primary site is the prostate, followed by the lung, melanoma, gastrointestinal tract, and kidney. While treatment is mainly dictated by the primary tumor, orchiectomy may be considered for palliative reasons.

References

Aass N, Fossa SD, Theodorsen L et al (1991) Prediction of long-term gonadal toxicity after standard treatment for testicular cancer. Eur J Cancer 27:1087–1091

Abratt RP, Pontin AR, Barnes RD et al (1994) Adjuvant chemotherapy for stage I non-seminomatous testicular cancer. S Afr Med J 84:605–607

Aggarwal N, Parwani AV (2009) Spermatocytic seminoma. Arch Pathol Lab Med 133:1985–1988

Akre O, Pettersson A, Richiardi L (2009) Risk of contralateral testicular cancer among men with unilaterally undescended testis: a meta-analysis. Int J Cancer 124(3):687–689

Albers P, Miller GA, Orazi A et al (1995) Immunohistochemical assessment of tumor proliferation and volume of embryonal carcinoma identify patients with clinical stage A nonseminomatous testicular germ cell tumor at low risk for occult metastasis. Cancer 75:844–850

Albers P, Bender H, Yilmaz H et al (1999) Positron emission tomography in the clinical staging of patients with stage I and II testicular germ cell tumors. Urology 53:808–811

Albers P, Ganz A, Hannig E et al (2000) Salvage surgery of chemorefractory germ cell tumors with elevated tumor markers. J Urol 164:381–384

Albers P, Siener R, Kliesch S et al (2003) Risk factors for relapse in clinical stage I nonseminomatous testicular germ cell tumors: results of the German Testicular Cancer Study Group Trial. J Clin Oncol 21:1505–1512

Albers P, Weissbach L, Krege S et al (2004) Prediction of necrosis after chemotherapy of advanced germ cell tumors: results of a prospective multicenter trial of the German Testicular Cancer Study Group. J Urol 171: 1835–1838

Albers P, Albrecht W, Algaba F et al (2005) Guidelines on testicular cancer. Eur Urol 48:885–894

Albers P, Siener R, Krege S et al (2008) Randomized phase III trial comparing retroperitoneal lymph node dissection with one course of bleomycin and etoposide plus cisplatin chemotherapy in the adjuvant treatment of clinical stage I nonseminomatous testicular germ cell tumors: AUO trial AH 01/94 by the German Testicular Cancer Study Group. J Clin Oncol 26: 2966–2972

Alexandre J, Fizazi K, Mahe C et al (2001) Stage I nonseminomatous germ-cell tumours of the testis: identification of a subgroup of patients with a very low risk of relapse. Eur J Cancer 37:576–582

Altena R, de Haas EC, Nuver J et al (2009) Evaluation of sub-acute changes in cardiac function after cisplatin-based combination chemotherapy for testicular cancer. Br J Cancer 100:1861–1866

Amato RJ, Ro JY, Ayala AG et al (2004) Risk-adapted treatment for patients with clinical stage I nonseminomatous germ cell tumor of the testis. Urology 63:144–148; discussion 148–149

Andre F, Fizazi K, Culine S et al (2000) The growing teratoma syndrome: results of therapy and long-term follow-up of 33 patients. Eur J Cancer 36:1389–1394

Aparicio J, Garcia del Muro X, Maroto P et al (2003) Multicenter study evaluating a dual policy of postorchiectomy surveillance and selective adjuvant single-agent carboplatin for patients with clinical stage I seminoma. Ann Oncol 14:867–872

Aparicio J, Germa JR, Garcia del Muro X et al (2005) Risk-adapted management for patients with clinical stage I seminoma: the Second Spanish Germ Cell Cancer Cooperative Group study. J Clin Oncol 23:8717–8723

Bajorin DF, Sarosdy MF, Pfister DG et al (1993) Randomized trial of etoposide and cisplatin versus etoposide and carboplatin in patients with good-risk germ cell tumors: a multiinstitutional study. J Clin Oncol 11:598–606

Baniel J, Foster RS, Gonin R et al (1995) Late relapse of testicular cancer. J Clin Oncol 13:1170–1176

Beck SD, Foster RS, Bihrle R et al (2002) Teratoma in the orchiectomy specimen and volume of metastasis are predictors of retroperitoneal teratoma in post-chemotherapy nonseminomatous testis cancer. J Urol 168:1402–1404

Beck SD, Patel MI, Sheinfeld J (2004) Tumor marker levels in post-chemotherapy cystic masses: clinical implications for patients with germ cell tumors. J Urol 171:168–171

Beck SD, Foster RS, Bihrle R et al (2005) Outcome analysis for patients with elevated serum tumor markers at postchemotherapy retroperitoneal lymph node dissection. J Clin Oncol 23:6149–6156

Behnia M, Foster R, Einhorn LH et al (2000) Adjuvant bleomycin, etoposide and cisplatin in pathological stage II non-seminomatous testicular cancer: the Indiana University experience. Eur J Cancer 36:472–475

Beyer J, Kramar A, Mandanas R et al (1996) High-dose chemotherapy as salvage treatment in germ cell tumors: a multivariate analysis of prognostic variables. J Clin Oncol 14:2638–2645

Beyer J, Stenning S, Gerl A et al (2002) High-dose versus conventional-dose chemotherapy as first-salvage treatment in patients with non-seminomatous germ-cell tumors: a matched-pair analysis. Ann Oncol 13: 599–605

Bhayani SB, Ong A, Oh WK et al (2003) Laparoscopic retroperitoneal lymph node dissection for clinical stage I nonseminomatous germ cell testicular cancer: a long-term update. Urology 62:324–327

Blomberg Jensen M, Leffers H, Petersen JH et al (2008) Association of the polymorphism of the CAG repeat in the mitochondrial DNA polymerase gamma gene (POLG) with testicular germ-cell cancer. Ann Oncol 19:1910–1914

Bohlen D, Borner M, Sonntag RW et al (1999) Long-term results following adjuvant chemotherapy in patients with clinical stage I testicular nonseminomatous malignant germ cell tumors with high risk factors. J Urol 161:1148–1152

Bokemeyer C, Berger CC, Kuczyk MA et al (1996a) Evaluation of long-term toxicity after chemotherapy for testicular cancer. J Clin Oncol 14:2923–2932

Bokemeyer C, Kohrmann O, Tischler J et al (1996b) A randomized trial of cisplatin, etoposide and bleomycin (PEB) versus carboplatin, etoposide and bleomycin (CEB) for patients with 'good-risk' metastatic non-seminomatous germ cell tumors. Ann Oncol 7: 1015–1021

Bokemeyer C, Kollmannsberger C, Flechon A et al (2002a) Prognostic factors in patients (pts) with advanced metastatic seminoma (SEM) treated with either single agent carboplatin (CP) or cisplatin-based (DDP) combination chemotherapy (CTX): a meta-analysis of prospective European trials. Proc Am Soc Clin Oncol 21:740

Bokemeyer C, Nichols CR, Droz JP et al (2002b) Extragonadal germ cell tumors of the mediastinum and retroperitoneum: results from an international analysis. J Clin Oncol 20:1864–1873

Bokemeyer C, Kollmannsberger C, Stenning S et al (2004) Metastatic seminoma treated with either single agent carboplatin or cisplatin-based combination chemotherapy: a pooled analysis of two randomised trials. Br J Cancer 91:683–687

Bosl GJ, Vogelzang NJ, Goldman A et al (1981) Impact of delay in diagnosis on clinical stage of testicular cancer. Lancet 2:970–973

Bosl GJ, Geller NL, Bajorin D et al (1988) A randomized trial of etoposide + cisplatin versus vinblastine + bleomycin + cisplatin + cyclophosphamide + dactinomycin in patients with good-prognosis germ cell tumors. J Clin Oncol 6:1231–1238

Bosl GJ, Dmitrovsky E, Reuter VE et al (1989) Isochromosome of the short arm of chromosome 12: clinically useful markers for male germ cell tumors. J Natl Cancer Inst 81:1874–1878

Bray F, Richiardi L, Ekbom A et al (2006) Trends in testicular cancer incidence and mortality in 22 European countries: continuing increases in incidence and declines in mortality. Int J Cancer 118(12):3099–3111

Bredael JJ, Vugrin D, Whitmore WF Jr (1982) Autopsy findings in 154 patients with germ cell tumors of the testis. Cancer 50:548–551

Brenner DJ, Hall EJ (2007) Computed tomography—an increasing source of radiation exposure. N Engl J Med 357:2277–2284

Brenner PC, Herr HW, Morse MJ et al (1996) Simultaneous retroperitoneal, thoracic, and cervical resection of postchemotherapy residual masses in patients with metastatic nonseminomatous germ cell tumors of the testis. J Clin Oncol 14:1765–1769

Brydoy M, Fossa SD, Klepp O et al (2005) Paternity following treatment for testicular cancer. J Natl Cancer Inst 97:1580–1588

Brydoy M, Oldenburg J, Klepp O et al (2009) Observational study of prevalence of long-term Raynaud-like phenomena and neurological side effects in testicular cancer survivors. J Natl Cancer Inst 101:1682–1695

Burger H, Nooter K, Boersma AW et al (1998) Expression of p53, Bcl-2 and Bax in cisplatin-induced apoptosis in testicular germ cell tumour cell lines. Br J Cancer 77:1562–1567

Calvert AH, Egorin MJ (2002) Carboplatin dosing formulae: gender bias and the use of creatinine-based methodologies. Eur J Cancer 38:11–16

Carmignani L, Morabito A, Gadda F et al (2005) Prognostic parameters in adult impalpable ultrasonographic lesions of the testicle. J Urol 174:1035–1038

Carver BS, Serio AM, Bajorin D et al (2007a) Improved clinical outcome in recent years for men with metastatic nonseminomatous germ cell tumors. J Clin Oncol 25:5603–5608

Carver BS, Shayegan B, Eggener S et al (2007b) Incidence of metastatic nonseminomatous germ cell tumor outside the boundaries of a modified postchemotherapy retroperitoneal lymph node dissection. J Clin Oncol 25:4365–4369

Carver BS, Shayegan B, Serio A et al (2007c) Long-term clinical outcome after postchemotherapy retroperitoneal lymph node dissection in men with residual teratoma. J Clin Oncol 25:1033–1037

Castedo SM, de Jong B, Oosterhuis JW et al (1989) Chromosomal changes in human primary testicular nonseminomatous germ cell tumors. Cancer Res 49:5696–5701

Chaganti RS, Houldsworth J (2000) Genetics and biology of adult human male germ cell tumors. Cancer Res 60:1475–1482

Chamie K, Kurzrock EA, Romero V et al (2008) Increased risk of secondary malignancy in patients on surveillance for NSGCT. J Urol 179:172–173; abstract 492

Cheville JC (1999) Classification and pathology of testicular germ cell and sex cord–stromal tumors. Urol Clin North Am 26:595–609

Chevreau C, Mazerolles C, Soulie M et al (2004) Long-term efficacy of two cycles of BEP regimen in high-risk stage I nonseminomatous testicular germ cell tumors with embryonal carcinoma and/or vascular invasion. Eur Urol 46:209–214; discussion 214–215

Choo R, Thomas G, Woo T et al (2005) Long-term outcome of postorchiectomy surveillance for Stage I testicular seminoma. Int J Radiat Oncol Biol Phys 61:736–740

Christensen TB, Daugaard G, Geertsen PF et al (1998) Effect of chemotherapy on carcinoma in situ of the testis. Ann Oncol 9:657–660

Chung P, Parker C, Panzarella T et al (2002) Surveillance in stage I testicular seminoma—risk of late relapse. Can J Urol 9:1637–1640

Chung PW, Warde PR, Panzarella T et al (2003) Appropriate radiation volume for stage IIA/B testicular seminoma. Int J Radiat Oncol Biol Phys 56: 746–748

Chung PW, Bayley AJ, Sweet J et al (2004a) Spermatocytic seminoma: a review. Eur Urol 45:495–498

Chung PW, Gospodarowicz MK, Panzarella T et al (2004b) Stage II testicular seminoma: patterns of recurrence and outcome of treatment. Eur Urol 45: 754–759; discussion 759–760

Classen J, Dieckmann K, Bamberg M et al (2003a) Radiotherapy with 16 Gy may fail to eradicate testicular intraepithelial neoplasia: preliminary communication of a dose-reduction trial of the German Testicular Cancer Study Group. Br J Cancer 88:828–831

Classen J, Schmidberger H, Meisner C et al (2003b) Radiotherapy for stages IIA/B testicular seminoma: final report of a prospective multicenter clinical trial. J Clin Oncol 21:1101–1106

Classen J, Schmidberger H, Meisner C et al (2004) Paraaortic irradiation for stage I testicular seminoma: results of a prospective study in 675 patients: a trial of the German testicular cancer study group (GTCSG). Br J Cancer 90:2305–2311

Coleman J, Brennan MF, Alektiar K et al (2003) Adult spermatic cord sarcomas: management and results. Ann Surg Oncol 10:669–675

Collette L, Sylvester RJ, Stenning SP et al (1999) Impact of the treating institution on survival of patients with "poor-prognosis" metastatic nonseminoma. European Organization for Research and Treatment of Cancer Genito-Urinary Tract Cancer Collaborative Group and the Medical Research Council Testicular Cancer Working Party. J Natl Cancer Inst 91:839–846

Colls BM, Harvey VJ, Skelton L et al (1999) Late results of surveillance of clinical stage I nonseminoma germ cell testicular tumours: 17 years' experience in a national study in New Zealand. BJU Int 83:76–82

Comiter CV, Kibel AS, Richie JP et al (1998) Prognostic features of teratomas with malignant transformation: a clinicopathological study of 21 cases. J Urol 159: 859–863

Connolly SS, D'Arcy FT, Gough N et al (2006) Carefully selected intratesticular lesions can be safely managed with serial ultrasonography. BJU Int 98:1005–1007; discussion 1007

Culine S, Theodore C, Terrier-Lacombe MJ et al (1996) Primary chemotherapy in patients with nonseminomatous germ cell tumors of the testis and biological disease only after orchiectomy. J Urol 155:1296–1298

Culine S, Theodore C, Court BH et al (1997) Evaluation of primary standard cisplatin-based chemotherapy for clinical stage II non-seminomatous germ cell tumours of the testis. Br J Urol 79:258–262

Culine S, Kerbrat P, Kramar A et al (2007) Refining the optimal chemotherapy regimen for good-risk metastatic nonseminomatous germ-cell tumors: a randomized trial of the Genito-Urinary Group of the French Federation of Cancer Centers (GETUG T93BP). Ann Oncol 18:917–924

Culine S, Kramar A, Theodore C et al (2008) Randomized trial comparing bleomycin/etoposide/cisplatin with alternating cisplatin/cyclophosphamide/doxorubicin and vinblastine/bleomycin regimens of chemotherapy for patients with intermediate- and poor-risk metastatic nonseminomatous germ cell tumors: Genito-Urinary Group of the French Federation of Cancer Centers Trial T93MP. J Clin Oncol 26:421–427

Cullen MH, Stenning SP, Parkinson MC et al (1996) Short-course adjuvant chemotherapy in high-risk stage I nonseminomatous germ cell tumors of the testis: a Medical Research Council report. J Clin Oncol 14:1106–1113

Daugaard G, Petersen PM, Rorth M (2003) Surveillance in stage I testicular cancer. APMIS 111:76–83; discussion 83–85

Davis BE, Herr HW, Fair WR et al (1994) The management of patients with nonseminomatous germ cell tumors of the testis with serologic disease only after orchiectomy. J Urol 152:111–113; discussion 114

De Santis M, Becherer A, Bokemeyer C et al (2004) 2–18Fluoro-deoxy-d-glucose positron emission tomography is a reliable predictor for viable tumor in postchemotherapy seminoma: an update of the Prospective Multicentric SEMPET Trial. J Clin Oncol 22:1034–1039

de Wit R, Stoter G, Kaye SB et al (1997) Importance of bleomycin in combination chemotherapy for good-prognosis testicular nonseminoma: a randomized study of the European Organization for Research and Treatment of Cancer Genitourinary Tract Cancer Cooperative Group. J Clin Oncol 15:1837–1843

de Wit R, Stoter G, Sleijfer DT et al (1998) Four cycles of BEP vs four cycles of VIP in patients with intermediate-prognosis metastatic testicular non-seminoma: a randomized study of the EORTC Genitourinary Tract Cancer Cooperative Group. European Organization for Research and Treatment of Cancer. Br J Cancer 78:828–832

de Wit R, Roberts JT, Wilkinson PM et al (2001) Equivalence of three or four cycles of bleomycin, etoposide, and cisplatin chemotherapy and of a 3- or 5-day schedule in good-prognosis germ cell cancer: a randomized study of the European Organization for Research and Treatment of Cancer Genitourinary Tract Cancer Cooperative Group and the Medical Research Council. J Clin Oncol 19:1629–1640

de Wit M, Brenner W, Hartmann M et al (2008) [18F]-FDG-PET in clinical stage I/II non-seminomatous germ cell tumours: results of the German multicentre trial. Ann Oncol 19:1619–1623

Dearnaley DP, Horwich A, A'Hern R et al (1991) Combination chemotherapy with bleomycin, etoposide and cisplatin (BEP) for metastatic testicular teratoma: long-term follow-up. Eur J Cancer 27:684–691

Dearnaley DP, Fossa SD, Kaye SB et al (2005) Adjuvant bleomycin, vincristine and cisplatin (BOP) for high-risk stage I non-seminomatous germ cell tumours: a prospective trial (MRC TE17). Br J Cancer 92:2107–2113

