The BOSTON IVF

Handbook of Infertility

A practical guide for practitioners who care for infertile couples

Second Edition

Edited by
Steven R Bayer MD
Michael M Alper MD
Alan S Penzias MD

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Steven R Bayer MD
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Harvard Medical School
Boston, MA
USA

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First published in the United Kingdom in 2007 by Informa Healthcare, 4 Park Square, Milton Park, Abingdon, Oxon OX14 4RN. Informa Healthcare is a trading division of Informa UK Ltd. Registered Office: 37/41 Mortimer Street, London W1T 3JH. Registered in England and Wales Number 1072954.

Tel.: +44 (0)20 7017 6000
Fax.: +44 (0)20 7017 6699
E-mail: info.medicine@tandf.co.uk
Website: www.informahealthcare.com

A CIP record for this book is available from the British Library.

Library of Congress Cataloging-in-Publication Data

Data available on application

ISBN 10 0 415 39432 5
ISBN 13 978 0 415 39432 1

Distributed in North and South America by

Taylor & Francis
6000 Broken Sound Parkway, NW (Suite 300)
Boca Raton, FL 33487, USA

Within Continental USA
Tel: 1(800)272 7737; Fax: 1(800)374 3401
Outside Continental USA
Tel: (561)994 0555; Fax: (561)361 6018
E-mail: orders@crcpress.com

Distributed in the rest of the world by
Thomson Publishing Services
Cheriton House
North Way
Andover, Hampshire SP10 5BE, UK
Tel.: +44 (0)1264 332424
E-mail: tps.tandfsalesorder@thomson.com

Composition by C&M Digitals (P) Ltd, Chennai, India

Printed and bound by Replika Press Pvt Ltd

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Contributors

Michael M Alper MD
Boston IVF
Harvard Medical School
Boston, MA
USA

Steve R Bayer MD
Boston IVF
Harvard Medical School
Boston, MA
USA

Brian M Berger MD
Boston IVF
Harvard Medical School
Boston, MA
USA

Merle J Berger MD
Boston IVF
Harvard Medical School
Boston, MA
USA

Alice D Domar PhD
Boston IVF
Harvard Medical School
Boston, MA
USA

Lynn Nichols LICSW BCD
Boston IVF
Boston, MA
USA

Selwyn P Oskowitz MD
Boston IVF
Harvard Medical School
Boston, MA
USA

Karen Parlee
Boston IVF
Waltham, MA
USA

Alan S Penzias MD
Boston IVF
Harvard Medical School
Boston, MA
USA

Terry Chen Rothchild LICSW BCD
Boston IVF
Boston, MA
USA

David A Ryley MD
Boston IVF
Harvard Medical School
Boston, MA
USA

Kim L Thornton MD
Boston IVF
Harvard Medical School
Boston, MA
USA

Jeanie Ungerleider LICSW BCD
Boston IVF
Boston, MA
USA

Alison E Zimon MD
Boston IVF
Harvard Medical School
Boston, MA
USA

Preface

Boston IVF (BIVF) has been one of our country's premier reproductive medicine centers for nearly 25 years. With a long list of "firsts" in New England and in the United States, it has provided leadership in both clinical care and academic medicine. Ten years ago, I joined the Department of Obstetrics and Gynecology at Beth Israel Deaconess Medical Center (BIDMC), Harvard Medical School, as the Director of the Division of Reproductive Endocrinology and Infertility. Dr. Benjamin Sachs, Chairman of the Department, forged new ground and merged Boston IVF with the Academic Department and, as a result, Boston IVF became the Clinical Arm of the REI Division. During my 10 years with Boston IVF and BIDMC, this group became the largest US IVF center developing cutting edge protocols for clinical care and making quality assurance and quality improvement top priorities. At the same time, it opened its doors to education and research, rounding out its mission in reproductive medicine. Becoming the first US IVF program to obtain ISO 9000-2000 certification and being awarded the largest infertility trial at a single center by the National Institute of Health (called the FASTT Trial) are just 2 examples of this mission of excellence. Throughout these past years BIVF clinicians have continually presented data from their extensive database at national meetings and in our medical journals, a process through which they have been able to provide the answers to numerous key questions about infertility care. Now with the second edition of *The Boston IVF Handbook of Infertility*, Boston IVF clinicians are sharing their expertise, their vast experience, their protocols, clinical algorithms, and the forms they use on a day-to-day basis with other providers of infertility care. From A to Z, this handbook will undoubtedly help you provide your patients with those aspects of contemporary care available in your office as well as an understanding of the processes they will encounter when they are referred on for higher tech care.

It was an honor and privilege for me to work with the clinicians and staff at Boston IVF for nearly a decade. As you read and refer to this handbook, you will soon see why!

Richard H. Reindollar MD
Chair
Department of Obstetrics and Gynecology
Dartmouth Medical School
Dartmouth Hitchcock Medical Center
Hanover, NH
USA

Acknowledgments

We would like to thank the physicians and scientists at Boston IVF for their help and input into this project. We are also very grateful to our wives and families for their patience and support of our endeavors.

About Boston IVF

Boston IVF was established in 1986 as one of the first freestanding IVF centers in the United States. The unique practice model and commitment to the highest quality medical care for the infertile couple has resulted in continued growth and success within the organization. To this end, Boston IVF has established itself as one of the largest IVF centers in the United States and has been responsible for the birth of more than 15 000 babies. As a testament to its commitment to quality Boston IVF became the first IVF center in North America to become ISO 9001–2000 certified. The strong affiliation of Boston IVF with the Beth Israel Deaconess Medical Center and the Harvard Medical School has resulted in broad-based clinical and basic science research in the field of reproductive medicine. Boston IVF also has maintained a strong commitment to education. There is active teaching of nurses, medical students, physicians in training, and staff physicians. Through its commitment to quality patient care, medical research, and education, Boston IVF is recognized as a world leader in infertility.