Debono DJ, Heilman DK, Einhorn LH et al (1997) Decision analysis for avoiding postchemotherapy surgery in patients with disseminated nonseminomatous germ cell tumors. J Clin Oncol 15:1455–1464

DeCastro BJ, Peterson AC, Costabile RA (2008) A 5-year followup study of asymptomatic men with testicular microlithiasis. J Urol 179:1420–1423; discussion 1423

Dieckmann KP, Loy V (1996) Prevalence of contralateral testicular intraepithelial neoplasia in patients with testicular germ cell neoplasms. J Clin Oncol 14:3126–3132

Dieckmann KP, Pichlmeier U (2004) Clinical epidemiology of testicular germ cell tumors. World J Urol 22:2–14

Dieckmann KP, Skakkebaek NE (1999) Carcinoma in situ of the testis: review of biological and clinical features. Int J Cancer 83:815–822

Dieckmann KP, Bruggeboes B, Pichlmeier U et al (2000) Adjuvant treatment of clinical stage I seminoma: is a single course of carboplatin sufficient? Urology 55:102–106

Dieckmann KP, Classen J, Loy V (2003) Diagnosis and management of testicular intraepithelial neoplasia (carcinoma in situ)—surgical aspects. APMIS 111:64–68; discussion 68–69

Dieckmann KP, Albers P, Classen J et al (2005) Late relapse of testicular germ cell neoplasms: a descriptive analysis of 122 cases. J Urol 173:824–829

Donadio AC, Motzer RJ, Bajorin DF et al (2003) Chemotherapy for teratoma with malignant transformation. J Clin Oncol 21:4285–4291

Donohue JP, Foster RS (1998) Retroperitoneal lymphadenectomy in staging and treatment: the development of nerve-sparing techniques. Urol Clin North Am 25:461–468

Donohue JP, Zachary JM, Maynard BR (1982) Distribution of nodal metastases in nonseminomatous testis cancer. J Urol 128:315–320

Donohue JP, Rowland RG, Kopecky K et al (1987) Correlation of computerized tomographic changes and histological findings in 80 patients having radical retroperitoneal lymph node dissection after chemotherapy for testis cancer. J Urol 137:1176–1179

Donohue JP, Thornhill JA, Foster RS et al (1993) Retroperitoneal lymphadenectomy for clinical stage A testis cancer (1965 to 1989): modifications of technique and impact on ejaculation. J Urol 149:237–243

Donohue JP, Thornhill JA, Foster RS et al (1995) Clinical stage B non-seminomatous germ cell testis cancer: the Indiana University experience (1965–1989) using routine primary retroperitoneal lymph node dissection. Eur J Cancer 31A:1599–1604

Donohue JP, Leviovitch I, Foster RS et al (1998) Integration of surgery and systemic therapy: results and principles of integration. Semin Urol Oncol 16:65–71

Dotan ZA, Tal R, Golijanin D et al (2006) Adult genitourinary sarcoma: the 25-year Memorial Sloan-Kettering experience. J Urol 176:2033–2038; discussion 2038–2039

Doyle DM, Einhorn LH (2008) Delayed effects of whole brain radiotherapy in germ cell tumor patients with central nervous system metastases. Int J Radiat Oncol Biol Phys 70:1361–1364

Droz JP, Kramar A, Biron P et al (2007) Failure of high-dose cyclophosphamide and etoposide combined with double-dose cisplatin and bone marrow support in patients with high-volume metastatic nonseminomatous germ-cell tumours: mature results of a randomised trial. Eur Urol 51:739–746; discussion 747–748

Duchesne GM, Stenning SP, Aass N et al (1997) Radiotherapy after chemotherapy for metastatic seminoma—a diminishing role. MRC Testicular Tumour Working Party. Eur J Cancer 33:829–835

Duran I, Sturgeon JF, Jewett MA et al (2007) Initial versus recent outcomes with a non-risk adapted surveillance policy in stage I non-seminomatous germ cell tumors (NSGCT). J Clin Oncol 25:240s; abstract 5021

Eastham JA, Wilson TG, Russell C et al (1994) Surgical resection in patients with nonseminomatous germ cell tumor who fail to normalize serum tumor markers after chemotherapy. Urology 43:74–80

Eble JN (1994) Spermatocytic seminoma. Hum Pathol 25:1035–1042

Eggener SE, Carver BS, Loeb S et al (2007a) Pathologic findings and clinical outcome of patients undergoing retroperitoneal lymph node dissection after multiple chemotherapy regimens for metastatic testicular germ cell tumors. Cancer 109:528–535

Eggener SE, Carver BS, Sharp DS et al (2007b) Incidence of disease outside modified retroperitoneal lymph node dissection templates in clinical stage I or IIA nonseminomatous germ cell testicular cancer. J Urol 177:937–943

Ehrlich Y, Brames MJ, Beck SD et al (2010) Long-term follow-up of cisplatin combination chemotherapy in patients with disseminated nonseminomatous germ cell tumors: is a postchemotherapy retroperitoneal lymph node dissection needed after complete remission? J Clin Oncol 28:531–536

Einhorn LH (1981) Testicular cancer as a model for a curable neoplasm: the Richard and Hinda Rosenthal Foundation Award Lecture. Cancer Res 41: 3275–3280

Einhorn LH (1990) Treatment of testicular cancer: a new and improved model. J Clin Oncol 8:1777–1781

Einhorn LH, Williams SD, Loehrer PJ et al (1989) Evaluation of optimal duration of chemotherapy in favorable-prognosis disseminated germ cell tumors: a Southeastern Cancer Study Group protocol. J Clin Oncol 7:387–391

Einhorn LH, Williams SD, Chamness A et al (2007) High-dose chemotherapy and stem-cell rescue for metastatic germ-cell tumors. N Engl J Med 357: 340–348

El Mesbahi O, Terrier-Lacombe MJ, Rebischung C et al (2007) Chemotherapy in patients with teratoma with malignant transformation. Eur Urol 51:1306–1311; discussion 1311–1312

Epstein JI (2010) The lower urinary tract and male genital system. In: Kumar V, Abbas AK, Fausto N et al (eds) Robbins and Cotran pathologic basis of disease, 8th edn. Elsevier, Philadelphia

Fagundes MA, Zietman AL, Althausen AF et al (1996) The management of spermatic cord sarcoma. Cancer 77:1873–1876

Feldman DR, Bosl GJ, Sheinfeld J et al (2008) Medical treatment of advanced testicular cancer. JAMA 299:672–684

Fernandez EB, Moul JW, Foley JP et al (1994) Retroperitoneal imaging with third and fourth generation computed axial tomography in clinical stage I nonseminomatous germ cell tumors. Urology 44: 548–552

Feuer EJ, Frey CM, Brawley OW et al (1994) After a treatment breakthrough: a comparison of trial and population-based data for advanced testicular cancer. J Clin Oncol 12:368–377

Fizazi K, Tjulandin S, Salvioni R et al (2001) Viable malignant cells after primary chemotherapy for disseminated nonseminomatous germ cell tumors: prognostic factors and role of postsurgery chemotherapy—results from an international study group. J Clin Oncol 19:2647–2657

Fizazi K, Oldenburg J, Dunant A et al (2008) Assessing prognosis and optimizing treatment in patients with postchemotherapy viable nonseminomatous germ-cell tumors (NSGCT): results of the sCR2 international study. Ann Oncol 19:259–264

Flechon A, Bompas E, Biron P et al (2002) Management of post-chemotherapy residual masses in advanced seminoma. J Urol 168:1975–1979

Fossa SD, Aass N, Kaalhus O (1989a) Radiotherapy for testicular seminoma stage I: treatment results and long-term post-irradiation morbidity in 365 patients. Int J Radiat Oncol Biol Phys 16:383–388

Fossa SD, Ous S, Lien HH et al (1989b) Post-chemotherapy lymph node histology in radiologically normal patients with metastatic nonseminomatous testicular cancer. J Urol 141:557–559

Fossa SD, Qvist H, Stenwig AE et al (1992) Is postchemotherapy retroperitoneal surgery necessary in patients with nonseminomatous testicular cancer and minimal residual tumor masses? J Clin Oncol 10:569–573

Fossa SD, Oliver RT, Stenning SP et al (1997) Prognostic factors for patients with advanced seminoma treated with platinum-based chemotherapy. Eur J Cancer 33:1380–1387

Fossa SD, Bokemeyer C, Gerl A et al (1999a) Treatment outcome of patients with brain metastases from malignant germ cell tumors. Cancer 85:988–997

Fossa SD, Horwich A, Russell JM et al (1999b) Optimal planning target volume for stage I testicular seminoma: a Medical Research Council randomized trial. Medical Research Council Testicular Tumor Working Group. J Clin Oncol 17:1146

Fossa SD, Stenning SP, Gerl A et al (1999c) Prognostic factors in patients progressing after cisplatin-based chemotherapy for malignant non-seminomatous germ cell tumours. Br J Cancer 80:1392–1399

Fossa SD, Aass N, Harvei S et al (2004) Increased mortality rates in young and middle-aged patients with malignant germ cell tumours. Br J Cancer 90: 607–612

Fossa SD, Chen J, Schonfeld SJ et al (2005) Risk of contralateral testicular cancer: a population-based study of 29,515 U.S. men. J Natl Cancer Inst 97:1056–1066

Fossa SD, Gilbert E, Dores GM et al (2007) Noncancer causes of death in survivors of testicular cancer. J Natl Cancer Inst 99:533–544

Fossa SD, Oldenburg J, Dahl AA (2009) Short- and long-term morbidity after treatment for testicular cancer. BJU Int 104:1418–1422

Foster RS, Baniel J, Leibovitch I et al (1996) Teratoma in the orchiectomy specimen and volume of metastasis are predictors of retroperitoneal teratoma in low stage nonseminomatous testis cancer. J Urol 155: 1943–1945

Fox EP, Weathers TD, Williams SD et al (1993) Outcome analysis for patients with persistent nonteratomatous germ cell tumor in postchemotherapy retroperitoneal lymph node dissections. J Clin Oncol 11:1294–1299

Francis R, Bower M, Brunstrom G et al (2000) Surveillance for stage I testicular germ cell tumours: results and cost benefit analysis of management options. Eur J Cancer 36:1925–1932

Freedman LS, Parkinson MC, Jones WG et al (1987) Histopathology in the prediction of relapse of patients with stage I testicular teratoma treated by orchidectomy alone. Lancet 2:294–298

Garcia del Muro X, Maroto P, Guma J et al (2008) Chemotherapy as an alternative to radiotherapy in the treatment of stage IIA and IIB testicular seminoma: a Spanish Germ Cell Cancer Group Study. J Clin Oncol 26:5416–5421

Geldart TR, Simmonds PD, Mead GM (2002) Orchidectomy after chemotherapy for patients with metastatic testicular germ cell cancer. BJU Int 90:451–455

Gels ME, Hoekstra HJ, Sleijfer DT et al (1995) Detection of recurrence in patients with clinical stage I nonseminomatous testicular germ cell tumors and consequences for further follow-up: a single-center 10-year experience. J Clin Oncol 13:1188–1194

George DW, Foster RS, Hromas RA et al (2003) Update on late relapse of germ cell tumor: a clinical and molecular analysis. J Clin Oncol 21:113–122

Gerl A, Clemm C, Schmeller N et al (1994) Sequential resection of residual abdominal and thoracic masses after chemotherapy for metastatic non-seminomatous germ cell tumours. Br J Cancer 70:960–965

Gerl A, Clemm C, Schmeller N et al (1995) Outcome analysis after post-chemotherapy surgery in patients with non-seminomatous germ cell tumours. Ann Oncol 6:483–488

Gerl A, Clemm C, Schmeller N et al (1997) Late relapse of germ cell tumors after cisplatin-based chemotherapy. Ann Oncol 8:41–47

Gholam D, Fizazi K, Terrier-Lacombe MJ et al (2003) Advanced seminoma—treatment results and prognostic factors for survival after first-line, cisplatin-based chemotherapy and for patients with recurrent disease: a single-institution experience in 145 patients. Cancer 98:745–752

Greene FL, Page DL, Fleming ID et al (2002) AJCC cancer staging manual, 6th edn. Springer, New York

Gremmer R, Schroder ML, Ten Huinink WW et al (2008) Successful management of brain metastasis from malignant germ cell tumours with standard induction chemotherapy. J Neurooncol 90:335–339

Hao D, Seidel J, Brant R et al (1998) Compliance of clinical stage I nonseminomatous germ cell tumor patients with surveillance. J Urol 160:768–771

Harding MJ, Paul J, Gillis CR et al (1993) Management of malignant teratoma: does referral to a specialist unit matter? Lancet 341:999–1002

Hartmann JT, Candelaria M, Kuczyk MA et al (1997a) Comparison of histological results from the resection of residual masses at different sites after chemotherapy for metastatic non-seminomatous germ cell tumours. Eur J Cancer 33:843–847

Hartmann JT, Schmoll HJ, Kuczyk MA et al (1997b) Postchemotherapy resections of residual masses from metastatic non-seminomatous testicular germ cell tumors. Ann Oncol 8:531–538

Hartmann JT, Bamberg M, Albers P et al (2003) Multidisciplinary treatment and prognosis of patients (pts) with central nervous system metastases (CNS) from testicular germ cell tumor (GCT) origin. Proc Am Soc Clin Oncol 22:Abst 1607

Heidenreich A, Sesterhenn IA, Mostofi FK et al (1998) Prognostic risk factors that identify patients with clinical stage I nonseminomatous germ cell tumors at low risk and high risk for metastasis. Cancer 83:1002–1011

Heidenreich A, Weissbach L, Holtl W et al (2001) Organ sparing surgery for malignant germ cell tumor of the testis. J Urol 166:2161–2165

Heidenreich A, Albers P, Hartmann M et al (2003) Complications of primary nerve sparing retroperitoneal lymph node dissection for clinical stage I nonseminomatous germ cell tumors of the testis: experience of the German Testicular Cancer Study Group. J Urol 169:1710–1714

Hemminki K, Chen B (2006) Familial risks in testicular cancer as aetiological clues. Int J Androl 29:205–210

Hendry WF, Norman AR, Dearnaley DP et al (2002) Metastatic nonseminomatous germ cell tumors of the testis: results of elective and salvage surgery for patients with residual retroperitoneal masses. Cancer 94:1668–1676

Hermans BP, Sweeney CJ, Foster RS et al (2000) Risk of systemic metastases in clinical stage I nonseminoma germ cell testis tumor managed by retroperitoneal lymph node dissection. J Urol 163:1721–1724

Herr HW, Sheinfeld J, Puc HS et al (1997) Surgery for a post-chemotherapy residual mass in seminoma. J Urol 157:860–862

Hilton S, Herr HW, Teitcher JB et al (1997) CT detection of retroperitoneal lymph node metastases in patients with clinical stage I testicular nonseminomatous germ cell cancer: assessment of size and distribution criteria. AJR Am J Roentgenol 169:521–525

Hindley RG, Chandra A, Saunders A et al (2003) Impalpable testis cancer. BJU Int 92:572–574

Hinton S, Catalano PJ, Einhorn LH et al (2003) Cisplatin, etoposide and either bleomycin or ifosfamide in the treatment of disseminated germ cell tumors: final analysis of an intergroup trial. Cancer 97:1869–1875

Hinz S, Schrader M, Kempkensteffen C et al (2008) The role of positron emission tomography in the evaluation of residual masses after chemotherapy for advanced stage seminoma. J Urol 179:936–940

Holmes L Jr, Escalante C, Garrison O et al (2008) Testicular cancer incidence trends in the USA (1975–2004): plateau or shifting racial paradigm? Public Health 122:862–872

Honecker F, Wermann H, Mayer F et al (2009) Microsatellite instability, mismatch repair deficiency, and BRAF mutation in treatment-resistant germ cell tumors. J Clin Oncol 27:2129–2136

Horan G, Rafique A, Robson J et al (2007) CT of the chest can hinder the management of seminoma of the testis; it detects irrelevant abnormalities. Br J Cancer 96:882–885

Horner MJ, Ries LAG, Krapcho M et al (2009) SEER cancer statistics review, 1975–2006. National Cancer Institute, Bethesda

Horwich A, Alsanjari N, A'Hern R et al (1992) Surveillance following orchidectomy for stage I testicular seminoma. Br J Cancer 65:775–778

Horwich A, Norman A, Fisher C et al (1994) Primary chemotherapy for stage II nonseminomatous germ cell tumors of the testis. J Urol 151:72–77; discussion 77–78

Horwich A, Sleijfer DT, Fossa SD et al (1997) Randomized trial of bleomycin, etoposide, and cisplatin compared with bleomycin, etoposide, and carboplatin in good-prognosis metastatic nonseminomatous germ cell cancer: a Multiinstitutional Medical Research Council/European Organization for Research and Treatment of Cancer Trial. J Clin Oncol 15:1844–1852

Horwich A, Oliver RT, Wilkinson PM et al (2000) A Medical Research Council randomized trial of single agent carboplatin versus etoposide and cisplatin for advanced metastatic seminoma. MRC Testicular Tumour Working Party. Br J Cancer 83:1623–1629