Disclaimer

This handbook presents an understanding and a perspective of the current clinical and scientific advances in the field of reproductive medicine and infertility as of the date of its writing. The field of reproductive medicine and infertility is an emerging discipline and is subject to change. The information presented in this handbook should not be considered as dictating an exclusive course of treatment or procedure to be followed. Rather it is intended to be an educational aid to the physician on current information.

1.

Overview of infertility

Alan S Penzias

Significant advances have been made in the field of reproductive medicine over the past several decades. The knowledge that has been gained has provided a better understanding of the science of infertility and has resulted in the development of reproductive technologies that have greatly benefited infertile couples. However, with the introduction of these new therapies, there is a realization that infertility is not a simple medical problem but there are legal, economic, moral, and ethical issues that must be addressed. This chapter will provide an overview of infertility and discuss its broader impact on society today.

HISTORICAL PERSPECTIVE

Realizing the importance of reproduction early scientists, philosophers, and others have ventured to gain an understanding of the human reproduction system and the disorders that alter its function. While most of our understanding of human reproduction has been gained over the past 50 years this could not have been possible without the insight and knowledge from early investigation.

Infertility in the Bible

The earliest references to reproduction date back to antiquity with the biblical directive to 'be fruitful, and multiply'.[1] In fact, those words are used three separate times in the book of Genesis.[2,3] It is no surprise therefore that fertility and procreation played a cornerstone of early life and beliefs. A woman was measured by her ability to bear children and infertility was viewed as a punishment for wrongdoing, with God being the source of fertility and infertility.

Problems with infertility beset our ancestors from the start. Sarah and Abraham were unable to conceive.[4] Sarah considered the problem and asked Abraham to 'go in unto my maid; it may be that I may obtain children by her'.[5] Abraham honored Sarah's request and Hagar conceived. We can probably view this as the first recorded test of male infertility, but in retrospect it confirmed that the infertility resided with Sarah.

Ancient Greece

Hippocrates (460–380 BC) was one of the first authors of various medical works dealing with gynecology. Six treatises which deal with reproduction were attributed to him. The diagnosis of infertility was based on the concept of free passage or continuity of the external genitalia and the vagina with the rest of the body. In the Aphorisms of Hippocrates he wrote 'If a woman do not conceive, and wish to ascertain whether she can conceive, having wrapped her up in blankets, fumigate below, and if it appear that the scent passes through the body to the nostrils and mouth, know that of herself she is not unfruitful'.[6] In the same treatise Hippocrates speculated on the conditions needed to foster pregnancy: 'Women who have the uterus cold and dense do not conceive; and those also who have the uterus humid, do not conceive, for the semen is extinguished, and in women whose uterus is very dry, and very hot, the semen is lost from the want of food; but women whose uterus is in an intermediate state between these temperaments prove fertile'.[6]

Aristotle of Stagira (384–322 BC), one of the greatest Greek philosophers of his time, was also one of the greatest zoologists and naturalists of antiquity. Although not a physician, he discussed many issues relating to reproduction in his thesis 'The Generation of Animals'. Aristotle gave to medicine certain fundamentals such as comparative anatomy and embryology. A common ancient method of interfering with male fertility was castration. Aristotle knew that castration makes a male infertile despite his belief that the testes are only weights holding down the spermatic passages and not the source of the seed: 'For the testes are no part of the ducts but are only attached to them, as women fasten stones to the loom when weaving'.[7] He was probably misled by his observation that a recently castrated bull succeeded in impregnating a cow: 'a bull mounting immediately after castration has caused conception in the cow because the ducts had not yet been drawn up'.[7]

The Renaissance

Andreas Vesalius (1514–1564), a Belgian physician and anatomist, published his revolutionary book *De Humani Corporis Fabrica* (On the Structure of the Human Body) in 1543. Vesalius contributed to an accurate description of the entire female genital system including ligaments, tubes, and blood supply. He was the first to use the terms pelvis and decidua. He also was the first to describe the ovarian follicle.

Gabrielle Fallopio (1523–1562) of Modena was a student of Vesalius. He described the oviducts in greater depth and wrote further on the morphology of the ovaries. His name has been permanently connected with the oviduct or fallopian tube. He also named the clitoris, the vagina, and the placenta.

Lazzaro Spallanzani (1729–1799), although not a physician, made enormous contributions to our understanding of fertility. In his monograph, *Fecondazione*

Artificiale, he showed that conception was achieved as a result of contact between eggs and sperm. He succeeded in fertilizing frog eggs by placing them in immediate contact with the secretions expressed from the testicles of the male. He also performed some of the first successful artificial insemination experiments on lower animals and on a dog.[8]

The modern era

J Marion Sims (1813–1883) is considered the father of American gynecology. Among his numerous contributions Sims played an important part in establishing how cervical secretions affect sperm survival in the genital tract. On the basis of Sims' work, Max Huhner (1873–1947), in his 1913 book 'Sterility in the Male and Female and its Treatment' introduced the postcoital test called the Sims–Huhner test.

IC Rubin introduced the first clinical test to determine tubal patency. Initially, he started by using a radioactive material, but realized that this approach had its limitations. In 1920 he used oxygen for the insufflation. This was later changed to carbon dioxide as it was reabsorbed more easily, caused less discomfort, and avoided the danger of embolism. In the test the insufflation is usually carried out at a gas pressure of less than 120 mm of mercury. The manometer reading decreases to 100 or less if the tubes are clear; if between 120 and 130, there is probably partial stricture; if it rises to 200 and above, it suggests that the tubes are obstructed.[9] This test is no longer performed and has been replaced by the modern day hysterosalpingogram.