Hotte S, Mayhew LA, Jewett M et al Management of stage I nonseminomatous testicular cancer: guideline

recommendations. http://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=140482008. Accessed 10 Nov 2010
Houldsworth J, Xiao H, Murty VV et al (1998) Human male germ cell tumor resistance to cisplatin is linked to TP53 gene mutation. Oncogene 16:2345–2349
Howard GC, Clarke K, Elia MH et al (1995) A Scottish national audit of current patterns of management for patients with testicular non-seminomatous germ-cell tumours. The Scottish Radiological Society and the Scottish Committee of the Royal College of Radiologists. Br J Cancer 72:1303–1306
Hu GX, Lian QQ, Ge RS et al (2009) Phthalate-induced testicular dysgenesis syndrome: Leydig cell influence. Trends Endocrinol Metab 20:139–145
Huddart RA, Norman A, Shahidi M et al (2003) Cardiovascular disease as a long-term complication of treatment for testicular cancer. J Clin Oncol 21:1513–1523
Huddart RA, O'Doherty MJ, Padhani A et al (2007) 18Fluorodeoxyglucose positron emission tomography in the prediction of relapse in patients with high-risk, clinical stage I nonseminomatous germ cell tumors: preliminary report of MRC Trial TE22—the NCRI Testis Tumour Clinical Study Group. J Clin Oncol 25:3090–3095
Hunt BM, Vallieres E, Buduhan G et al (2009) Sarcoidosis as a benign cause of lymphadenopathy in cancer patients. Am J Surg 197:629–632; discussion 632
Hussain SA, Ma YT, Palmer DH et al (2008) Biology of testicular germ cell tumors. Expert Rev Anticancer Ther 8:1659–1673
Huyghe E, Matsuda T, Thonneau P (2003) Increasing incidence of testicular cancer worldwide: a review. J Urol 170:5–11
Huyghe E, Matsuda T, Daudin M et al (2004) Fertility after testicular cancer treatments: results of a large multicenter study. Cancer 100:732–737
International Germ Cell Consensus Classification: a prognostic factor-based staging system for metastatic germ cell cancers. International Germ Cell Cancer Collaborative Group (1997) J Clin Oncol 15: 594–603
Janetschek G, Hobisch A, Peschel R et al (2000) Laparoscopic retroperitoneal lymph node dissection for clinical stage I nonseminomatous testicular carcinoma: long-term outcome. J Urol 163:1793–1796
Jemal A, Siegel R, Xu J, Ward E (2010) Cancer statistics, 2010. CA Cancer J Clin 60:277–300
Jewett MA (1990) Nerve-sparing technique for retroperitoneal lymphadenectomy in testis cancer. Urol Clin North Am 17:449–456
Jones WG, Fossa SD, Mead GM et al (2005) Randomized trial of 30 versus 20 Gy in the adjuvant treatment of stage I Testicular Seminoma: a report on Medical Research Council Trial TE18, European Organisation for the Research and Treatment of Cancer Trial 30942 (ISRCTN18525328). J Clin Oncol 23:1200–1208
Joudi FN, Konety BR (2005) The impact of provider volume on outcomes from urological cancer therapy. J Urol 174:432–438
Kanetsky PA, Mitra N, Vardhanabhuti S et al (2009) Common variation in KITLG and at 5q31.3 predisposes to testicular germ cell cancer. Nat Genet 41:811–815
Karellas ME, Damjanov I, Holzbeierlein JM (2007) ITGCN of the testis, contralateral testicular biopsy and bilateral testicular cancer. Urol Clin North Am 34:119–125; abstract vii
Kesler KA, Rieger KM, Hammoud ZT et al (2008) A 25-year single institution experience with surgery for primary mediastinal nonseminomatous germ cell tumors. Ann Thorac Surg 85:371–378
Kollmannsberger C, Nichols C, Bamberg M et al (2000) First-line high-dose chemotherapy +/−radiation therapy in patients with metastatic germ-cell cancer and brain metastases. Ann Oncol 11:553–559
Kollmannsberger C, Beyer J, Bokemeyer C (2009) High-dose chemotherapy in nonseminomatous germ cell cancer. BJU Int 104:1398–1403
Kollmannsberger C, Daneshmand S, So A et al (2010a) Management of disseminated nonseminomatous germ cell tumors with risk-based chemotherapy followed by response-guided postchemotherapy surgery. J Clin Oncol 28:537–542
Kollmannsberger C, Moore C, Chi KN et al (2010b) Non-risk-adapted surveillance for patients with stage I nonseminomatous testicular germ-cell tumors: diminishing treatment-related morbidity while maintaining efficacy. Ann Oncol 21:1296–1301
Kondagunta GV, Sheinfeld J, Mazumdar M et al (2004) Relapse-free and overall survival in patients with pathologic stage II nonseminomatous germ cell cancer treated with etoposide and cisplatin adjuvant chemotherapy. J Clin Oncol 22:464–467
Kondagunta GV, Bacik J, Donadio A et al (2005) Combination of paclitaxel, ifosfamide, and cisplatin is an effective second-line therapy for patients with relapsed testicular germ cell tumors. J Clin Oncol 23:6549–6555
Kondagunta GV, Bacik J, Sheinfeld J et al (2007) Paclitaxel plus ifosfamide followed by high-dose carboplatin plus etoposide in previously treated germ cell tumors. J Clin Oncol 25:85–90
Krege S, Beyer J, Souchon R et al (2008a) European consensus conference on diagnosis and treatment of germ cell cancer: a report of the second meeting of the European Germ Cell Cancer Consensus Group (EGCCCG): I. Eur Urol 53:478–496
Krege S, Beyer J, Souchon R et al (2008b) European consensus conference on diagnosis and treatment of germ cell cancer: a report of the second meeting of the European Germ Cell Cancer Consensus Group (EGCCCG): II. Eur Urol 53:497–513
Lackner JE, Koller A, Schatzl G et al (2009) Androgen deficiency symptoms in testicular cancer survivors are associated with sexual problems but not with serum testosterone or therapy. Urology 74:825–829
Leibovitch L, Foster RS, Kopecky KK et al (1995) Improved accuracy of computerized tomography based clinical staging in low stage nonseminomatous

germ cell cancer using size criteria of retroperitoneal lymph nodes. J Urol 154:1759–1763
Lerner SE, Mann BS, Blute ML et al (1995) Primary chemotherapy for clinical stage II nonseminomatous germ cell testicular tumors: selection criteria and long-term results. Mayo Clin Proc 70:821–828
Levi JA, Raghavan D, Harvey V et al (1993) The importance of bleomycin in combination chemotherapy for good-prognosis germ cell carcinoma. Australasian Germ Cell Trial Group. J Clin Oncol 11:1300–1305
Little JS Jr, Foster RS, Ulbright TM et al (1994) Unusual neoplasms detected in testis cancer patients undergoing post-chemotherapy retroperitoneal lymphadenectomy. J Urol 152:1144–1149
Liu S, Wen SW, Mao Y et al (1999) Birth cohort effects underlying the increasing testicular cancer incidence in Canada. Can J Public Health 90:176–180
Loehrer PJ Sr, Einhorn LH, Williams SD (1986) VP-16 plus ifosfamide plus cisplatin as salvage therapy in refractory germ cell cancer. J Clin Oncol 4:528–536
Loehrer PJ Sr, Birch R, Williams SD et al (1987) Chemotherapy of metastatic seminoma: the Southeastern Cancer Study Group experience. J Clin Oncol 5:1212–1220
Loehrer PJ Sr, Lauer R, Roth BJ et al (1988) Salvage therapy in recurrent germ cell cancer: ifosfamide and cisplatin plus either vinblastine or etoposide. Ann Intern Med 109:540–546
Loehrer PJ Sr, Johnson D, Elson P et al (1995) Importance of bleomycin in favorable-prognosis disseminated germ cell tumors: an Eastern Cooperative Oncology Group trial. J Clin Oncol 13:470–476
Loehrer PJ Sr, Gonin R, Nichols CR et al (1998) Vinblastine plus ifosfamide plus cisplatin as initial salvage therapy in recurrent germ cell tumor. J Clin Oncol 16:2500–2504
Logothetis CJ, Samuels ML, Trindade A et al (1982) The growing teratoma syndrome. Cancer 50:1629–1635
Logothetis CJ, Swanson DA, Dexeus F et al (1987) Primary chemotherapy for clinical stage II nonseminomatous germ cell tumors of the testis: a follow-up of 50 patients. J Clin Oncol 5:906–911
Lorch A, Kollmannsberger C, Hartmann JT et al (2007) Single versus sequential high-dose chemotherapy in patients with relapsed or refractory germ cell tumors: a prospective randomized multicenter trial of the German Testicular Cancer Study Group. J Clin Oncol 25:2778–2784
Lorch A, Beyer J, International Prognostic Factors Study Group et al (2010) Prognostic factors in patients with metastatic germ cell tumors who experienced treatment failure with cisplatin-based first-line chemotherapy. J Clin Oncol 28:4906–4911
Lowrance WT, Cookson MS, Clark PE et al (2007) Assessing retroperitoneal lymphadenectomy experience in United States urological residency programs. J Urol 178:500–503; discussion 503
Lutke Holzik MF, Hoekstra HJ, Mulder NH et al (2003) Non-germ cell malignancy in residual or recurrent mass after chemotherapy for nonseminomatous testicular germ cell tumor. Ann Surg Oncol 10:131–135
Mai PL, Chen BE, Tucker K et al (2009) Younger age-at-diagnosis for familial malignant testicular germ cell tumor. Fam Cancer 8:451–456
Mardiak J, Salek T, Sycova-Mila Z et al (2005) Gemcitabine plus cisplatine and paclitaxel (GCP) in second-line treatment of germ cell tumors (GCT): a phase II study. Neoplasma 52:243–247
Martin OV, Shialis T, Lester JN et al (2008) Testicular dysgenesis syndrome and the estrogen hypothesis: a quantitative meta-analysis. Environ Health Perspect 116:149–157
Mayer F, Stoop H, Scheffer GL et al (2003) Molecular determinants of treatment response in human germ cell tumors. Clin Cancer Res 9:767–773
McCaffrey JA, Mazumdar M, Bajorin DF et al (1997) Ifosfamide- and cisplatin-containing chemotherapy as first-line salvage therapy in germ cell tumors: response and survival. J Clin Oncol 15:2559–2563
McGlynn KA, Devesa SS, Sigurdson AJ et al (2003) Trends in the incidence of testicular germ cell tumors in the United States. Cancer 97:63–70
McGlynn KA, Devesa SS, Graubard BI et al (2005) Increasing incidence of testicular germ cell tumors among black men in the United States. J Clin Oncol 23:5757–5761
McGuire MS, Rabbani F, Mohseni H et al (2003) The role of thoracotomy in managing postchemotherapy residual thoracic masses in patients with nonseminomatous germ cell tumours. BJU Int 91:469–473
McKenney JK, Heerema-McKenney A, Rouse RV (2007) Extragonadal germ cell tumors: a review with emphasis on pathologic features, clinical prognostic variables, and differential diagnostic considerations. Adv Anat Pathol 14:69–92
McKiernan JM, Goluboff ET, Liberson GL et al (1999) Rising risk of testicular cancer by birth cohort in the United States from 1973 to 1995. J Urol 162:361–363
McLeod DG, Weiss RB, Stablein DM et al (1991) Staging relationships and outcome in early stage testicular cancer: a report from the Testicular Cancer Intergroup Study. J Urol 145:1178–1183; discussion 1182–1183
Mead GM, Stenning SP, Parkinson MC et al (1992) The Second Medical Research Council study of prognostic factors in nonseminomatous germ cell tumors. Medical Research Council Testicular Tumour Working Party. J Clin Oncol 10:85–94
Mead GM, Cullen MH, Huddart R et al (2005) A phase II trial of TIP (paclitaxel, ifosfamide and cisplatin) given as second-line (post-BEP) salvage chemotherapy for patients with metastatic germ cell cancer: a medical research council trial. Br J Cancer 93:178–184
Mead GM, Fossa SD, Oliver RT et al (2008) Relapse patterns in 2,466 stage 1 seminoma patients (pts) entered into Medical Research Council randomised trials. J Clin Oncol 26:255s; abstract 5020
Meinardi MT, Gietema JA, van der Graaf WT et al (2000) Cardiovascular morbidity in long-term survivors of metastatic testicular cancer. J Clin Oncol 18:1725–1732
Mencel PJ, Motzer RJ, Mazumdar M et al (1994) Advanced seminoma: treatment results, survival, and prognostic factors in 142 patients. J Clin Oncol 12:120–126

Michael H, Lucia J, Foster RS et al (2000) The pathology of late recurrence of testicular germ cell tumors. Am J Surg Pathol 24:257–273

Miller KD, Loehrer PJ, Gonin R et al (1997) Salvage chemotherapy with vinblastine, ifosfamide, and cisplatin in recurrent seminoma. J Clin Oncol 15:1427–1431

Montgomery E, Fisher C (2003) Paratesticular liposarcoma: a clinicopathologic study. Am J Surg Pathol 27:40–47

Montironi R (2002) Intratubular germ cell neoplasia of the testis: testicular intraepithelial neoplasia. Eur Urol 41:651–654

Mosharafa AA, Foster RS, Leibovich BC et al (2003) Is post-chemotherapy resection of seminomatous elements associated with higher acute morbidity? J Urol 169:2126–2128

Motzer R, Bosl G, Heelan R et al (1987) Residual mass: an indication for further therapy in patients with advanced seminoma following systemic chemotherapy. J Clin Oncol 5:1064–1070

Motzer RJ, Amsterdam A, Prieto V et al (1998) Teratoma with malignant transformation: diverse malignant histologies arising in men with germ cell tumors. J Urol 159:133–138

Motzer RJ, Bolger GB, Boston B et al (2006) Testicular cancer: clinical practice guidelines in oncology. J Natl Compr Canc Netw 4:1038–1058

Motzer RJ, Nichols CJ, Margolin KA et al (2007) Phase III randomized trial of conventional-dose chemotherapy with or without high-dose chemotherapy and autologous hematopoietic stem-cell rescue as first-line treatment for patients with poor-prognosis metastatic germ cell tumors. J Clin Oncol 25:247–256

Moul JW, Paulson DF, Dodge RK et al (1990) Delay in diagnosis and survival in testicular cancer: impact of effective therapy and changes during 18 years. J Urol 143:520–523

Muller T, Gozzi C, Akkad T et al (2006) Management of incidental impalpable intratesticular masses of < or = 5 mm in diameter. BJU Int 98:1001–1004

Murphy BR, Breeden ES, Donohue JP et al (1993) Surgical salvage of chemorefractory germ cell tumors. J Clin Oncol 11:324–329

Nelson JB, Chen RN, Bishoff JT et al (1999) Laparoscopic retroperitoneal lymph node dissection for clinical stage I nonseminomatous germ cell testicular tumors. Urology 54:1064–1067

Nguyen CT, Fu AZ, Gilligan TD et al (2010) Defining the optimal treatment for clinical stage I nonseminomatous germ cell testicular cancer using decision analysis. J Clin Oncol 28:119–125

Nichols CR, Catalano PJ, Crawford ED et al (1998) Randomized comparison of cisplatin and etoposide and either bleomycin or ifosfamide in treatment of advanced disseminated germ cell tumors: an Eastern Cooperative Oncology Group, Southwest Oncology Group, and Cancer and Leukemia Group B Study. J Clin Oncol 16:1287–1293

Nicolai N, Miceli R, Artusi R et al (2004) A simple model for predicting nodal metastasis in patients with clinical stage I nonseminomatous germ cell testicular tumors undergoing retroperitoneal lymph node dissection only. J Urol 171:172–176

Nielsen ME, Lima G, Schaeffer EM et al (2007) Oncologic efficacy of laparoscopic RPLND in treatment of clinical stage I nonseminomatous germ cell testicular cancer. Urology 70:1168–1172

Nonomura N, Nagahara A, Oka D et al (2009) Brain metastases from testicular germ cell tumors: a retrospective analysis. Int J Urol 16:887–893

Nord C, Bjoro T, Ellingsen D et al (2003) Gonadal hormones in long-term survivors 10 years after treatment for unilateral testicular cancer. Eur Urol 44:322–328

Nuver J, Smit AJ, Wolffenbuttel BHR et al (2005) The metabolic syndrome and disturbances in hormone levels in long-term survivors of disseminated testicular cancer [see comment]. J Clin Oncol 23:3718–3725

Oechsle K, Hartmann M, Brenner W et al (2008) [18F] Fluorodeoxyglucose positron emission tomography in nonseminomatous germ cell tumors after chemotherapy: the German multicenter positron emission tomography study group. J Clin Oncol 26:5930–5935

Oldenburg J, Alfsen GC, Lien HH et al (2003) Postchemotherapy retroperitoneal surgery remains necessary in patients with nonseminomatous testicular cancer and minimal residual tumor masses. J Clin Oncol 21:3310–3317

Oldenburg J, Alfsen GC, Waehre H et al (2006) Late recurrences of germ cell malignancies: a population-based experience over three decades. Br J Cancer 94:820–827

Oliver RT, Edmonds PM, Ong JY et al (1994) Pilot studies of 2 and 1 course carboplatin as adjuvant for stage I seminoma: should it be tested in a randomized trial against radiotherapy? Int J Radiat Oncol Biol Phys 29:3–8

Oliver RT, Ong J, Shamash J et al (2004) Long-term follow-up of Anglian Germ Cell Cancer Group surveillance versus patients with stage 1 nonseminoma treated with adjuvant chemotherapy. Urology 63:556–561

Oliver RT, Mason MD, Mead GM et al (2005) Radiotherapy versus single-dose carboplatin in adjuvant treatment of stage I seminoma: a randomised trial. Lancet 366:293–300

Oliver RT, Mead GM, Fogarty PJ et al (2008) Radiotherapy versus carboplatin for stage I seminoma: updated analysis of the MRC/EORTC randomized trial (ISRCTN27163214). J Clin Oncol 26:5s; abstract 1

Ondrus D, Hornak M, Matoska J et al (1992) Primary chemotherapy in the management of low stage (IIA and IIB) non-seminomatous germ cell testicular tumours. Int Urol Nephrol 24:299–304

Ondrus D, Matoska J, Belan V et al (1998) Prognostic factors in clinical stage I nonseminomatous germ cell testicular tumors: rationale for different risk-adapted treatment. Eur Urol 33:562–566

Osada K, Iijima H, Imasawa M et al (2004) Metastatic uveal tumor secondary to testicular choriocarcinoma. Jpn J Ophthalmol 48:85–87

Patterson H, Norman AR, Mitra SS et al (2001) Combination carboplatin and radiotherapy in the management of

stage II testicular seminoma: comparison with radiotherapy treatment alone. Radiother Oncol 59:5–11
Peckham MJ, Hendry WF (1985) Clinical stage II non-seminomatous germ cell testicular tumours. Results of management by primary chemotherapy. Br J Urol 57:763–768
Pico JL, Rosti G, Kramar A et al (2005) A randomised trial of high-dose chemotherapy in the salvage treatment of patients failing first-line platinum chemotherapy for advanced germ cell tumours. Ann Oncol 16:1152–1159
Pizzocaro G (1987) Retroperitoneal lymph node dissection in clinical stage IIA and IIB nonseminomatous germ cell tumours of the testis. Int J Androl 10:269–275
Pizzocaro G, Monfardini S (1984) No adjuvant chemotherapy in selected patients with pathologic stage II nonseminomatous germ cell tumors of the testis. J Urol 131:677–680
Pont J, Albrecht W, Postner G et al (1996) Adjuvant chemotherapy for high-risk clinical stage I nonseminomatous testicular germ cell cancer: long-term results of a prospective trial. J Clin Oncol 14:441–448
Powles TB, Bhardwa J, Shamash J et al (2005) The changing presentation of germ cell tumours of the testis between 1983 and 2002. BJU Int 95:1197–1200
Puc HS, Heelan R, Mazumdar M et al (1996) Management of residual mass in advanced seminoma: results and recommendations from the Memorial Sloan-Kettering Cancer Center. J Clin Oncol 14:454–460
Purdue MP, Devesa SS, Sigurdson AJ et al (2005) International patterns and trends in testis cancer incidence. Int J Cancer 115:822–827
Rabbani F, Sheinfeld J, Farivar-Mohseni H et al (2001) Low-volume nodal metastases detected at retroperitoneal lymphadenectomy for testicular cancer: pattern and prognostic factors for relapse. J Clin Oncol 19:2020–2025
Raina V, Singh SP, Kamble N et al (1993) Brain metastasis as the site of relapse in germ cell tumor of testis. Cancer 72:2182–2185
Rajpert-de Meyts E, Hoei-Hansen CE (2007) From gonocytes to testicular cancer: the role of impaired gonadal development. Ann N Y Acad Sci 1120:168–180
Ravi R, Ong J, Oliver RT et al (1999) The management of residual masses after chemotherapy in metastatic seminoma. BJU Int 83:649–653
Rayson D, Burch PA, Richardson RL (1998) Sarcoidosis and testicular carcinoma. Cancer 83:337–343
Read G, Stenning SP, Cullen MH et al (1992) Medical Research Council prospective study of surveillance for stage I testicular teratoma. Medical Research Council Testicular Tumors Working Party. J Clin Oncol 10:1762–1768
Reiter WJ, Brodowicz T, Alavi S et al (2001) Twelve-year experience with two courses of adjuvant single-agent carboplatin therapy for clinical stage I seminoma. J Clin Oncol 19:101–104
Richiardi L, Akre O, Montgomery SM et al (2004) Fecundity and twinning rates as measures of fertility before diagnosis of germ-cell testicular cancer. J Natl Cancer Inst 96:145–147
Richiardi L, Scelo G, Boffetta P et al (2007) Second malignancies among survivors of germ-cell testicular cancer: a pooled analysis between 13 cancer registries. Int J Cancer 120:623–631
Richie JP (1990) Clinical stage 1 testicular cancer: the role of modified retroperitoneal lymphadenectomy. J Urol 144:1160–1163
Richie JP, Kantoff PW (1991) Is adjuvant chemotherapy necessary for patients with stage B1 testicular cancer? J Clin Oncol 9:1393–1396
Risk MC, Foster RS (2011) Postchemotherapy retroperitoneal lymph node dissection for testis cancer. Expert Rev Anticancer Ther 11:95–106
Roeleveld TA, Horenblas S, Meinhardt W et al (2001) Surveillance can be the standard of care for stage I nonseminomatous testicular tumors and even high risk patients. J Urol 166:2166–2170
Ronnen EA, Kondagunta GV, Bacik J et al (2005) Incidence of late-relapse germ cell tumor and outcome to salvage chemotherapy. J Clin Oncol 23:6999–7004
Rossen PB, Pedersen AF, Zachariae R et al (2009) Health-related quality of life in long-term survivors of testicular cancer. J Clin Oncol 27:5993–5999
Rustin GJ, Mead GM, Stenning SP et al (2007) Randomized trial of two or five computed tomography scans in the surveillance of patients with stage I non-seminomatous germ cell tumors of the testis: Medical Research Council Trial TE08, ISRCTN56475197—the National Cancer Research Institute Testis Cancer Clinical Studies Group. J Clin Oncol 25:1310–1315
Salvati M, Piccirilli M, Raco A et al (2006) Brain metastasis from non-seminomatous germ cell tumors of the testis: indications for aggressive treatment. Neurosurg Rev 29:130–137
Saxman SB, Nichols CR, Foster RS et al (1996) The management of patients with clinical stage I nonseminomatous testicular tumors and persistently elevated serologic markers. J Urol 155:587–589
Saxman SB, Finch D, Gonin R et al (1998) Long-term follow-up of a phase III study of three versus four cycles of bleomycin, etoposide, and cisplatin in favorable-prognosis germ-cell tumors: the Indian University experience. J Clin Oncol 16:702–706
Schmelz HU, Port M, Stockinger M et al (2010) Testis cancer cells have a genetic determination for a high sensitivity to apoptosis inducing stimuli. Urol Oncol 28:49–58
Schmoll HJ, Jordan K, Huddart R et al (2009a) Testicular non-seminoma: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol 20:iv89–iv96
Schmoll HJ, Jordan K, Huddart R et al (2009b) Testicular seminoma: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol 20(Suppl 4):83–88
Scholz M, Zehender M, Thalmann GN et al (2002) Extragonadal retroperitoneal germ cell tumor: evidence of origin in the testis. Ann Oncol 13:121–124
Schwarzman MI, Russo P, Bosl GJ et al (1989) Hormone-secreting metastatic interstitial cell tumor of the testis. J Urol 141:620–622

Scully RE (1970) Gonadoblastoma: a review of 74 cases. Cancer 25:1340–1356

Sella A, el Naggar A, Ro JY et al (1991) Evidence of malignant features in histologically mature teratoma. J Urol 146:1025–1028

Shahidi M, Norman AR, Dearnaley DP et al (2002) Late recurrence in 1263 men with testicular germ cell tumors: multivariate analysis of risk factors and implications for management. Cancer 95:520–530

Sharir S, Jewett MA, Sturgeon JF et al (1999) Progression detection of stage I nonseminomatous testis cancer on surveillance: implications for the followup protocol. J Urol 161:472–475; discussion 475–476

Sharp DS, Carver BS, Eggener SE et al (2008) Clinical outcome and predictors of survival in late relapse of germ cell tumor. J Clin Oncol 26:5524–5529

Sheinfeld J (1994) Nonseminomatous germ cell tumors of the testis: current concepts and controversies. Urology 44:2–14

Sheinfeld J (2003) Risks of the uncontrolled retroperitoneum. Ann Surg Oncol 10:100–101

Sheinfeld J, Motzer RJ (2008) Stage I testicular cancer management and necessity for surgical expertise. J Clin Oncol 26:2934–2936

Sheinfeld J, Motzer RJ, Rabbani F et al (2003) Incidence and clinical outcome of patients with teratoma in the retroperitoneum following primary retroperitoneal lymph node dissection for clinical stages I and IIA nonseminomatous germ cell tumors. J Urol 170:1159–1162

Skakkebaek NE, Berthelsen JG, Muller J (1982) Carcinoma-in-situ of the undescended testis. Urol Clin North Am 9:377–385

Sobin LH, Wittekind CH (2002) UICC: TNM classification of malignant tumors, 6th edn. Wiley-Liss, New York

Socinski MA, Garnick MB, Stomper PC et al (1988) Stage II nonseminomatous germ cell tumors of the testis: an analysis of treatment options in patients with low volume retroperitoneal disease. J Urol 140:1437–1441

Sogani PC, Perrotti M, Herr HW et al (1998) Clinical stage I testis cancer: long-term outcome of patients on surveillance. J Urol 159:855–858

Sonne SB, Kristensen DM, Novotny GW et al (2008) Testicular dysgenesis syndrome and the origin of carcinoma in situ testis. Int J Androl 31:275–287

Sonne SB, Almstrup K, Dalgaard M et al (2009) Analysis of gene expression profiles of microdissected cell populations indicates that testicular carcinoma in situ is an arrested gonocyte. Cancer Res 69:5241–5250

Sonneveld DJ, Sleijfer DT, Koops HS et al (1998) Mature teratoma identified after postchemotherapy surgery in patients with disseminated nonseminomatous testicular germ cell tumors: a plea for an aggressive surgical approach. Cancer 82:1343–1351

Sonneveld DJ, Sleijfer DT, Schrafford Koops H et al (1999) Familial testicular cancer in a single-centre population. Eur J Cancer 35:1368–1373

Spears WT, Morphis JG 2nd, Lester SG et al (1992) Brain metastases and testicular tumors: long-term survival. Int J Radiat Oncol Biol Phys 22:17–22

Spiess PE, Brown GA, Liu P et al (2006a) Predictors of outcome in patients undergoing postchemotherapy retroperitoneal lymph node dissection for testicular cancer. Cancer 107:1483–1490

Spiess PE, Brown GA, Pisters LL et al (2006b) Viable malignant germ cell tumor in the postchemotherapy retroperitoneal lymph node dissection specimen: can it be predicted using clinical parameters? Cancer 107:1503–1510

Spiess PE, Kassouf W, Brown GA et al (2007) Surgical management of growing teratoma syndrome: the M. D. Anderson cancer center experience. J Urol 177:1330–1334; discussion 1334

Steiner H, Holtl L, Wirtenberger W et al (2002) Long-term experience with carboplatin monotherapy for clinical stage I seminoma: a retrospective single-center study. Urology 60:324–328

Stenning SP, Parkinson MC, Fisher C et al (1998) Postchemotherapy residual masses in germ cell tumor patients: content, clinical features, and prognosis. Medical Research Council Testicular Tumour Working Party. Cancer 83:1409–1419

Stephenson AJ, Russo P, Kaplinsky R et al (2004) Impact of unnecessary exploratory laparotomy on the treatment of patients with metastatic germ cell tumor. J Urol 171:1474–1477

Stephenson AJ, Bosl GJ, Bajorin DF et al (2005a) Retroperitoneal lymph node dissection in patients with low stage testicular cancer with embryonal carcinoma predominance and/or lymphovascular invasion. J Urol 174:557–560

Stephenson AJ, Bosl GJ, Motzer RJ et al (2005b) Retroperitoneal lymph node dissection for nonseminomatous germ cell testicular cancer: impact of patient selection factors on outcome. J Clin Oncol 23: 2781–2788

Stephenson AJ, Bosl GJ, Motzer RJ et al (2007) Nonrandomized comparison of primary chemotherapy and retroperitoneal lymph node dissection for clinical stage IIA and IIB nonseminomatous germ cell testicular cancer. J Clin Oncol 25:5597–5602

Stephenson AJ, Aprikian AG, Gilligan TD et al (2011) Clinical practice guidelines on the management of low-stage nonseminomatous germ cell tumors of the testis. Urology 78:S444–S455

Steyerberg EW, Keizer HJ, Fossa SD et al (1995) Prediction of residual retroperitoneal mass histology after chemotherapy for metastatic nonseminomatous germ cell tumor: multivariate analysis of individual patient data from six study groups. J Clin Oncol 13:1177–1187

Steyerberg EW, Keizer HJ, Messemer JE et al (1997) Residual pulmonary masses after chemotherapy for metastatic nonseminomatous germ cell tumor: prediction of histology. ReHiT Study Group. Cancer 79:345–355

Steyerberg EW, Gerl A, Fossa SD et al (1998) Validity of predictions of residual retroperitoneal mass histology in nonseminomatous testicular cancer. J Clin Oncol 16:269–274

Stomper PC, Kalish LA, Garnick MB et al (1991) CT and pathologic predictive features of residual mass histologic findings after chemotherapy for nonseminomatous germ cell tumors: can residual malignancy or teratoma be excluded? Radiology 180:711–714

Subramanian VS, Nguyen CT, Stephenson AJ et al (2010) Complications of open primary and post-chemotherapy retroperitoneal lymph node dissection for testicular cancer. Urol Oncol 28:504–509

Suzumura S, Ioka A, Nakayama T et al (2008) Hospital procedure volume and prognosis with respect to testicular cancer patients: a population-based study in Osaka, Japan. Cancer Sci 99:2260–2263

Sweeney CJ, Hermans BP, Heilman DK et al (2000) Results and outcome of retroperitoneal lymph node dissection for clinical stage I embryonal carcinoma—predominant testis cancer. J Clin Oncol 18:358–362

Tandstad T, Dahl O, Cohn-Cedermark G et al (2009) Risk-adapted treatment in clinical stage I nonseminomatous germ cell testicular cancer: the SWENOTECA management program. J Clin Oncol 27:2122–2128

Tarin TV, Sonn G, Shinghal R (2009) Estimating the risk of cancer associated with imaging related radiation during surveillance for stage I testicular cancer using computerized tomography. J Urol 181:627–632; discussion 632–633

Theodore C, Terrier-Lacombe MJ, Laplanche A et al (2004) Bilateral germ-cell tumours: 22-year experience at the Institut Gustave Roussy. Br J Cancer 90:55–59

Tiffany P, Morse MJ, Bosl G et al (1986) Sequential excision of residual thoracic and retroperitoneal masses after chemotherapy for stage III germ cell tumors. Cancer 57:978–983

Tinkle LL, Graham BS, Spillane TJ et al (2001) Testicular choriocarcinoma metastatic to the skin: an additional case and literature review. Cutis 67:117–120

Tjan-Heijnen VC, Vlasveld LT, Pernet FP et al (1998) Coincidence of seminoma and sarcoidosis: a myth or fact? Ann Oncol 9:321–325

Tognoni PG, Foster RS, McGraw P et al (1998) Combined post-chemotherapy retroperitoneal lymph node dissection and resection of chest tumor under the same anesthetic is appropriate based on morbidity and tumor pathology. J Urol 159:1833–1835

Toner GC, Panicek DM, Heelan RT et al (1990) Adjunctive surgery after chemotherapy for nonseminomatous germ cell tumors: recommendations for patient selection. J Clin Oncol 8:1683–1694

Toner GC, Stockler MR, Boyer MJ et al (2001) Comparison of two standard chemotherapy regimens for good-prognosis germ-cell tumours: a randomised trial. Australian and New Zealand Germ Cell Trial Group. Lancet 357:739–745

Travis LB, Fossa SD, Schonfeld SJ et al (2005) Second cancers among 40,576 testicular cancer patients: focus on long-term survivors. J Natl Cancer Inst 97:1354–1365

Ulbright TM (2004) Testicular and paratesticular tumors. In: Mills SE, Greenson JK, Oberman HA et al (eds) Sternberg's diagnostic surgical pathology, 4th edn. Lippincott Williams & Wilkins, Philadelphia, pp 2168–2190

Ulbright TM (2005) Germ cell tumors of the gonads: a selective review emphasizing problems in differential diagnosis, newly appreciated, and controversial issues. Mod Pathol 18(Suppl 2):S61–S79

Ulbright TM, Young RH (2008) Metastatic carcinoma to the testis: a clinicopathologic analysis of 26 nonincidental cases with emphasis on deceptive features. Am J Surg Pathol 32:1683–1693

van den Belt-Dusebout AW, de Wit R, Gietema JA et al (2007) Treatment-specific risks of second malignancies and cardiovascular disease in 5-year survivors of testicular cancer. J Clin Oncol 25:4370–4378

van Dijk MR, Steyerberg EW, Habbema JD (2006) Survival of non-seminomatous germ cell cancer patients according to the IGCC classification: an update based on meta-analysis. Eur J Cancer 42: 820–826

Vergouwe Y, Steyerberg EW, Foster RS et al (2001) Validation of a prediction model and its predictors for the histology of residual masses in nonseminomatous testicular cancer. J Urol 165:84–88; discussion 88

Vergouwe Y, Steyerberg EW, Eijkemans MJ et al (2003) Predictors of occult metastasis in clinical stage I nonseminoma: a systematic review. J Clin Oncol 21:4092–4099

Verhoeven R, Houterman S, Kiemeney B et al (2008) Testicular cancer: marked birth cohort effects on incidence and a decline in mortality in southern Netherlands since 1970. Int J Cancer 122:639–642

Vogelzang NJ, Fraley EE, Lange PH et al (1983) Stage II nonseminomatous testicular cancer: a 10-year experience. J Clin Oncol 1:171–178

von der Maase H, Specht L, Jacobsen GK et al (1993) Surveillance following orchidectomy for stage I seminoma of the testis. Eur J Cancer 29A:1931–1934

von Eyben FE, Jacobsen GK, Rorth M et al (2004) Microinvasive germ cell tumour (MGCT) adjacent to testicular germ cell tumours. Histopathology 44: 547–554