In 1935 Stein and Levanthal described a series of patients with amenorrhea, hirsutism, and obesity. They named the condition the Stein–Levanthal syndrome (later termed polycystic ovarian syndrome). They noted that several of these women started to menstruate after they underwent an ovarian biopsy. This led to the development of the wedge resection as a treatment for this condition which proved to be quite effective in the restoration of menstrual function. To this day we still do not have an understanding as to why an ovarian wedge resection or the modern day ovarian drilling procedure is effective.

1960s: the development of the radioimmunoassay

In the 1950s the radioimmunoassay (RIA) was developed by Solomon Aaron Berson and Rosalyn Sussman Yalow. It facilitated the detection and measurement of steroid and peptide hormones that are present in the serum and urine in very low concentrations. As a result of this monumental work Yalow received the Nobel Prize in physiology in 1977. The introduction of RIA was pivotal and developed the foundation to endocrinology. The information gained helped us to understand the steroid pathways in endocrine organs and also helped with the diagnosis and characterization of endocrine disorders. The RIA also provided an important tool to monitor the patient undergoing ovulation induction.

1960s: the introduction of fertility medications

The oral medication clomiphene citrate (CC) was introduced in 1962. It was the first medical therapy developed to correct ovulatory dysfunction secondary to anovulation. To this day it continues to be the most commonly prescribed medication for the infertile female.

In the 1960s FSH and LH were extracted from the urine of menopausal women which gave rise to the development of an injectable medication called human menopausal gonadotropins. This medication was used for ovulatory dysfunction that was refractory to CC. It was a much stronger agent and required closer monitoring of serum estradiol levels which could now be measured by RIA. In 1962 Dr Bruno Lunenfeld in Israel reported the first pregnancy achieved with the use of human menopausal gonadotropins.

1980s: reproductive surgery

During the 1980s there was an emphasis on reproductive surgery to correct tubal/peritoneal factors which were causing infertility. Laparoscopy was becoming increasingly popular and evolved into a routine part of the infertility evaluation. Laparoscopy was first introduced in the United States in 1911 by Bertram Bernheim at The Johns Hopkins Hospital. However, not until the introduction of the automatic insufflator in 1960 and the development of a fiber optic light source did the procedure become practical. Initially laparoscopy was only a diagnostic tool and the surgeon would have to resort to a laparotomy to correct altered pelvic anatomy. In the ensuing years, with the advent of laparoscopic instrumentation, operative laparoscopy was born which allowed the surgeon to not only diagnose but also to treat most abnormalities that were encountered. However, in the 1990s rising IVF success rates soon surpassed the success rates resulting from corrective surgery. Presently there are fewer indications to resort to surgery.

1990–2000–: the IVF revolution

On 25 July 1978 Louise Joy Brown, the world's first successful 'test-tube' baby, was born in Great Britain. However, what is today considered commonplace was a generation in the making. In 1944, Harvard scientists Miriam F Menkin and John Rock fertilized the first human egg in a test tube. On 6 February 1944 they produced the first laboratory-fertilized, two-cell human egg.[10]

Author Martin Hutchinson summarized the chronology of IVF technology when he wrote:[11]

> The idea of in vitro fertilisation had first been put forward as early as the 1930s, but it was not until the 1950s that anyone managed to fertilise a mammal egg in a test tube. Rabbits were one thing, but, as scientists were

> finding out, the secrets of the human reproductive system proved to be hard-won indeed. Professor Edwards said: 'By 1965 I'd been trying to mature human eggs for the past five years. There was nobody racing against us – nobody had figured any of the ideas of this concept. It took further years of effort to produce a magical figure – 37 hours – the length of time it took for a human egg to become ready for fertilisation after a particular point in a woman's cycle.'

Nearly 200 000 IVF cycles are performed worldwide annually and it has been estimated that more than 1 000 000 children have been born through this technique. Today, advances in IVF technology enable conception and childbirth in couples with conditions that were previously thought to be uncorrectable. Direct aspiration of sperm from the testes, use of gestational carriers for women born without a uterus, and transplantation of frozen ovarian tissue were beyond anyone's wildest imagination in 1978. Advances in genetic diagnosis in concert with information and techniques spun off the human genome project allow the identification of diseased embryos prior to implantation.

THE DEFINITION OF INFERTILITY

There has been considerable debate about an acceptable definition of infertility.[12] First there is confusion about the use of the word itself – 'infertility' which upon translation means 'not fertile' and therefore would be synonymous with sterility. While it is true that all women who are sterile would be considered infertile, the contrary is not true – not all women who are infertile are sterile. Therefore many women would be better categorized as being 'subfertile' instead of infertile. Despite these shortcomings, the all-inclusive term 'infertility' is here to stay and there is little that can be done to change it.

The most succinct definition of infertility has been published by the American Society for Reproductive Medicine Practice Committee:[12]

> Infertility is a disease. The duration of the failure to conceive should be twelve or more months before an investigation is undertaken unless medical history and physical findings dictate earlier evaluation and treatment.