Vuky J, Tickoo SK, Sheinfeld J et al (2002) Salvage chemotherapy for patients with advanced pure seminoma. J Clin Oncol 20:297–301

Warde P, Gospodarowicz MK, Panzarella T et al (1995) Stage I testicular seminoma: results of adjuvant irradiation and surveillance. J Clin Oncol 13:2255–2262

Warde P, Specht L, Horwich A et al (2002) Prognostic factors for relapse in stage I seminoma managed by surveillance: a pooled analysis. J Clin Oncol 20:4448–4452

Warde P, Gospodarowicz M, Panzarella T et al (2005) Outcome in stage I seminoma managed by radiation therapy and surveillance. J Urol 196(Suppl 4):[abstract 719]

Weissbach L, Bussar-Maatz R, Flechtner H et al (2000) RPLND or primary chemotherapy in clinical stage IIA/B nonseminomatous germ cell tumors? Results of a prospective multicenter trial including quality of life assessment. Eur Urol 37:582–594

Westergaard T, Olsen JH, Frisch M et al (1996) Cancer risk in fathers and brothers of testicular cancer patients

in Denmark: a population-based study. Int J Cancer 66:627–631

Williams SD, Birch R, Einhorn LH et al (1987a) Treatment of disseminated germ-cell tumors with cisplatin, bleomycin, and either vinblastine or etoposide. N Engl J Med 316:1435–1440

Williams SD, Stablein DM, Einhorn LH et al (1987b) Immediate adjuvant chemotherapy versus observation with treatment at relapse in pathological stage II testicular cancer. N Engl J Med 317:1433–1438

Williams DH, Karpman E, Sander JC et al (2009a) Pretreatment semen parameters in men with cancer. J Urol 181:736–740

Williams SB, McDermott DW, Dock W et al (2009b) Retroperitoneal lymph node dissection in patients with high risk testicular cancer. J Urol 181:2097–2101; discussion 2101–2102

Wood HM, Elder JS (2009) Cryptorchidism and testicular cancer: separating fact from fiction. J Urol 181:452–461

Wood DP Jr, Herr HW, Motzer RJ et al (1992) Surgical resection of solitary metastases after chemotherapy in patients with nonseminomatous germ cell tumors and elevated serum tumor markers. Cancer 70:2354–2357

Younger C, Ulbright TM, Zhang S et al (2003) Molecular evidence supporting the neoplastic nature of some epidermoid cysts of the testis. Arch Pathol Lab Med 127:858–860

Zagars GK, Pollack A (2001) Radiotherapy for stage II testicular seminoma. Int J Radiat Oncol Biol Phys 51:643–649

Zagars GK, Ballo MT, Lee AK et al (2004) Mortality after cure of testicular seminoma. J Clin Oncol 22: 640–647

Zuniga A, Kakiashvili D, Jewett MA (2009) Surveillance in stage I nonseminomatous germ cell tumours of the testis. BJU Int 104:1351–1356

Penile Cancer

16

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16.1 Penile Anatomy

The penis is the external male sexual organ and also contains the urethra that represents the most distal part of the urinary system.

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V. Mirone (ed.), *Clinical Uro-Andrology*,
DOI 10.1007/978-3-662-45018-5_16, © Springer-Verlag Berlin Heidelberg 2015

It is made of a combination of several types of tissue, including skin, nerves, smooth muscle and blood vessels.

The main part of the penis is known as the *shaft*, and the head of the penis is called the *glans*. At birth, the glans is covered by a piece of skin called the *foreskin*, or prepuce.

The internal part of the penis is made of three chambers that contain a soft, spongy network of blood vessels. Two of these cylinder-shaped chambers, known as the *corpora cavernosa*, lie on either side of the upper part of the penis. The third component known as the *corpus spongiosum* lies below them and widens at its end to form the glans. The corpus spongiosum surrounds the *urethra*, a thin tube that starts at the bladder and runs through the penis ending in the *meatus* that represents an opening in the glans of the penis.

The penis is anchored to the pubis through a thick ligament named *suspensory ligament*.

16.2 Penile Functioning

As anticipated, the penis is part of both the male genital and urinary system. The latter is simply represented by the penile tract of the urethra that contributes to emission of urine coming from the bladder.

The role of the penis in the male genital system is more complicated and is linked to both sexual and reproductive functions. With regard to reproduction, its function is limited to the emission of the semen that is made up of fluid produced by the prostate gland and the seminal vesicles, plus sperm cells that come from the testicles. The produced semen is stored in the seminal vesicles, and during ejaculation it passes into the penile urethra and out the meatus at the tip of the penis.

With regard to sexual function, the penis is involved in erection mechanism. When a man is sexually stimulated, tactile, auditive and visual stimuli translate into a peripheral nerve signal that activates erectile mechanism. In particular an intense vasodilator effect at the level of the corpora cavernosa increases the blood income in this compartment. As the blood fills the chambers, the spongy tissue expands, causing the penis to increase its volume and stiffen. After ejaculation, the blood rapidly flows back into the body through the venous system and the penis returns to being flaccid.

16.3 Benign Lesions of the Penis

Various lesions can develop as benign and usually look like warts or irritated patches of skin. Like penile cancer, they are most often found on the glans or on the foreskin, but they can also occur along the shaft of the penis.

16.3.1 Condylomas

These are wartlike growths that look like tiny cauliflowers. Some are so small that they can only be seen when the skin is looked at under a magnifying lens. Others may be as large as an inch or more across. Condylomas are caused by infection with the human papillomavirus (HPV).

16.3.2 Bowenoid Papulosis

In this condition, dysplastic (abnormal) cells are seen only in the surface layer of the penile skin. This condition tends to occur in younger men and is seen as small, reddish, pimple-like patches on the shaft of the penis. Bowenoid papulosis can be confused with early-stage cancer called *carcinoma in situ* (CIS), but it is agreed that these lesions do not represent a cancer or a precancerous condition.

16.4 Epidemiology

In Western countries, primary malignant penile cancer is uncommon, with an incidence of less than 1.00 per 100,000 males in Europe and the USA (Barnholtz-Sloan et al. 2007; ENCR 1999).

However, there are significant geographical variations within Europe (Spain, Malta, Switzerland, France, Italy showed the highest

rates) reporting an incidence greater than 1.00 per 100,000 men (Parkin et al. 2002).

Incidence is also affected by race and ethnicity in North America (1), with the highest incidence of penile cancer found in white Hispanics (1.01 per 100,000), followed by Alaskan, Native/American Indians (0.77 per 100,000), Blacks (0.62 per 100,000) and white non-Hispanics (0.51 per 100,000).

In contrast, in the non-Western world, the incidence of penile cancer is much higher and can represent 10–20 % of malignant diseases in men ranging from an age-adjusted incidence of 0.7–3 per 100,000 men in India to 8.3 per 100,000 men in Brazil and even higher in Uganda, where it is the most commonly diagnosed cancer.

Important risk factors include social and cultural habits and hygienic and religious practices (Misra et al. 2004). Penile carcinoma is rare in communities that practise circumcision in newborns or before puberty (Jews, Muslims and the Ibos of Nigeria). Early circumcision reduces the risk of penile cancer by 3–5 times. Adult circumcision does not protect against penile cancer.

In the USA, the overall age-adjusted incidence rate decreased considerably between 1973 and 2002 from 0.84 per 100,000 in 1973–1982 to 0.69 per 100,000 in 1983–1992 and further to 0.58 per 100,000 in 1993–2002 (1).

16.5 Risk Factors

16.5.1 Circumcision

The circumcision represents a protective condition against the development of penile cancer and consists in removing all (or a part of) the foreskin. This procedure is most often done in infants, but it can be done later in life, generally because of the presence of a phimosis and accumulation of a thick and sometimes smelly secretion known as *smegma*.

Circumcision seems to protect against development of a penile cancer when it is performed during childhood. In fact, men who were circumcised as children have a lower chance of getting penile cancer than those who were not, but other studies have showed that the same protective effect is not achieved if the foreskin is removed during adulthood.

Furthermore, circumcision protects against infection with the human papillomavirus (HPV), and this protective effect is higher the earlier the procedure is performed (Dillner et al. 2000).

16.5.2 Phimosis

Phimosis represents a frequent alteration of the foreskin that results in tightness and difficult retraction, causing smegma accumulation. This secretion consists of a mixture of oily secretions from the skin, along with dead skin cells and bacteria.

Men affected with phimosis may be at higher risk for penile cancer even if the reason is not totally clear. Probably, the presence of smegma can cause local inflammatory processes that if frequent, can increase the risk of developing cancer (Daling et al. 2005).

16.5.3 Human Papillomavirus (HPV) Infection

HPV is a large group of related viruses that cause superficial lesions (warts) growing on the skin or mucosal tissues. Most typical localisations are in the hands, feet and oral mucosa. Furthermore, certain HPV types can infect the outer female and male genital organs and the anal area, causing raised, bumpy warts. The medical term for genital warts is *condyloma acuminatum*. Two types of HPV, HPV 6 and HPV 11, cause most cases of genital warts. These two *low-risk* types of HPV are seldom linked to cancer arising from the genital area. However, other HPV types (16, 18, 31 and others) have been linked with cancers and so are known as *high-risk* types. HPV infection is frequently detected in penile and anal cancers in males and cervical, vaginal, vulvar and anal cancers in females.

Often infection with a high-risk HPV may produce no visible signs until pre-cancerous changes or cancer develops.

HPV is transmitted from one person to another during skin-to-skin contact with an infected area of the body. Furthermore, HPV infection is able to be spread from one part of the body to another (i.e. infection may start in the penis and then spread to the anus).

Because HPV infection is extremely frequent, widespread prevention by vaccine has been adopted in many developed countries (Nordenvall et al. 2006; Muñoz et al. 2006).

16.5.4 Age

The risk of penile cancer increases with age, with the highest rate reached over age 55.

16.5.5 Smoking

Men who smoke are more likely to develop penile cancer than those who do not smoke, in particular if they have a concomitant HPV infection.

16.5.6 UV Light Treatment of Psoriasis

Men affected with psoriasis are routinely treated with drugs called psoralens, followed by exposure of the body to an ultraviolet A (UVA) light source. Men who have received this treatment have been found to have a higher rate of penile cancer. Because of this risk, men being treated with PUVA now have their genitals covered during treatment.

16.5.7 AIDS

Men affected with AIDS (*a*cquired *i*mmuno*d*eficiency *s*yndrome) present a higher risk of penile cancer, maybe because of an altered immune response, although specific lifestyle factors may also play a role. Some authors have described that men with penile cancer who were HIV positive were more likely to smoke and to be infected with HPV than men with penile cancer but HIV negative.

16.6 Prevention

The large variations in penile cancer rates throughout the different world areas strongly suggest that penile cancer is a preventable disease. The best way to reduce the risk of penile cancer is to avoid known risk factors whenever possible.

In the past, circumcision has been suggested as the most important way to prevent penile cancer. This was based on studies that reported much lower penile cancer rates among circumcised men than among uncircumcised men. But in many of those studies, the protective effect of circumcision was no longer seen after factors like smegma accumulation and phimosis were taken into account.

Most experts believe that the risk of penile cancer is low also among uncircumcised men without known risk factors, in particular HPV infection, good genital hygiene and smoking. For this reason most experts agree that circumcision should not be recommended solely as a way to prevent penile cancer.

16.6.1 Genital Hygiene

Perhaps the most important factor in preventing penile cancer in uncircumcised men is good genital hygiene. Uncircumcised men need to retract the foreskin and clean the entire penis. If the foreskin is constricted and difficult to retract, special products (creams or ointment) can be applied to the foreskin to make it easier to retract.

16.6.2 Avoiding HPV Infection

The two main factors influencing the risk of genital HPV infection in men are circumcision and the number of sexual partners.

All men should be advised to avoid infection with the HPV, either for decreasing penile cancer risk or reducing the risk of cervical cancer in female partners.

Using condoms helps in protecting against HPV infection, although a total protection is not

achieved because condoms do not cover every possible HPV-infected area of the body, such as the skin on the genital or anal area.

However, men who regularly use condoms are less likely to be infected with HPV and pass it on to their female partners.

Vaccines have been developed to help prevent infection with some types of HPV. Gardasil® protects against HPV types 6 and 11, which can cause genital warts, and types 16 and 18, which cause some types of cancer. Another vaccine, Cervarix®, protects against HPV types 16 and 18. Both Gardasil and Cervarix are approved for use in females, but only Gardasil is approved for use in males (Markowitz et al. 2007; Giuliano 2007).

16.6.3 Not Smoking

Since smoking also increases penile cancer risk, not smoking may lower that risk.

16.7 Early Diagnosis

Although no screening test can be recommended for penile cancer, it normally presents as a skin lesion that can be noted and more deeply evaluated when it appears.

In the case that a phimosis is present, the foreskin can cover the lesion and make an early diagnosis more difficult.

Males should be advised to take special care of any new growing penile lesion (warts, blisters, sores, ulcers, white patches or other abnormal areas) and consult a doctor.

Unfortunately most of the patients are still diagnosed with delay, presenting large and advanced lesions that were ignored for a long time, and for this reason they need a more aggressive and demolitive treatment.

16.8 Clinical Presentation

Clinical onset of penile cancer is usually represented by the growth of an evident lesion of the penile surface, besides different histological types that can develop. Almost all penile cancers start in skin cells of the penis (American Cancer Society 2012).

16.8.1 Squamous Cell Carcinoma

About 95 % of penile cancers develop from flat skin cells called *squamous cells*. Squamous cell cancers can develop anywhere on the penis. Most of these cancers start from the foreskin or from the glans and their growth is generally slow. It is extremely important to diagnose it at an early stage in order to potentially cure it.

16.8.2 Verrucous Carcinoma

This is a rare variant of squamous cell cancer also called *Buschke-Lowenstein tumour*. A verrucous carcinoma looks a lot like a large benign genital and can start on every part of the penile skin. These cancers tend to grow slowly but can sometimes present as very large lesions invading deeply into surrounding tissue, but they rarely spread to other parts of the body.

16.8.3 Carcinoma In Situ (CIS)

CIS represents a precursor stage of squamous cell cancer of the penis, and it starts as a superficial, non-invasive lesion of the top layers of the skin.

Based on the different locations of the CIS lesion on the penile area, it can be also defined as *erythroplasia of Queyrat* (lesion of the glans) or *Bowen's disease* (lesion of the shaft).

16.8.4 Melanoma

Melanoma develops from the brownish-coloured cells of the skin named melanocytes and, as normally happens in other sites of the body, this represents a rapidly growing and spreading lesion that often induces metastasis. Luckily only less than 2 % of penile cancers are represented by melanoma.

Table 16.1 Classification of premalignant lesions

Lesions sporadically associated with SCC of the penis
Cutaneous horn of the penis
Bowenoid papulosis of the penis
Balanitis xerotica obliterans (lichen sclerosus et atrophicus)
Lesions at high risk of developing SCC of the penis (up to one-third transform to invasive SCC)
Penile intraepithelial neoplasia (carcinoma in situ): erythroplasia of Queyrat and Bowen's disease

Table 16.2 Squamous cell carcinoma

Types of SCC
Classic
Basaloid
Verrucous and its varieties
Warty (condylomatous) carcinoma
Verrucous carcinoma
Papillary carcinoma
Hybrid verrucous carcinoma
Mixed carcinomas (warty basaloid and adenobasaloid carcinoma)
Sarcomatoid
Adenosquamous
Growth patterns of SCC
Superficial spread
Nodular or vertical-phase growth
Verrucous

16.8.5 Basal Cell Cancer

Basal cell cancer is another rare histological variant of skin cancer of the penis. It grows very slowly and rarely spreads to other parts of the body.

16.8.6 Adenocarcinoma (Paget Disease of the Penis)

This very rare histological type of penile cancer starts from -sweat glands in the skin of the penis and its appearance is very similar to CIS of the penis. Initially it presents as a superficial lesion, then it can spread within the skin and later on can invade the deep tissues and spread to the lymph nodes.

16.8.7 Sarcoma

Sarcoma represents an extremely rare histological variety of penile cancer. It can start from the blood vessels, smooth muscle or other connective tissue cells of the organ, and it tends to express an aggressive clinical behaviour with a rapid local and distant spreading (Tables 16.1 and 16.2).

16.9 Signs and Symptoms

In most cases, the very first sign of penile cancer is a superficial asymptomatic modification of the skin of the penis represented by a colour change or a tissue thickening that can start everywhere on the penis, although the most frequent localisations are represented by the penile glans and foreskin.

Sometimes the lesion can present as an ulcer (sore) or a lump on the penis or can appear as a reddish, velvety rash, small crusty bumps or flat growths that are bluish brown. In some cases a secretion, sometimes with a bad smell, can be found; this can represent the first sign in the case of a patient with phimosis where the foreskin is not retractable.

In case the tumour spreads to the lymph nodes, patients can feel tumescence at the level of the inguinal area (American Joint Committee on Cancer 2010).

16.10 Diagnosis

The most important diagnostic step is represented by medical history and physical examination that can suggest the presence of a penile cancer, although specific procedures (biopsy and imaging tests) are needed to confirm the diagnosis (Pizzocaro et al. 2010).

Physical examination of a patient with penile cancer includes careful evaluation of the primary lesion. The following aspects should always be carefully evaluated:

- Diameter of the penile lesion or suspicious areas
- Location of lesion on the penis
- Number of lesions

- Morphology of lesion: papillary, nodular, ulcerous or flat
- Relationship of lesion to other structures, e.g. sub-mucosa, tunica albuginea and urethra
- Corpus spongiosum and corpus cavernosum
- Colour and boundaries of lesion
- Penis length

16.10.1 Biopsy Procedures

A biopsy is needed to make an accurate diagnosis of cancer, when a suspicious lesion of the penis is present. An incisional biopsy foresees the removal of a small piece of tissue, usually from a large lesion. An excisional biopsy is performed when the entire lesion (usually small) is removed. In the case of patients presenting palpable enlarged lymph nodes, a fine-needle aspiration (FNA) can be performed (Saisorn et al. 2006; Kroon et al. 2005).

There is no need for biopsy if there is no doubt about the diagnosis and/or treatment of the lymph nodes is postponed after treatment of the primary tumour and/or after histological examination of the sentinel node(s).

16.10.2 Imaging Tests

Imaging tests can be used to perform a local staging of the penile lesion or a distant staging of the original tumour. The most used tests for local staging are ultra-sonography (US) or magnetic resonance imaging (MRI) with prostaglandin E1 intra-cavernous injection (Solsona et al. 2001; Kayes et al. 2007).

Imaging techniques (e.g. CT and MRI) are widely used, but they are only useful for staging patients with centrimetrical or lymph node metastases >1 cm. So far, no current imaging modality can identify microscopic invasion.

An assessment of distant metastases should be performed in patients with positive inguinal nodes. Positron emission tomography/CT is reliable for identification of pelvic and distant metastases in patients with positive inguinal nodes (Graafland et al. 2009).

16.11 Tumour Staging

The new 2009 TNM classification for penile cancer includes a change for the T1 category (Table 16.3). This classification needs a further update for the definition of the T2 category. Two recent publications have shown that the prognosis for corpus spongiosum invasion is much better than for corpora cavernosa invasion (Sobin et al. 2009; Rees et al. 2008; Leijte et al. 2008a) (Table 16.4).

16.12 Survival Rates for Penile Cancer

Because penile cancer is not common, it is hard to find accurate survival rates based on the TNM stage of the cancer. The numbers below come from the National Cancer Institute's SEER database, looking at more than 1,000 men diagnosed with penile cancer between 1988 and 2001.

For cancers that are still confined to the penis (like stage I and II), the 5-year relative survival rate is around 85 %.

If the cancer has spread to nearby tissues or lymph nodes (like stage III and some stage IV), the 5-year relative survival rate is around 59 %.

If the cancer has spread to distant parts of the body, the 5-year relative survival rate is about 11 % (Howlader et al. 2011).

16.13 Treatment

After the cancer is diagnosed and staged, a cancer care team should discuss different treatment options with the patient also taking into account several factors:

- The type and stage of the cancer
- Overall patient's physical health
- Patient's preferences about treatments and their side effects

The main treatment options that can be used to treat penile cancers are:

- Surgery
- Radiation therapy
- Chemotherapy

Table 16.3 TNM staging

Clinical classification	
T – Primary tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma in situ
Ta	Non-invasive verrucous carcinoma, not associated with destructive invasion
T1	Tumour invades subepithelial connective tissue
T1a	Tumour invades subepithelial connective tissue without lymphovascular invasion and is not poorly differentiated or undifferentiated (T1G3–T1G4)
T1b	Tumour invades subepithelial connective tissue with lymphovascular invasion or is poorly differentiated or undifferentiated (T1G3–T1G4)
T2	Tumour invades corpus spongiosum/corpora cavernosa
T3	Tumour invades urethra
T4	Tumour invades other adjacent structures
N – Regional lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No palpable or visibly enlarged inguinal lymph node
N1	Palpable mobile unilateral inguinal lymph node
N2	Palpable mobile multiple or bilateral inguinal lymph nodes
N3	Fixed inguinal nodal mass or pelvic lymphadenopathy, unilateral or bilateral
M – Distant metastasis	
M0	No distant metastasis
M1	Distant metastasis
Pathological classification	
The pT categories correspond to the T categories. The pN categories are based upon biopsy or surgical excision	
pN – Regional lymph nodes	
pNX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Intranodal metastasis in a single inguinal lymph node
pN2	Metastasis in multiple or bilateral inguinal lymph nodes
pN3	Metastasis in pelvic lymph node(s), unilateral or bilateral or extranodal extension of regional lymph node metastasis
pM – Distant metastasis	
pM0	No distant metastasis
pM1	Distant metastasis
G – Histopathological grading	
GX	Grade of differentiation cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3–G4	Poorly differentiated/undifferentiated

Surgery is the main method of treatment for nearly all penile cancers, but sometimes radiation therapy may be used, either instead of or in addition to surgery. Chemotherapy is usually indicated in the case of meta-static disease.

16.13.1 Surgery for Penile Cancer

Surgery is the most common treatment for all stages of penile cancer. If the cancer is detected early, the tumour can often be treated without

Table 16.4 Staging categories

Stage	TNM	Definition
0	Tis Ta, N0, M0	The cancer has not grown into tissue below the top layers of skin and has not spread to lymph nodes or distant sites
I	T1a, N0, M0	The cancer has grown into tissue just below the superficial layer of skin but has not grown into blood or lymph vessels. It is a grade 1 or 2. It has not spread to lymph nodes or distant sites
II	T1b, N0, M0	The cancer has grown into tissue just below the superficial layer of skin and is either high grade or has grown into blood or lymph vessels. It has not spread to lymph nodes or distant sites
	T2, N0, M0	The cancer has grown into one of the internal chambers of the penis (the corpus spongiosum or corpora cavernosa). The cancer has not spread to lymph nodes or distant sites
	T3, N0, M0	The cancer has grown into the urethra. It has not spread to lymph nodes or distant sites
IIIa	T1 to T3, N1, M0	The cancer has grown into tissue below the superficial layer of skin (T1). It may also have grown into the corpus spongiosum, the corpus cavernosum or the urethra (T2 or T3). The cancer has spread to a single groin lymph node (N1). It has not spread to distant sites
IIIb	T1 to T3, N2, M0	The cancer has grown into the tissues of the penis and may have grown into the corpus spongiosum, the corpus cavernosum or the urethra (T1 to T3). It has spread to 2 or more groin lymph nodes. It has not spread to distant sites
IV	T4, any N, M0	The cancer has grown into the prostate or other nearby structures. It may or may not have spread to groin lymph nodes. It has not spread to distant sites
	Any T, N3, M0	The cancer has spread to lymph nodes in the pelvis OR the cancer spread in the groin lymph nodes has grown through the lymph nodes' outer covering and into the surrounding tissue. The cancer has not spread to distant sites
	Any T, any N, M1	The cancer has spread to distant sites

having to remove part of the penis (conservative surgery) (Minhas et al. 2005).

If the cancer is detected at a more advanced stage, part or all of the penis might have to be removed with the tumour.

Patients with cancers that have invaded deep within the penis (stage T2 or higher) usually need to have some nearby lymph nodes removed as well to check for cancer spread.

Instead of removing all of the groin lymph nodes to look for cancer, in some cases it is possible to perform a sentinel lymph node biopsy.

Based on the extension of the penile lesion, various operations can be performed.

16.13.1.1 Circumcision

This operation consists in the removal of the foreskin and some nearby skin and can represent a valid option only for patients with small lesion of the foreskin that are early diagnosed.

In rare cases, circumcision is also performed to remove the foreskin before radiation therapy to the penis, in order to avoid subsequent local side effects.

16.13.1.2 Simple Excision

This operation is indicated for larger but still confined tumours and foresees the removal of the lesion itself along with some surrounding normal tissues.

Based on the extension of the lesion, the residual skin can then be simply stitched back together or can require a skin graft to cover the defect.

16.13.2 Mohs Surgery (Microscopically Controlled Surgery)

In the case of pre-cancerous lesions or early-diagnosed cancers (stage I), this highly sophisticated technique can be applied to spare as more

healthy tissues as possible but still performing an oncologically safe procedure.

By using the Mohs technique, the surgeon removes a layer of the skin that the tumour may have invaded and then checks the sample under a microscope right away. If it contains cancer, another layer is removed and examined. This process is repeated until the skin samples are found to be free of cancer cells (Shindel et al. 2007).

16.13.3 Laser Surgery

This approach uses a beam of laser light to vaporise cancer cells. It is useful for squamous cell carcinoma in situ (involving only the outer layer of the skin) and for very thin or shallow basal cell cancers (Windalh and Andersson 2003; Bandieramonte et al. 2008).

16.13.4 Cryosurgery

This approach freezes the cancer cells with a probe cooled with liquid nitrogen. It is indicated in the case of superficial verrucous penile cancers and carcinoma in situ of the glans.

16.13.5 Partial or Total Penectomy

This approach is always indicated when a lesion has grown deeply inside the penis. The goal of the operation is to remove entirely the lesion, but generally a portion of surrounding healthy tissue has to be removed to reduce the risk of local recurrence (Minhas et al. 2005).

Conservative treatment may be less suitable in cases of multifocal lesions, which are responsible for 15 % of recurrences. Total treatment of the glans surface combined with concomitant circumcision is recommended to avoid multiple recurrences (Bandieramonte et al. 2008).

When the lesion interests only the distal part of the penis, a partial penectomy is indicated, in order to preserve a segment of the penile shaft adequate for sexual activity and standing micturition. Total removal of the glans (glansectomy) and prepuce does have the lowest recurrence rate among the treatment modalities for small penile lesions (2 %).

If the lesion is more extended (category T2 with invasion into the corpus cavernosum), a partial amputation with a tumour-free margin (5–10 mm) is considered standard treatment.

For patients with T3 tumours, a total penectomy with perineal urethrostomy is the standard surgical treatment (Ornellas et al. 2008). In more advanced disease (T4), neoadjuvant chemotherapy is advised, followed by radical surgery in responding patients.

16.13.6 Lymphadenectomy

In the case of larger or more invasive lesions (stage T2 or higher), an extensive lymphadenectomy is mandatory, with a staging and curative intent (the inguinal region is the first drainage node station of the penis). In about 50 % of the cases, men with penile cancer present swollen groin lymph nodes when they are first diagnosed, and the swelling derives from infection or inflammation. In similar cases, a course of antibiotic therapy was routinely prescribed in the past, waiting for the swelling to disappear. According to recent recommendations formulated and discussed by the full panel of the International Consultation on Penile Cancer in November 2008, antibiotic treatment for 3–6 weeks before ILND in patients with palpable inguinal nodes is not recommended (Heyns et al. 2010).

16.13.7 Sentinel Lymph Node Biopsy

The concept of the sentinel lymph node (SLN) was first described in 1977 for penile carcinoma where lymphangiograms were performed via the dorsal lymphatics of the penis to locate the primary lymphatic drainage zone of the penis situated near the sapheno-femoral junction. Then, in 1992, the lymphatic mapping concept was further advanced by performing intra-dermal injections of blue dye to directly visualise the lymphatic channels and SLN in the treatment of melanoma.

In 1994, investigators from the Netherlands pioneered the use of dynamic sentinel lymph node biopsies (DSLNB) for penile cancer by combining the use of peri-lesional blue dye injection, lympho-scintigraphy and other future modifications of the technique to achieve low false-negative biopsy rates (4.8 %) as well as much lower morbidity (5.7 %), compared with the 30–50 % morbidity associated with a full inguinal node dissection.

DSLNB significantly decreases the morbidity associated with performing a standard or even modified inguinal lymph node dissection in patients with clinically negative inguinal lymph nodes. Performing DSLNB requires a multidisciplinary team of urologists, nuclear medicine radiologists and pathologists working in cohesion to attain the best SLN detection rates with the lowest possible false-negative rates (Yeung and Brandes 2013).

16.13.8 Side Effects of Lymph Node Surgery

The main side effect of inguinal lymph node removal is the onset of a severe *lymphedema* of the legs, because of the interruption of lymphatic fluid drain.

The severity of the lymphedema is proportional to the extension of the node dissection.

Other rarer side effects are wound healing, infection and skin breakdown (necrosis).

16.13.9 Lymph Node Management in Penile Cancer (Heyns et al. 2010)

Fine-needle aspiration cytology should be performed in all patients (with ultrasound guidance in those with non-palpable nodes). If the findings are positive, therapeutic, rather than diagnostic, inguinal lymph node dissection (ILND) can be performed.

Abdomino-pelvic computed tomography (CT) and magnetic resonance imaging (MRI) are not useful in patients with non-palpable nodes. However, these imaging tools can be used in those patients with large, palpable inguinal nodes.

The statistical probability of inguinal micro-metastases can be estimated using risk group stratification. In an attempt to establish better discrimination, a nomogram has been developed that includes the tumour thickness, microscopic growth pattern, histological grade, presence of vascular or lymphatic embolisation and infiltration of the corpora cavernosa, corpus spongiosum or urethra (Ficarra et al. 2006; Ficarra et al. 2009).

After treatment of the primary tumour, a surveillance strategy with regular follow-up examination of the inguinal areas has the advantage that the potential complications of ILND could be avoided. However, it should be kept in mind that a missed diagnosis of lymph node invasion could delay the opportunity of cure.

Surveillance is recommended if the nomogram probability of positive nodes is <0.1 (10 %). Surveillance is also recommended if the primary lesion is grade 1, pTis, pTa (verrucous carcinoma) or pT1, with no lympho-vascular invasion and clinically non-palpable inguinal nodes, but only provided the patient is willing to comply with regular follow-up.

In the presence of factors that impede reliable surveillance (obesity, previous inguinal surgery or radiotherapy), prophylactic ILND might be a preferable option. In the intermediate-risk group (nomogram probability 1–5 [10–50 %] or primary tumour grade 1–2, T1–T2, cN0, no lympho-vascular invasion), surveillance is acceptable, provided the patient is informed of the risks and is willing and able to comply. If not, sentinel node biopsy (SNB) or limited (modified) ILND should be performed. In the high-risk group (nomogram probability >5 [50 %] or primary tumour grade 2–3 or T2–T4 or cN1–cN2 or with lympho-vascular invasion), bilateral ILND should be performed. ILND can be performed at the same time as penectomy, instead of 2–6 weeks later.

16.13.10 Radiotherapy

Radiotherapy of the primary tumour is an alternative organ-preserving approach with good results in selected patients with T1–T2 lesions <4 cm in diameter. Best results have been obtained with

brachytherapy with local control rates ranging from 70 to 90 % (de Crevoisier et al. 2009; Crook et al. 2007). Patients with lesions >4 cm are not candidates for brachytherapy. A minimum dose of 60 Gy is given for external radiotherapy combined with a brachytherapy boost or brachytherapy alone (Zouhair et al. 2001). The penile preservation rate after radiotherapy is approximately 80 %. Local failure rates after radiotherapy are higher than after partial penectomy, but salvage surgery can restore local control (Azrif et al. 2006). The following complications are the most prevalent: urethral stenosis (20–35 %), glans necrosis (10–20 %) and late fibrosis of the corpora cavernosa.

Radiation therapy also represents an option for the adjuvant treatment of penile cancer after surgical removal of primitive penile lesion.

Several studies showed that radiotherapy does not eradicate micro-metastases, with a risk of developing inguinal metastases in 22–25 % of patients who underwent radiotherapy of clinically impalpable nodes.

If compared with surgical treatment, radiotherapy of inguinal metastases is less efficacious (50 % 5-year survival rate for surgically treated group against 25 % for irradiated group) (Azrif et al. 2006), confirming that radiotherapy for inguinal metastases is not therapeutically effective.

Differently, some studies showed that radiotherapy is indicated in large lymph node metastases and extra-nodal extension (ENE). In a study of 106 patients presenting with clinically metastatic inguinal lymphadenopathy, those with nodes larger than 4 cm were irradiated before ILND. Peri-nodal infiltration was found in 33 % of non-irradiated but only in 9 % of irradiated patients, showing that a statistically significant difference is present in groin recurrences in the radiated and non-irradiated groups (3 % vs.-19 %, respectively).

A large study concluded that preoperative inguinal radiotherapy significantly increased the incidence of wound complications and lymphedema.

16.13.11 Chemotherapy

Adjuvant chemotherapy after resection of nodal metastases has been reported in a few small heterogeneous series. The largest experience has been reported by the National Cancer Institute in Milan, Italy, where a long-term disease-free survival (DFS) rate of 84 % was obtained in 25 consecutive node-positive patients treated with 12 adjuvant weekly courses of vincristine, bleomycin and methotrexate (VBM) during the period 1979–1990 (Pizzocaro and Piva 1988; Pizzocaro et al. 1997).

Since 1991, category pN2–pN3 patients have received three courses of adjuvant cisplatin and 5-FU, with lower toxicity and even better results compared to VBM. Category pN1 patients do not need adjuvant chemotherapy.

In the case of patients presenting with fixed or relapsed inguinal nodes, a combined therapy with upfront chemotherapy followed by surgery represents a promising approach. Multiple regimens have been used in a small series of patients. Cisplatin, methotrexate and bleomycin (BMP) at the Memorial Sloan Kettering Cancer Center in New York have shown promising results, but a confirmatory study by the Southwest Oncology Group has reported unacceptable toxicity and only modest results (Dexeus et al. 1991). Leijte et al. have reported on 20 patients with five different neoadjuvant chemotherapy regimens in the 1972–2005 period (Leijte et al. 2007). Responders underwent post-chemotherapy surgery and achieved a 37 % long-term survival rate. At the MD Anderson Cancer Center, combination therapy with paclitaxel, carboplatin or paclitaxel, cisplatin and ifosfamide has been used in seven patients, followed by surgery (Barmejo et al. 2007). Four patients were long-term survivors (48–84 months), but none of the other three patients treated with BMP achieved significant remission.