A deficiency of this definition is that there is a lack of clarity as to what is meant by 'failure to conceive'. Obviously this means failure to conceive following unprotected intercourse, but of what degree? The timing and frequency of intercourse greatly impact on a woman's chance of conceiving. However, if one woman has failed to conceive after having intercourse multiple times around the time of ovulation and another woman has failed after having poorly timed intercourse once a month – as long as each woman has tried for 12 months both would be classified as having infertility. The time threshold of 12 months that is needed to substantiate the diagnosis is purely arbitrary. While the financiers of

health-care services have every reason to adhere to this definition, there is reason for health-care providers to have a different perspective. Of those pregnancies that do occur, 78–85% are achieved in the first 6 months of trying.[13] With this in mind one could argue that an evaluation is warranted if the couple has failed to achieve a pregnancy after 6 months of trying. Other reasons to move up the time of the evaluation is when the woman is over the age of 35 or when there is a known or suspected cause of infertility (i.e. anovulation, blockage of the Fallopian tubes, endometriosis, etc.).

EPIDEMIOLOGY

Infertility continues to be a prevalent problem in our society today. Over the past few years, the many issues surrounding infertility have become popular topics in the lay press. This has resulted in an increased awareness of infertility, but has also given the impression that we are amidst an epidemic of this problem. The National Survey of Family Growth performed by the National Center for Health Statistics has provided insight into the prevalence of infertility in the US. This survey has been performed several times since 1965; the most recent survey of over 7000 women was performed in 2002 and the results were published in 2005.[14] The results of the survey, excluding women who were surgically sterile from the final calculation, are as follows:

- 11.3% of married women, or approximately 2.1 million women were infertile.
- The rate of infertility was correlated with age
  - 15–29 7.2%
  - 30–34 10.9%
  - 35–39 10.5%
  - 40–44 20.3%
- The rate of infertility is impacted on by parity (Figure 1.1).
- The overall rate of rate of infertility in 2002 was 11.3% of all women. The rate of infertility has decreased progressively. The rate of infertility in the 1965, 1982, 1988, and 1995 surveys was 13.3, 13.9, 13.7, and 12.0% (Figure 1.2).[15]
- 35% of infertile women presented for medical help within the previous year.
- The incidence of infertility was influenced by race. The incidence in the Caucasian, Hispanic-American, and African-American populations was 10.8, 11.7, and 20.6%, respectively.

Infertility continues to be a persistent problem in the US, but it has implications worldwide as well. The World Health Organization has estimated that infertility affects 50–80 million women worldwide, and this may be an underestimate.[16] In developing countries the incidence of infertility has been estimated to be as high as 50%.[17] One reason for the higher rate of infertility in developing countries is reduced access to medical treatments including antibiotics to reduce the transmission and consequences of sexually transmitted diseases. The ramifications of

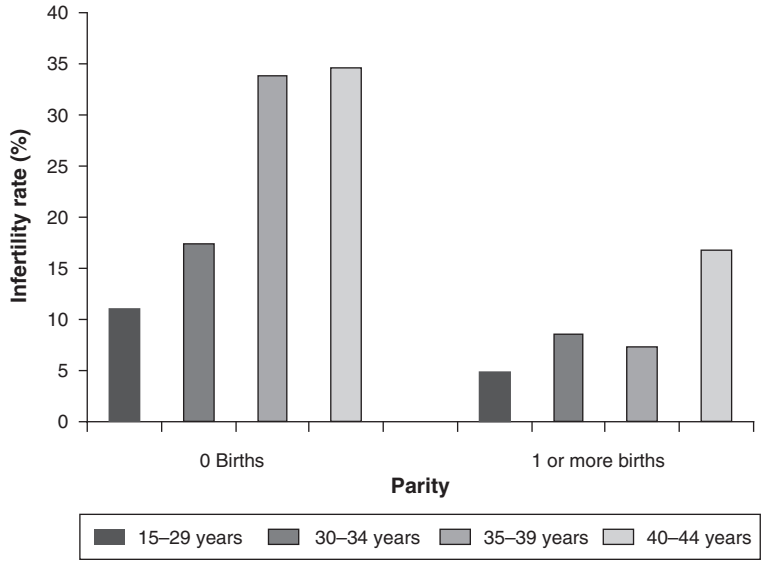

Figure 1.1 Percentage of married women 15–44 years of age with 12 months' infertility, by parity and age: United States, 2002. Note: the calculation of percentage of infertility in age groups did not include women who had undergone a sterilization procedure. Data obtained from the National Survey of Family Growth, 2002[14]

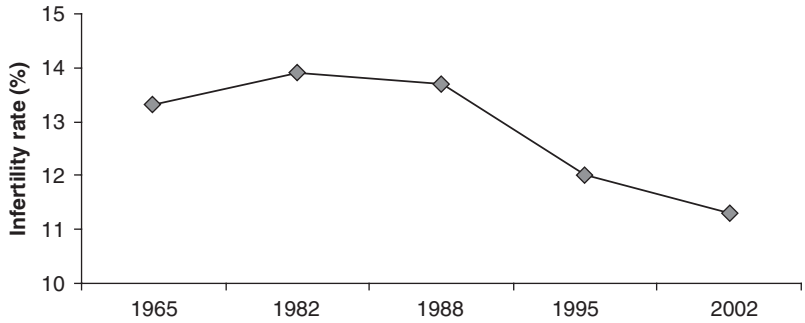

Figure 1.2 This figure shows the percentage of married women 15–44 years of age with 12 months' infertility, from 1965 to 2002. The rate of infertility has decreased over time. From 1982 to 2002 the rate dropped by almost 20% (13.9 to 11.3). Data were obtained from the National Survey of Family Growth, 2002.[14] Those women who were surgically sterile were not included in the final calculation

infertility in these populations are far reaching. Many societies depend on their offspring for survival. In addition, the inability to bear children for some cultures results in a social stigma that can result in loss of social status and violence. The challenge is how to provide infertility services in a cost-effective and accessible

way to all women. However, many countries are less apt to provide infertility services since their ultimate goal may be to control population growth.

ECONOMICS

The total expenditure on infertility services in the United States is estimated to be $2–3 billion per year. While this initially appears to be a significant amount of health-care dollars, it is a fraction of the total money expended on health care in the US, which in 2004 was estimated to be close to $1.7 trillion. Many countries provide infertility services within their national health-care system. However, insurance coverage for infertility treatment in the US is left up to employers and insurance plans which can be influenced by state insurance mandates. Most American women do not have insurance coverage for this medical problem. Presently, only 14 states have mandates that stipulate insurers to pay for infertility coverage, but the degree of coverage, varies from state to state.

How do we achieve broader coverage for infertility services? First, the stigma of infertility must be overcome. Society does not view infertility as a medical problem and considers the treatment to be elective, likened to plastic surgery. It is paradoxical that, as a society, there are no qualms about paying for the medical expenses for individuals who have been irresponsible and caused themselves harm with smoking or alcohol abuse. In contrast, for infertile couples, irresponsible behavior is not a cause of their plight. The solution is to establish infertility as a medical diagnosis. Some states have already done this to some degree, but we have to get other states to follow suit. The federal government has also taken a stand – in 1998, the Supreme Court ruled that reproduction is a major life activity under the American with Disabilities Act.

The other misconception that must be overcome is that the costs of infertility treatment are a drain on the health-care system. This is in part fueled by the costly price tag of some of the treatments. For instance, the cost of an *in vitro* fertilization (IVF) cycle can range from $5000 to $15 000. However, since those seeking IVF treatment are only a small percentage of the population, the expense of treatment has minimal impact on society, namely the insurance companies. In a previous publication Griffin and Panak reported on the impact of infertility expenditures on Health Maintenance Organizations (HMOs) in Massachusetts, where infertility coverage is a mandated benefit.[18] Infertility expenditures amounted to only 0.41% of total expenditures by the HMOs. This translates into an additional cost of $1.71 to each member per month. While this is an added minimal expense, there may be substantial savings to the insurance company to cover IVF related services, since high order multiple pregnancies which are extremely costly are more likely to occur with other treatments. The truth is that infertility coverage is an inexpensive benefit for the insurance companies to bear. Fortunately, the national trend in the US is for more states to have mandates to cover this disease state. For example, New York, New Jersey, and Connecticut

recently passed laws including infertility coverage to some degree. These are important steps in the right direction.

The consequences of fertility treatments, namely multiple pregnancies, also pose a cost to society. The utilization of fertility treatments including ovulation induction drugs (with and without inseminations) and IVF has resulted in a significant increase in the number of multiple pregnancies. There is special concern over high order multiple pregnancies (triplets and more) which have a higher rate of complications. The rate of high order multiple pregnancies has quadrupled from 1980 to 1997 (37 vs 174 per 100 000 live born infants).[19] This is no doubt the result of an increased number of patients seeking infertility treatments. While IVF success rates have continued to increase, most couples opt to transfer multiple embryos to increase their chance of success. This is more likely to occur if the couple is paying out of pocket for the treatment, which will limit the number of cycles they can afford. A previous report demonstrated that the multiple pregnancy rates were lower in states that had laws in place to provide IVF coverage (38 vs 43%).[20]

The impact of a high order multiple pregnancy is immense. There is an increased risk of maternal and fetal complications, with the most significant complication being prematurity and its attended consequences. Babies born from a triplet pregnancy have a 20% chance of a major handicap, a 17-fold increase in cerebral palsy, and a 20-fold increase in death during the first year after birth (as compared to a singleton pregnancy).[21] There is a substantial cost to care for these premature infants; the cost estimates in 2005 for a twin, triplet, and quadruplet pregnancy are $79 000, $228 000, and $377 000, respectively.[22] On the bright side, since 1997 there has been a plateau in the number of high order multiple pregnancies (Figure 1.3). In the 1990s there was a concerted effort from the American College of Obstetricians and Gynecologists and the American Society for Reproductive Medicine to develop guidelines to help reduce the number of embryos transferred.[24,25] In addition, the continued progress in the field has produced higher implantation rates, which also has provided a further impetus to reduce the number of embryos transferred without impacting on pregnancy rates.[26] With the continued improvement in outcomes there is now consideration to transferring a single embryo in selected cases.

ETHICS

The right to procreate is an undeniable human right. This is not refuted, but the major question in society today is how far are we willing to go with technology to produce an offspring? The surge in ethical issues no doubt has resulted following the advent of IVF and IVF related procedures. The first IVF success in 1978 was the result of historic work by Drs Patrick Steptoe and Robert Edwards that spanned almost an entire decade. When it became apparent where they were heading with their research, two notable ethicists voiced vehement objections

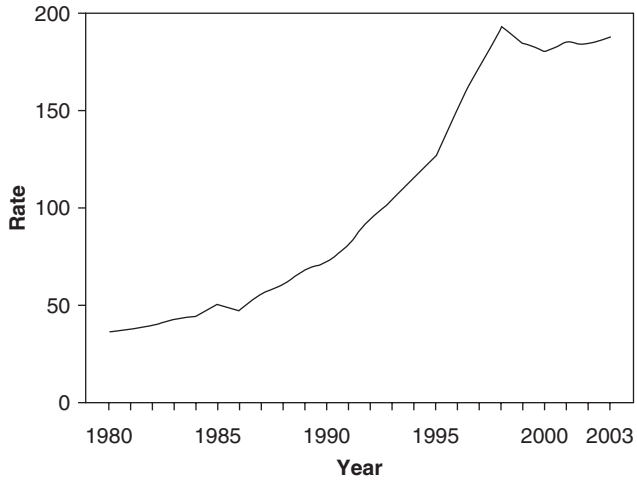

Figure 1.3 Rate of triplet and other higher order multiple births: United States, 1980–2003 (rate per 100 000 live births). From MMWR 2005; 54(41):1058.[23]