A preliminary study on taxol combined with cisplatin and 5-FU has shown significant responses in five of six patients with fixed or relapsed inguinal nodes, but only

Table 16.5 Treatment options for penile cancer by stage categories

Primary tumour	Conservative treatment is to be considered whenever possible
Categories Tis, Ta, T1a (G1, G2)	CO_2 or Nd:YAG laser surgery, wide local excision, glans resurfacing or glans resection, depending on size and location of the tumour Mohs micrographic surgery or photodynamic therapy for well-differentiated superficial lesions (Tis, G1, Ta)
Categories T1b (G3) and T2 (glans only)	Glansectomy, with or without tip amputation or reconstruction
Category T2 (invasion of the corpora)	Partial amputation
Category T3 (invasion of urethra)	Total amputation with perineal urethrostomy
Category T4 (other adj. structures)	Eligible patients: neoadjuvant chemotherapy followed by surgery in responders Alternative: external radiation
Local disease recurrence after conservative therapy	Salvage surgery, consisting of penis-preserving treatment in small recurrences Larger recurrence: some form of amputation
Radiotherapy	Organ-preserving treatment in selected patients with T1–T2 of glans or coronal sulcus, lesions <4 cm
Chemotherapy	Neoadjuvant, before surgery Palliation in advanced or metastatic disease

the three who underwent post-chemotherapy surgery achieved durable complete remission (Pizzocaro et al. 2009).

A phase 2 trial on paclitaxel in a population of pre-treated metastatic penile cancer patients showed that this mono-therapy regimen seems to offer an acceptable tolerance profile and activity in this setting. Twenty-five patients from five different institutions were enrolled in this single-arm phase 2 study, and eligibility criteria included previous diagnosis of SCC of the penis; previous treatment with platinum-based regimen in neoadjuvant, adjuvant or advanced setting; prior treatment with surgery or radiotherapy and current metastatic disease (Di Lorenzo et al. 2011) (Table 16.5).

16.14 Follow-Up

Follow-up in penile carcinoma is crucial because it enables early detection of recurrences that are potentially curable and it is the only way to assess treatment and anticipate early and late complications.

Based on the results of a retrospective study (Leijte et al. 2008b), an intensive programme of follow-up during the first 2 years is rational, with less intensive follow-up needed thereafter. In well-educated and motivated patients, follow-up can stop after 5 years, although they must continue to carry out regular self-examination.

Traditional follow-up methods are physical evaluation, while US imaging and PET/CT represent valid imaging support.

16.14.1 Primary Tumour

Local recurrence has been reported in up to 30 % of patients treated with penis-preserving surgery, during the first 2 years following treatment. Local recurrence is more likely with all types of local therapy, that is, local resection, laser therapy, brachytherapy, Mohs procedure and associated therapies. However, in contrast to regional recurrence, local recurrence does not have an impact on survival.

Following penis-preserving treatment, a follow-up visit every 3 months is advised in the first 2 years. We then advise a follow-up visit every 6 months, provided that the patient and his partner have been well instructed to examine the

Table 16.6 Follow-up scheme for penile cancer

	Interval of follow-up		Examinations and investigations	Maximum duration of follow-up
	Years 1 and 2	Years 3, 4 and 5		
Recommendations for follow-up of the primary tumour				
Penis-preserving treatment	3 months	6 months	Regular physician or self-examination	5 years
Amputation	6 months	1 year	Regular physician or self-examination	5 years
Recommendations for follow-up of the inguinal lymph nodes				
'Wait-and-see'	3 months	6 months	Regular physician or self-examination	5 years
pN0	6 months	1 year	Regular physician or self-examination Ultrasound with FNAB	5 years
pN+	3 months	6 months	Regular physician or self-examination Ultrasound with FNAB	5 years

penis regularly and to return if any abnormality is observed.

In case a larger surgery has been performed, a less frequent time interval of every 6 months is advised, because the risk of local recurrence is no more than 5 % (Horenblas and Newling 1993).

16.14.2 Regional Recurrence

Regular physical examination of the inguinal regions and ultrasound eventually integrated with immediate FNAB are the usual strategies for the detection of regional recurrences. Patients managed with a 'wait-and-see' policy have a higher risk of recurrence (9 %) than patients staged surgically (2.3 %), irrespective whether staging has been performed by lymphadenectomy or DSNB. PET/CT is used only in patients at risk of regional recurrence and distant metastases. Bone scan and other tests are only recommended in symptomatic patients (Table 16.6).

Bibliography

American Cancer Society (2012) Cancer facts & figures 2012. American Cancer Society, Atlanta

American Joint Committee on Cancer (2010) Penis. In: AJCC cancer staging manual, 7th edn. Springer, New York, pp 447–451

Azrif M, Logue GP, Swindell R et al (2006) External-beam radiotherapy in T1-2 N0 penile carcinoma. Clin Oncol (R Coll Radiol) 18(4):320–325

Bandieramonte G, Colecchia M, Mariani L et al (2008) Peniscopically controlled CO2 laser excision for conservative treatment of in situ and T1 penile carcinoma: report on 224 patients. Eur Urol 54(4):875–882

Barmejo C, Busby JK, Spiess PE et al (2007) Neoadjuvant chemotherapy followed by aggressive surgical consolidation for metastatic penile squamous cell carcinoma. J Urol 177(4):1335–1338

Barnholtz-Sloan JS, Maldonado JL, Pow-sang J et al (2007) Incidence trends in primary malignant penile cancer. Urol Oncol 25(5):361–367

Crook J, Esche B, Pond G (2007) Penile brachytherapy: results for 60 patients. Brachytherapy 6:82–92

Daling JR, Madeleine MM, Johnson LG et al (2005) Penile cancer: importance of circumcision, human papillomavirus and smoking in situ and invasive disease. Int J Cancer 116(4):606–616

de Crevoisier R, Slimane K, Sanfilippo N et al (2009) Long-term results of brachytherapy for carcinoma of the penis confined to the glans (N- or NX). Int J Radiat Oncol Biol Phys 74(4):1150–1156

Dexeus F, Logothetis C, Sella A et al (1991) Combination chemotherapy with methotrexate, bleomycin and cisplatin for advanced squamous cell carcinoma of the male genital tract. J Urol 146(5):1284–1287

Dillner J, von Krogh G, Horenblas S et al (2000) Etiology of squamous cell carcinoma of the penis. Scand J Urol Nephrol Suppl 205:189–193

Di Lorenzo G, Federico P, Buonerba C, Longo N, Cartenì G, Autorino R, Perdonà S, Ferro M, Rescigno P, D'Aniello C, Matano E, Altieri V, Palmieri G, Imbimbo C, De Placido S, Mirone V (2011) Paclitaxel in pretreated metastatic penile cancer: final results of a

phase 2 study. Eur Urol 60(6):1280–1284. doi:10.1016/j.eururo.2011.08.028, Epub 2011 Aug 22

ENCR (European Network of Cancer Registries) (2001) Eurocim version 4.0. European incidence database V2.2 (1999). IARC, Lyon, http://www.encr.com.fr/encr_EUROCIM1.htm

Ficarra V, Novara G, Boscolo Berto R et al (2009) How accurate are present risk group assignment tools in penile cancer? World J Urol 27:155–160

Ficarra V, Zattoni F, Artibani W et al (2006) GUONE penile cancer project members. Nomogram predictive of pathological inguinal lymph node involvement in patients with squamous cell carcinoma of the penis. J Urol 175:1700–1705

Giuliano AR (2007) Human papillomavirus vaccination in males. Gynecol Oncol 107(2 Suppl 1):S24–S26

Graafland NM, Leijte JA, Valdes Olmos RA et al (2009) Scanning with 18F.FDG-PET/CT for detection of pelvic nodal involvement in inguinal node positive penile carcinoma. Eur Urol 56(2):339–345

Heyns CF, Fleshner N, Sangar V, Schlenker B, Yuvaraja TB, van Poppel H (2010) Management of the lymph nodes in penile cancer. Urology 76(2 Suppl 1): S43–S57

Horenblas S, Newling DW (1993) Local recurrent tumour after penis-conserving therapy. A plea for long-term follow-up. Br J Urol 72(6):976

Howlader N, Noone AM, Krapcho M et al (eds) (2011) SEER cancer statistics review, 1975–2008, National Cancer Institute. Bethesda, http://seer.cancer.gov/csr/1975_2008/, based on Nov 2010 SEER data submission, posted to the SEER web site

Kayes O, Minhas S, Allen C et al (2007) The role of magnetic resonance imaging in the local staging of penile cancer. Eur Urol 51(5):1313–1318

Kroon BK, Horenblas S, Deurloo EE et al (2005) Ultrasonography-guided fine-needle aspiration cytology before sentinel node biopsy in patients with penile carcinoma. BJU Int 95(4):517–521

Leijte JA, Gallee M, Antonini N et al (2008a) Evaluation of current (2002) TNM classification of penile carcinoma. J Urol 180(3):933–938; discussion 938

Leijte JAP, Kerst JM, Bais E et al (2007) Neoadjuvant chemotherapy in advanced penile carcinoma. Eur Urol 52(2):488–494

Leijte JAP, Kirrander P, Antonini N et al (2008b) Recurrence patterns of squamous cell carcinoma of the penis: recommendations for follow-up based on a two-centre analysis of 700 patients. Eur Urol 54(1): 161–168

Markowitz LE, Dunne EF, Saraiya M, Centers for Disease Control and Prevention (CDC); Advisory Committee on Immunization Practices (ACIP) et al (2007) Quadrivalent human papillomavirus vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 56(RR-2):1–24

Minhas S, Kayes O, Hegarty P (2005) What surgical resection margins are required to achieve oncologic control in man with primary penile cancer? BJU Int 96(7):1040–1043

Misra S, Chaturvedi A, Misra NC (2004) Penile carcinoma: a challenge for the developing world. Lancet Oncol 5(4):240–247

Muñoz N, Castelisague X, de Gonzalez AB et al (2006) HPV in the etiology of human cancer. Vaccine 24(Suppl 3):S3/1–S3/10

Nordenvall C, Chang ET, Adami HO et al (2006) Cancer risk among patients with condylomata acuminata. Int J Cancer 119(4):888–893

Ornellas AA, Kinchin EW, No´brega BL et al (2008) Surgical treatment of invasive squamous cell carcinoma of the penis: Brazilian National Cancer Institute long-term experience. J Surg Oncol 97(6): 487–495

Parkin DM, Whelan SL, Ferlay J, et al (2002) Cancer incidence in five continents. Vol. VIII. IARC Scientific Publications. No. 155. IARC, Lyon. http://www.iarc.fr/en/Publications/PDFs-online/Cancer-Epidemiology/IARC-Scientific-Publication-No.-155

Pizzocaro G, Algaba F, Horenblas S, Solsona E, Tana S, Van Der Poel H, Watkin NA, European Association of Urology (EAU) Guidelines Group on Penile Cancer (2010) EAU penile cancer guidelines 2009. Eur Urol 57(6):1002–1012

Pizzocaro G, Nicolai N, Milani A (2009) Taxanes in combination with cisplatin and fluorouracil for advanced penile cancer: preliminary results. Eur Urol 55(3):546–551

Pizzocaro G, Piva L (1988) Adjuvant and neoadjuvant vincristine, bleomycin, and methotrexate for inguinal metastases from squamous cell carcinoma of the penis. Acta Oncol 27(6b):823–824

Pizzocaro G, Piva L, Bandieramonte G et al (1997) Up-to-date management of carcinoma of the penis. Eur Urol 32(1):5–15

Rees RW, Freeman A, Borley N et al (2008) PT2 penile squamous cell carcinomas: cavernosus vs. spongiosus invasion. Eur Urol Suppl 7(3):111, abstract #163

Saisorn I, Lawrentschut N, Leewansangtong S et al (2006) Fine-needle aspiration cytology predicts inguinal lymph node metastases without antibiotic pretreatment in penile carcinoma. BJU Int 97(6): 1125–1128

Shindel AW, Mann MW, Lev RY et al (2007) Mohs micrographic surgery for penile cancer: management and long-term followup. J Urol 178(5): 1980–1985

Sobin LH, Gospodariwics M, Wittekind C, UICC International Union Against Cancer (eds) (2009) TNM classification of malignant tumours, 7th edn. Wiley-Blackwell, Chichester/West Sussex/Hoboken, pp 239–242

Solsona E, Iborra I, Rubio J et al (2001) Prospective validation of the association of local tumor stage grade as a predictive factor for occult lymph node micrometastasis in patients with penile carcinoma and clinically negative inguinal lymph nodes. J Urol 165(5): 1506–1509

Windalh T, Andersson SO (2003) Combined laser treatment for penile carcinoma: results after long-term follow up. J Urol 169(6):2118–2121

Yeung LL, Brandes SB (2013) Dynamic sentinel lymph node biopsy as the new paradigm for the management of penile cancer. Urol Oncol 31(5):693–696

Zouhair A, Coucke PA, Jeanneret W et al (2001) Radiation therapy alone or combined surgery and radiation therapy in squamous-cell carcinoma of the penis? Eur J Cancer 37(2):198–203

Part VII

Andrological Emergencies

Emergencies in Andrology

17

C. Bettocchi and M. Spilotros

Contents

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17.1 Priapism

Priapism is a pathological condition characterized by a full or partial erection of more than 4 h without any sexual stimulation and which is not solved by orgasm. Essentially literature reports three kinds of priapism: ischaemic priapism when an uninterrupted venous occlusion causes a continued erection, non-ischaemic priapism determined by an increased arterial flow and stuttering priapism with a similar aetiology to the ischaemic but intermittent (Broderick et al. 2010).

Ischaemic priapism, between the subtypes, represents the most common form and must be managed as an emergency considering that there is an absent or poor cavernous arterial inflow and thus dramatic histological changes related to hypoxia, hypercarbia and acidosis. The first changes observed after 12 h are oedema and endothelium damages, while after 48 h, the coagulation cascade stimulated by thrombocyte adherence to the basement membrane has already caused a significant thrombosis of the corpora. At this moment necrosis is generally evident, and fibrosis is developing (Spycher and Hauri 1986). In the aetiology of this particular condition, haematological diseases and iatrogenic factors play the principal role. Between blood dyscrasias sickle-cell disease (SCD) represents a common cause due to erythrocyte entrapment in the corpora cavernosa with resulting obstructed venous outflow after an erection (Lue 2002). It is reckoned that one third of ischaemic priapism are related to

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V. Mirone (ed.), *Clinical Uro-Andrology*,
DOI 10.1007/978-3-662-45018-5_17, © Springer-Verlag Berlin Heidelberg 2015

Table 17.1 Futures of priapism subtypes

Priapism subtype	Cause	Symptoms	Blood gas	Treatment
Ischaemic (low flow)	SCD Malignancies Drugs	Painful full erection longer than 4 h	PO_2 <30 mmHg $PACO_2$ >60 mmHg ph <7.25	Blood aspiration ICI of sympathomimetic agents Percutaneous or open shunt
Stuttering	SCD	Intermittent episodes of prolonged erections	PO_2 <30 mmHg $PACO_2$ >60 mmHg ph <7.25	GnRh agonists Anti-androgens DES Ketoconazole Etilefrine
Non-ischaemic (high flow)	Traumas Iatrogenic	Prolonged erectile tumescence generally without pain	Normal range	Observation (spontaneous resolution) Arterial embolization Ligation of fistula

this condition, and for this reason a careful screening for SCD as first investigation is reasonable in these patients (Broderick et al. 2010).

Other common causes for low-flow priapism are treatment for erectile dysfunction (ED)–related complications. Particularly intracorporal injections (ICI) rather than oral drugs can be followed by prolonged erections and priapism. In literature different incidence rates of priapism are reported after ICI of vasoactive substances, and generally the range is between 0 and 35 %: combined therapy based on papaverine or phentolamine has higher rates, while in investigations conducted only with PGE1 (alprostadil), this percentage drops to 5 % for prolonged erection and only 1 % for priapism (Broderick and Lue 2002; Porst 1996). The involvement of PDE5 inhibitor in the aetiology of ischaemic priapism is debatable considering that a possible link is showed only by case reports in which, additionally, patients suffered from co-morbidities possibly related to the priapism onset themselves (Wilt and Fink 2004; Sur and Kane 2000). The above-mentioned factors are undoubtedly the commonest causes of ischaemic priapism, but malignancies such as pelvic and haematological tumours, recreational drugs and antipsychotic treatments have been related even if with lower rates (Broderick et al. 2010).

The aetiology of stuttering priapism is essentially linked to SCD, and the main difference with the previous subtype lies in the intermittence of its episodes which last several hours before resolution; generally stuttering priapism leads up to the onset of ischaemic priapism (Broderick et al. 2010).

The third kind of priapism, the non-ischaemic, is characterized by a persistent erection, not always painful, caused by unregulated cavernous arterial inflow. Considering its pathophysiology non-ischaemic priapism does not represent an emergency because there isn't any outflow obstruction or intrasinusoidal coagulation risk resulting in tissue necrosis. For this reason this condition can be managed with a conservative approach (Broderick et al. 2010). Generally non-ischaemic priapism is caused by a penile trauma, blunt or sharp, resulting in the formation of an arteriolar-sinusoidal fistula which supports the prolonged erection. Iatrogenic causes are represented by urological procedure including Nesbit or mini-invasive diagnostic investigations that could cause an arterial injury through a needle insertion (Liguori 2005).