over the direction and ultimate goal of their work.[27,28] The ethical concerns primarily focused on the potential harm to offspring that would be born as a result of IVF. The momentum of their work progressed and ultimately resulted in the birth of Louise Brown in 1978. Soon after, hundreds of IVF centers opened up in the United States and abroad. It has been estimated that 1 million babies have been born as a result of IVF technology. There have been multiple studies reporting on the babies born from IVF and there is no documented evidence that IVF increases the risk of birth defects. Therefore, as we look back, the previous ethical concerns about IVF were unfounded. However, IVF was only the beginning and has been a platform for other treatments including egg donation, gestational surrogacy, and preimplantation diagnosis (PGD), which has resulted in new ethical dilemmas.

There are ongoing ethical concerns about third party reproduction arrangements, the most common of which is egg donation. The majority of egg donation arrangements are with anonymous donors. While there may be an element of altruism, an important reason why women donate eggs is financial. Egg donors need to be paid for their services, but how much is too much to pay? Advertisements have appeared in college newspapers recruiting prospective donors with a certain level of intelligence, a particular look, and athletic ability – with price tags up to $50 000–$100 000! These high prices devalue the whole process and liken egg donation to the trading of a commodity. Most in the field regard these practices as improper. Furthermore, the financial enticement significantly weakens the informed consent process of the egg donor. In addition, it may affect the donor in being forthright in providing aspects of her medical and

family history that could disqualify her. The American Society for Reproductive Medicine has addressed this concern and provided some guidelines for fair payment to egg donors. While these guidelines are quite reasonable, the physician many times is not privy to the financial dealings between the recipient couple and the egg donor.

Preimplantation genetic diagnosis is another development of IVF and is now being offered by many IVF centers. The first case of PGD was performed on human embryos in 1992 to screen the embryos for cystic fibrosis.[29] There are now many genetic conditions that can be tested for using PGD. There is no disagreement that PGD should be performed to prevent the potential development of a serious disease, but what about its performance for other reasons? Presently we can assess embryos for their chromosomal makeup, which is beneficial for the woman with repeated miscarriages, the older woman undergoing IVF, or one who is a carrier of a balanced translocation. Usually up to twelve chromosomes are tested including the sex chromosomes. What do we do with the fertile couple who requests PGD for the purposes of sex selection? This brings up several ethical concerns and many IVF centers have taken the stand that they will not offer sex selection. But this is just the beginning; with the mapping of the human genome the fear is that one day a fertile couple presents for IVF and requests that only embryos with genes for intelligence, athleticism, blond hair, and blue eyes be replaced. The possibilities are daunting.

Other ethical questions surround IVF when it is not used for reproductive purposes. We have the ability to support the development of the human embryo in the laboratory to the blastocyst stage. At this stage of development, differentiation of the embryo has occurred into the inner cell mass and trophectoderm. Within the inner cell mass are totipent cells that have the ability to develop into any cell type within the body. In 1998, the first embryonic cell line was developed following the isolation of cells from a blastocyst. The possibilities are immense and these cell lines are now being used to gain a better understanding of disease processes and hopefully will lead to development of new therapies and possibly cures. Where do these embryos come from? Many have voiced concerns about paying egg donors to create these embryos for research purposes only. Another source is spare embryos that are already frozen. It is estimated that 100 000–200 000 human embryos are stored in IVF programs thoughout the US. The fate of most of these embryos is uncertain, but most will not be used by the couple for reproductive purposes. In 2000 Boston IVF was approached by scientists at Harvard University about developing human embryonic stem cell lines from blastocyts. The goal of the work was to better understand the pathogenesis and develop new therapies for Type I diabetes. The research was approved by the Institutional Review Board (IRB). The research is privately funded because federal sanctions prohibit the National Institute of Health (NIH) from funding this type of research. Patients who made a decision to discard their embryos were contacted to see if they would be interested in donating them for this research. The response was overwhelming and many couples have donated their spare

embryos for the research. Several stem cell lines have been developed and the research is currently in progress. There is an ongoing debate in society as to when life begins and whether the use of embryos in this fashion breeches ethical boundaries.

The manipulation of human gametes in the laboratory as part of IVF has also created another possibility which is cloning. Cloning is not a new concept. In the 1950s scientists used this technology to successfully clone salamanders and frogs. In the years that followed the technique was attempted with mammals but was fraught with failure and it was concluded at that time that mammalian cells were too specialized to clone. However, progress in the area continued and in 1996 Campbell et al[30] successfully cloned the first mammal, an adult sheep. To accomplish this feat these researchers took mammary gland cells from an adult sheep and placed them in a culture solution with only minimal nutrients essentially starving the cells and caused shut down of major genetic activity. With an electrical current they were able to fuse a mammary cell with an enucleated egg cell which was then transferred into a host uterus. The initial attempts were met with failure and some abnormal lambs were born and died. Finally after 300 attempts they were successful and 'Dolly' was born. Other mammals have been cloned since including cows, mice, pigs, and horses. There are many benefits to cloning. In the agriculture industry cloning animals allows the creation of better livestock for food production. Cloning animals that have been genetically altered allows the production of human proteins and organs that are suitable for transplantation. Cloning humans may also be beneficial in fighting disease. For instance it may be possible to take normal heart cells from an individual afflicted with heart disease, clone the normal cells and then inject them back into the diseased heart. This may also prove successful in treating those with spinal cord injuries, leukemia, kidney disease and other disorders. However, there is concern that human cloning may be used for reproductive purposes. There are many ethical concerns about human cloning for this purpose and many find simply appalling. Over the past several years, plans have been announced to proceed with human cloning for reproductive purposes. In response, many countries throughout the world have placed a ban on this research. To date there is no federal legislation in the United States placing a ban on the practice, but many states have enacted their own legislation.

REGULATION

There has been a call for the government to step in and regulate the infertility field. One piece of regulation that has been enacted in the US is the Fertility Clinic Success Rate and Certification Act of 1992. The objective behind the bill and ultimately the law is to make IVF units accountable for their statistics and make the statistics available to the consumers. It is now mandatory for all IVF units to submit their statistics to the Centers for Disease Control (CDC) on a yearly basis. The impetus behind this legislation is that these published statistics will allow consumers to compare 'quality' between centers and help them with their selection. Unfortunately, it does everything but accomplish this goal. By the

time the statistics are published they are 2–3 years old and do not reflect the practices of any clinic in the present time. The outcomes are impacted on by a clinic's inclusion and exclusion criteria used for patient selection. For instance, a center can increase their success rate by moving patients more quickly to IVF or discouraging those with a lower than average success rates from undergoing the treatment. In addition, clinics are encouraged to transfer more embryos to increase their rate, but of course this increases the chance of a multiple pregnancy. Furthermore, some IVF centers are misusing their statistics for self promotion and advertising. Quite amazingly, statistics are even being used by insurance companies to determine which centers they will contract with. This is a very poor practice and induces physician practices that are not in the patient or insurance company's interests. Unfortunately, the law is here to stay. There is a move for states to regulate IVF units. Many have enacted legislation dealing with embryo research and cloning and there is reason to believe that they will broaden their regulation in other areas of the specialty. Regulation is common in other countries as well. Many countries limit the number of embryos that are transferred and some have banned egg donation, sperm donation, and gestational surrogacy.

REFERENCES

1. Genesis 1: 28.
2. Genesis 9: 1.
3. Genesis 9: 7.
4. Genesis 16: 1.
5. Genesis 16: 2.
6. From the Aphorisms of Hippocrates. Translated by Francis Adams. Retrieved 5 May 2006 from http: //etext.library.adelaide.edu.au/mirror/classics.mit.edu/Hippocrates/aphorisms.5.v.html.
7. Aristotle. On the Generation of Animals. Translated by Arthur Platt. Retrieved 5 May 2006 from http: //etext.library.adelaide.edu.au/a/aristotle/generation/genani1.html.
8. Spallanzani L. Retrieved 5 May 2006 from http://www.whonamedit.com/doctor.cfm/2234.html.
9. Rubin's test. Encyclopedia Britannica. Retrieved 5 May 2006 from http: //wwwa.britannica.com/eb/article-9064325.
10. Today in Science. Retrieved 5 May 2006 from: http://www.todayinsci.com/cgi-bin/indexpage.pl?http: //www.todayinsci.com/2/2_06.htm.
11. Hutchinson M. Edwards: The IVF Pioneer. BBC News online staff. Retrieved 5 May 2006 from http: //news.bbc.co.uk/1/hi/health/3093429.htm.
12. Habbema JDF, Collins, J, Leridon H et al. Towards less confusing terminology in reproductive medicine: a proposal. Hum Reprod 2004; 19: 1497–501.
13. Definition of 'infertility'. The Practice Committee of the American Society for Reproductive Medicine. The American Society for Reproductive Medicine, Birmingham, Alabama. Fertil Steril 2004; 82 Suppl 1.3.
14. Fertility, family planning and reproductive health of U.S. women: data from the 2002 National Survey of Family Growth. http: //www.cdc.gov/nchs/nsfg.htm.
15. Mosher WD, Pratt WF. Fecundity and Infertility in the United States, 1965–98. Advance Data from Vital and Health Statistics, No 192. Hyattsville, MD: National Center for Health Statistics, 4 December 1990. (PHS) 91–1250. (See http://www.cdc.gov/nchs/products/pubs/pubd/ad/200-151/200-151.htm to download.)