Anamnesis can certainly help to understand the subtype of priapism considering that ischaemic and non-ischaemic show different factors as mentioned above. An accurate inspection of the patient has the aim to value the degree of tumescence considering that a partial erection not associated to pain is a common feature of non-ischaemic priapism, while the evidence of a full tumescence is more often related to the ischaemic and stuttering priapism. The presence of traumas in the external genitalia and the suspicion of

malignancies in the abdomen and perineal area with deep palpation can be further elements for a correct diagnosis. Past medical history and physical examination represent the first step in the diagnosis. The successive step is represented by investigations: a penile doppler ultrasound is indicated in case of high flow priapism in order to confirm high flow, the site of the trauma and the fistula if present (Broderick et al. 2010; Broderick and Lue 2002). A blood gas represents the instrumental investigation which determines if there are signs of ischaemia in the corpora: a PO_2 lower than 30 mmHg and a PCO_2 higher than 60 mmHg with a pH lower than 7.25 are typical signs of an ischaemic priapism (Montague et al. 2003). In selected cases in which a malignancy is supposed, a CT scan or an MRI of the abdomen/pelvis is recommended. It is important to determine the real nature of the priapism before any treatment considering that in case of ischaemia, the patient should be treated as soon as possible in order to avoid necrosis and fibrosis of the corpora, while in case of non-ischaemic priapism, a conservative approach can be adopted.

The immediate treatment of ischaemic priapism is mandatory to prevent erectile dysfunction (ED) which is evident after 24 h of ischaemic priapism in 90 % of patients (Pryor and Hehir 1982). The first treatment is the decompression of the corpora with local aspiration and ICI of sympathomimetic agents (Montague et al. 2003). Sympathomimetic drugs such as etilefrine and phenylephrine acting on smooth muscle contraction determine the contraction of the erectile tissue with resulting detumescence in a high percentage of patients. The rate of priapism resolution after this approach has been demonstrated to reach 81 %, while in case of aspiration alone with the irrigation of the corpora, the success rate is only 36 % (Montague et al. 2003). When this treatment is used, a careful monitoring of blood pressure and pulse is recommended considering that arrhythmia, hypertension, reflex bradycardia and tachycardia are reported side effects of ICI of sympathomimetics. If these preliminary approaches do not show any satisfactory results, the use of alpha-adrenergic agonists is contraindicated or has determined important side effects, and surgical therapy represents the only feasible strategy to re-oxygenate the cavernosal tissue. In order to achieve this aim, it is necessary to create a shunt between the corpora and the nearby structures including the glans, corpus spongiosum or saphenous vein. These techniques allow an outflow of the stagnant blood in the cavernosal tissue with the resulting re-establishment of arterial flow. The procedures can be divided in four groups: percutaneous and open distal shunts, open proximal and saphenous vein shunts (Broderick et al. 2010). Generally the first procedure adopted is an open distal shunt eventually followed by more proximal and aggressive approaches in case detumescence is not achieved and nil arterial flow within the corpora is detectable. Between the percutaneous procedure an outflow through the glans can be performed with biopsy needle (Winter 1976), n°11 blade (Ebbehoj 1974) or with a T-shape incision in the distal tip of the corpora (Brant et al. 2009). If priapism persists a more aggressive approach is recommended such as the open shunting between corporas and glans. With this technique the removal of a conic segment of tunica albuginea at the corporal tip is recommended and the dilatation of the corpora with Hegar dilators can be helpful to improve drainage (Burnett and Pierorazio 2009). Proximal shunt including cavernosum-spongiosum and saphenous shunt are the most aggressive techniques which have between their potential side effects the risk of pulmonary embolism, and for this reason their use is generally limited (Quackles 1964; Kandel et al. 1968).

In case of long-term ischaemic priapism in which necrosis of the corpora is evident, ED is unavoidable. In these cases a delayed insertion of a penile prosthesis can be extremely difficult and with higher complication rates. For this reason some authors recommend an immediate implantation to avoid penile shortening and increased peri-operative and post-operative complications such as infections (Ralph et al. 2009; Rees et al. 2002). A different management is necessary for stuttering priapism considering that in this case, medical treatments are employed more than surgical approaches. The main target of systemic therapy is represented by the suppression of the

androgenic effects on erection: this aim can be achieved using GnRh agonists and anti-androgens thanks to their inhibiting action, respectively, on the pituitary gland and peripheral androgen receptors or prescribing diethylstilbestrol (DES) and ketoconazole which have a negative feedback respectively on pituitary and adrenal glans (Broderick et al. 2010).

Regarding high-flow priapism a different treatment is advocated because this subtype does not represent an emergency considering the absence of cavernosal necrosis and thus of any negative impact on erectile function. An observational approach is generally suggested for this disease thanks to its spontaneous resolution; for this reason all patients should be counselled regarding the potential negative effects of the therapy more than non-ischaemic priapism itself. If the patient requires treatment due to remarkable discomfort, the options available are the selective embolization or the open ligation of the fistula responsible for the high flow. The first treatment is preceded by an arteriographic study in order to demonstrate the fistula, while in case of long-term arterial priapism, an intraoperative Doppler ultrasonography can be useful. Embolization has a high rate of success, but its principal side effect regardless of the kind of agent used is represented by ED which can occur in up to 39 % of patients treated (Savoca et al. 2004; Mwamukonda et al. 2010). Other adverse events are related to the possible occlusion of major arterial branches of the gluteal area and the penile shaft resulting in local ischaemia (Tønseth et al. 2006).

17.2 Genital Traumas

Genital traumas can be penetrating and blunt: to the first class belong injuries due to sharp objects, bites or explosions, while penile fractures represent the typical blunt trauma.

Penile fracture occurs in case of a lesion of the tunica albuginea while the erect penis hits the female pelvis during intercourse with an excessive ventral angulation (Garaffa et al. 2011). The rupture of the tunica albuginea is due to its thinning and elongation during erection and in the majority of cases is evident in the ventrolateral aspect of the shaft where the tunica is characterized by a single-layer structure (Garaffa et al. 2011; Miller and McAninch 1996).

Penile fracture onset is recognizable by a snapping sound followed by detumescence and a haematoma of the shaft which can be evident only on the shaft or in the scrotum, perineum and lower abdominal wall according to the site of the rupture (Miller and McAninch 1996; Gontero et al. 2000). If a concomitant urethral injury has occurred, additional signs are urethral bleeding and difficulty or impossibility to pass urine. A correct diagnosis is based for these reason on the physical examination followed, in case of any doubt regarding the exact location of the tear, by MRI, urethrography or flexible cystoscopy (Kamdar et al. 2008).

Treatment can be conservative or immediate, but a prompt surgical approach is recommended in case of urethral damage. Once it has been excluded, penile fracture can be treated with compressive dressings and administration of anti-androgens in order to avoid erections allowing a faster and better healing process. This kind of treatment is unfortunately characterized by several complications which limit its application: the most frequent is the formation of severe fibrosis of the tunica resulting in penile curvature in up to 50 % of cases and eventually in ED. Furthermore the conservative approach does not allow in all cases a control on bleeding, and for this reason haematomas can occur (Miller and McAninch 1996; Punekar and Kinne 1999).

The high complication rate has determined an increase in the immediate surgical management of patients with penile fracture. Early surgical repair in fact guarantees satisfactory outcomes in terms of erectile dysfunction and curvature which happen, respectively, in less than 1 and 5 % of patients treated (El Atat et al. 2008; Mydlo 2001). The incision can be subcoronal, transversal penoscrotal or longitudinal over the fracture. The circumferential subcoronal incision with shaft degloving guarantees a good exposure of the corpora even if it can be followed by several complications and mainly skin necrosis; for this reason a circumcision is recommended in order

to avoid foreskin complications. In case the injured area is easily detectable, a small longitudinal incision along the shaft can be performed. The aim of surgery is to remove the haematoma and to suture the tear in the tunica albuginea and eventually to sort out the urethral injury (Fernstrom 1957). The suture adopted for this kind of repair is generally 0 polydioxanone which guarantees a slow absorption and an adequate resistance to achieve a correct healing (Garaffa et al. 2011). On the operative table the urethra should be checked directly injecting methylene blue through the meatus in order to observe directly any leakage and in case suture it in multiple layers (Shaeer 2006).

In the post-operative management of these patients, it is mandatory to avoid sexual intercourse for 6 weeks, and for this reason antiandrogens can be prescribed to prevent nocturnal erections: penile tumescence in this period can cause suture tears and thus further injury of the tunica albuginea resulting in surgical revision.

Regarding penetrating traumas of the external genitalia, the management is characterized by several techniques and different approaches according to the spread of the lesions. Conservative debridement is preferable in patients with minimal damages in order to improve functional preservation, while in case of superficial injuries of the dartos and bucks fascia, the treatment should be nonsurgical (Shenfeld and Gnessin 2011). When severe injuries involve the external genitalia and the important lack of tissue becomes evident after debridement, a surgical reconstruction with grafting and flapping of the affected areas represents the only feasible approach to obtain satisfactory cosmetic and functional results (Perovic et al. 2009).

17.3 Paraphimosis

Paraphimosis is a pathological condition characterized by fixed foreskin in the retracted position which causes venous outflow obstruction from the glans resulting in ischaemia and, if not solved, in necrosis (Kessler and Bauml 2009). This condition is mainly determined by a pre-existing phimosis which, in case of retraction of the skin, causes a circular constriction on the veins and lymphatic vessels of the distal shaft (Filippone 2005). Balanoposthitis can play a similar role due to the presence of scar tissue which avoids the physiological repositioning of the foreskin over the glans (Samm and Dmochowski 1996).

Patients complain of glans pain associated with local oedema; the pathognomonic sign is represented by the impossibility to pull back the retracted foreskin. A differential diagnosis with traumas and allergic reaction should be excluded. Regarding therapy the first effort should be a manual repositioning of the foreskin using nerve-block, ice and compression in order to reduce pain and oedema. Further attempts performing needle punctures in the oedematous area can help the manual reduction thanks to the consequent local blood loss, but these procedures should not be repeated if unsuccessful in order to avoid a worse inflammation. A dorsal incision of the fibrotic tissue responsible for the constriction represents a rapid solution; this treatment reduces local oedema and improves venous outflow resulting in a better perfusion of the glans preventing the risk of local ischaemia.

Once the inflammatory situation has settled down, the principal aim is to avoid further episodes of paraphimosis in the future: for this reason circumcision is the therapy of choice thanks to the removal of the fibrotic ring and scar tissue in the foreskin (Kessler and Bauml 2009; Samm and Dmochowski 1996).

17.4 Fournier's Gangrene

The necrotizing fasciitis of Fournier is a dramatic infection of the perineum and the external genitalia, observed mainly in immunodepressed patients, which can be fatal up to 22 % of cases (Kessler and Bauml 2009). This is sustained by aerobic and anaerobic bacteria of the skin and gastrointestinal and genitourinary tract such as *Bacteroides fragilis*, *E. Coli*, *Klebsiella*, *Staphylococci* and *Clostridium* (Kessler and Bauml 2009). The infection generally starts from the skin and urethral or rectal mucosa and

involves the superficial and deep fascias of the perineum and can determinate consequent necrosis. The tissue affected is characterized by erythema and increased consistence, while air present in the underneath layers can be responsible for a typical crackling.

In the management of a patient with Fournier's gangrene, beyond physical examination, an exhaustive investigation using TC scan or MRI of the pelvis is mandatory to establish the correct spread of the necrotizing fasciitis and to schedule a proper treatment. In those cases in which an involvement of the urethra or rectum is suspected, a direct examination of these tracts with a urethroscopy, a retrograde urethrogram or a proctoscopy is recommended (Kessler and Bauml 2009).

Therapy for this aggressive disease is both medical and surgical: the first step is to re-establish a haemodynamic balance regulating hydro-electrolytes and pH disorders. Successively the principal aim of the treatment is to provide a suitable antibiotic coverage of broad spectrum towards gram-positive and gram-negative bacteria and especially anaerobes: in this case the use of penicillin, metronidazole and cephalosporins represents an indicated empirical approach. The use of hyperbaric oxygen therapy is a further attempt to control the diffusion of the infection even if a clear benefit has not been demonstrated, and thus it remains debatable (Kessler and Bauml 2009).

Together with antibiotic therapy surgery represents the principal way to treat the Fournier's gangrene. The procedure consists in removing the necrotized tissue with a wide debridement and repeated washing with peroxide, saline and Betadine: in case an extended lack of tissue becomes evident after this manoeuvre, a grafting of the affected area is necessary. Post-operative wound care is pivotal in order to avoid further infections, and thus a frequent dressing change with local disinfection is recommended. If further necrotic tissue is present after surgery, ulterior debridements followed by aggressive wound care represent the standard therapy.

References

Brant WO, Garcia MM, Bella AJ et al (2009) T-shaped shunt and intracavernous tunneling for prolonged ischemic priapism. J Urol 181:1699–1705

Broderick GA, Lue TF (2002) Evaluation and nonsurgical management of erectile dysfunction and priapism. Campbell's urology. W.B. Saunders, Philadelphia

Broderick GA, Kadioglu A, Bivalacqua TJ et al (2010) Priapism: pathogenesis, epidemiology, and management. J Sex Med 7:476–500

Burnett A, Pierorazio P (2009) Corporal "snake" maneuver: corporoglanular shunt surgical modification priapism: pathogenesis, epidemiology, and management for ischemic priapism. J Sex Med 6:1171–1176

Ebbehoj J (1974) A new operation for priapism. Scand J Plast Reconstr Surg 8:241

El Atat R, Sfaxi M, Benslama MR (2008) Fracture of the penis: management and long term results of surgical treatment. Experience in 300 cases. J Trauma 64: 121–125

Filippone LM (2005) Diagnosis: paraphimosis. Emerg Med News 27:18

Fernstrom U (1957) Rupture of the penis. Report of one operated case and review of the literature. Acta Chir Scand 113:211–217

Garaffa G, Raheem AA, Ralph DJ (2011) Penile fracture and penile reconstruction. Curr Urol Rep 12:427–431

Gontero P, Sidhu PS, Muir GH (2000) Penile fracture repair: assessment of early results and complications using color Doppler ultrasound. Int J Imp Res 12: 125–129

Kamdar C, Mooppan UMM, Kim H, Gulmi FA (2008) Penile fracture: preoperative evaluation and surgical technique for optimal patient outcome. BJU Int 102(11):1640–1644

Kandel GL, Bender LI, Grove JS (1968) Pulmonary embolism: a complication of corpus saphenous shunt for priapism. J Urol 99:196–197

Kessler CS, Bauml J (2009) Non-traumatic urologic emergencies in men: a clinical review. West J Emerg Med 10(4):281–287

Liguori G (2005) High flow priapism secondary to nesbit operation: management by percutaneous embolization and colour Doppler guided compression. Int J Impot Res 17:304–306

Lue TF (2002) Physiology of penile erection and pathophysiology of erectile dysfunction and priapism. Campbell's urology. W.B. Saunders, Philadelphia

Miller S, McAninch JW (1996) Penile fracture and soft tissue injury. In: McAninch JW (ed) Traumatic and reconstructive urology, ch 59. WB Saunders, Philadelphia

Montague DK, Jarow J, Broderick GA et al (2003) AUA erectile dysfunction guideline update panel. Urological association guideline on the management of priapism. J Urol 170:1318–1324

Mwamukonda KB, Chi T, Shindel AW et al (2010) Androgen blockade for the treatment of high-flow priapism. J Sex Med 7:2532–2537
Mydlo JH (2001) Surgeon experience with penile fracture. J Urol 166:526–528
Perovic SV, Djinovic RP, Bumbasirevic MZ et al (2009) Severe penile injuries: a problem of severity and reconstruction. BJU Int 104:676–687
Porst H (1996) The rational for prostaglandin E1 in erectile failure: a survey of worldwide experience. J Urol 155:802–815
Pryor JP, Hehir M (1982) The management of priapism. Br J Urol 54:751
Punekar SV, Kinne JS (1999) Penile refracture. BJU Int 84:183–184
Quackles R (1964) Treatment of a case of priapism by cavernospongious anastomosis. Acta Urol Belg 32: 5–13
Ralph DJ, Garaffa G, Muneer A et al (2009) The immediate insertion of a penile prosthesis for acute ischaemic priapism. Eur Urol 56:1033–1038
Rees RW, Kalsi J, Minhas S et al (2002) The management of low-flow priapism with the immediate insertion of a penile prosthesis. BJU Int 90:893–897
Samm BJ, Dmochowski RR (1996) Urologic emergencies. Postgrad Med 100:187–200
Savoca G, Pietropaolo F, Scieri F et al (2004) Sexual function after highly selective embolisation of cavernous artery in patients with high-flow priapism: long-term follow-up. J Urol 172:644–647
Shaeer O (2006) Methylene blue-guided repair of fractured penis. J Sex Med 3:349–354
Shenfeld OZ, Gnessin E (2011) Management of urogenital trauma: state of the art. Curr Opin Urol 21: 449–454
Spycher MA, Hauri D (1986) The ultrastructure of the erectile tissue in priapism. J Urol 135:142–147
Sur RL, Kane CJ (2000) Sildenafil citrate-associated priapism. Urology 55:950
Tønseth AK, Egge T, Kolbenstvedt A et al (2006) Evaluation of patients after treatment of arterial priapism with selective microembolization. Scand J Urol Nephrol 40:49–52
Wilt TJ, Fink HA (2004) Is antidepressant plus sildenafil a recipe for priapism? Postgrad Med 116:11–12
Winter CC (1976) Cure of idiopathic priapism: new procedure for creating fistula between glans penis and corpora cavernosa. Urology 8:389–391

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V. Mirone (ed.), *Clinical Uro-Andrology*,
DOI 10.1007/978-3-662-45018-5, © Springer-Verlag Berlin Heidelberg 2015

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