16. World Health Organization. Infertility: a tabulation of available data on prevalence of primary and secondary infertility. Geneva: WHO, Programme on Maternal and Child Health and Family Planning, Division of Family Health, 1991.
17. Cates W, Farley TM, Rowe PJ. Worldwide patterns of infertility: is Africa different? Lancet 1985; 2: 596–8.
18. Griffin M, Panak WF. The economic cost of infertility-related services: an examination of the Massachusetts infertility insurance mandate. Fertil Steril 1998; 70: 22–9.
19. Martin JA, Park MM. Trends in twin and triplet births: 1980–97. National Vital Statistics Report; Vol 47, No 24. Hyattsville, Maryland: US Department of Health and Human Services, CDC, National Center for Health Statistics, 1999.
20. Reynolds MA, Schieve LA, Jeng G, Peterson HB. Does insurance coverage decrease the risk for multiple births associated with assisted reproductive technology? Fertil Steril 2003; 89: 16–23.
21. American College of Obstetricians and Gynecologists. Clinical Management Guideline for Obstetricians and Gynecologists. Multiple gestation: complicated twin, triplet and high order multifetal pregnancy. Number 56, October 2004.
22. ESHRE Capri Workshop Group. Multiple gestation pregnancy. Hum Reprod 2000; 15: 1856–64.
23. Martin JA, Hamilton BE, Sutton PD et al. Births: final data for 2003. National vital statistics report. 2005; 54(2): Hyattsville, MD: National Center for Health Statistics. Available at http://www.cdc.gov/nchs/data/nvsr/nvsr54/nvsr54_02.pdf.
Reynolds MA, Schieve LA, Martin JA et al. Trends in multiple births conceived using assisted reproductive technology, United States, 1997–2000. Pediatrics 2003; III (5 pt2): 1159–62.
24. American Society for Reproductive Medicine. Guidelines on number of embryos transferred. A Practice Committee Report – A Committee Opinion (Revised). American Society for Reproductive Medicine, 1999.
25. American College of Obstetricians and Gynecologists. Nonselective embryo reduction: ethical guidance for the obstetrician–gynecologist ACOG Committee Opinion 215. Washington: American College of Obstetricians and Gynecologists, 1999.
26. Tepleton A, Morris JK. Reducing the risk of multiple births by transfer of two embryos after in vitro fertilization. N Engl J Med 1998; 339(9): 573–7.
27. Kass LR. Babies by means of in vitro fertilization: unethical experiments on the unborn? N Engl J Med 1971; 285(21): 1174–9.
28. Ramsey P. Manufacturing our offspring: weighting the risks. Hastings Cent Rep 1978; 8(5): 7–9.
29. Handyside AH, Lesko JG, Tarin JJ et al. Birth of a normal girl after in vitro fertilization and preimplantation diagnostic testing for cystic fibrosis. N Engl J Med 1992; 327: 905–9.
30. Campbell KHS, McWhir J, Ritchie WA, Wilmut I. Sheep cloned by nuclear transfer from a cultured cell line. Nature 1996; 380: 64–6.

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Factors affecting fertility

Steven R Bayer

There are many known and no doubt countless unknown factors that impact on the human reproductive system. Of the known factors some can be altered, thereby increasing the chances of pregnancy, while others can not. Some of the more important factors that have been studied are discussed below.

MATERNAL AGE

The single most important factor that influences a couple's chance of conceiving is the woman's age. A woman's fertility generally begins to decline after the age of 24 and there is acceleration of the decline after the age of 37 (Figure 2.1). The frequency of intercourse decreases with age but this does not solely account for the decline. In the past there were two theories proposed to explain the decreased fertility including an age related uterine dysfunction and reduced egg quality. There was support for the former theory in the animal model. However, the overwhelming success of egg donation in older women has established that the age related decrease in fertility is the result of declining egg quality.

In one respect, a woman's future fertility is in progressive decline from birth when one considers the contingent of oocytes that reside in the ovaries. Every female is endowed with the highest number of oocytes (6–7 million) *in utero* at 20 weeks of gestation. The eggs are present in the primordial follicles and arrested in prophase of meiosis I. From this time forward atresia sets in and the number of oocytes is reduced to 2 million at birth and 600 000–700 000 at puberty. There is data that suggests that the process of atresia is accelerated between the ages of 37 and 38.[1] While there is evidence in the mouse model that oocytes can undergo mitosis postnatally and be replenished, there is no evidence that this occurs in the human.[2] Up until the time of menopause follicular development is a continuum. For a follicle to progress to ovulation it must be at a critical stage of maturation and rescued by rising FSH levels that only occur for a short period of time during the early follicular phase.

In addition to the reduced number of eggs that occur with aging there is reduced quality of the eggs as well. With aging there is a greater chance that the

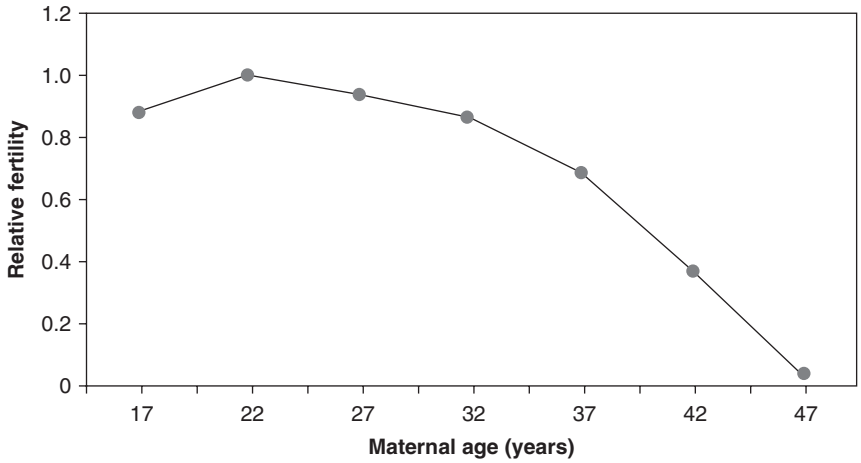

Figure 2.1 Relative fertility is graphed according to maternal age. An odds ratio of 1.0 was assigned to the 20–24 year age group that has the highest fertility rate. The data for this graph were modified from Coale AJ, Trussell TJ. Popul Indes 1974; 40: 185–256

egg released at ovulation has an abnormal chromosomal contingent that results from faulty meiosis. The actual cause of the aneuploidy is poorly understood, but could result from dysfunction of the mitotic spindles and/or a loss of adhesion between sister chromosomes which would interfere with their alignment during meiosis. These chromosomal imbalances can prevent normal fertilization and/or halt early embryonic development. Chromosomal abnormalities explain between 70 and 80% of first trimester losses. Studies performed on embryos resulting from *in vitro* fertilization have confirmed an increased incidence of aneuploidy in eggs obtained from older women.[3] The increased chance of chromosomal errors with advanced maternal age is further supported by the increased rate of spontaneous abortions and chromosomal anomalies in babies born to older women.[4]

PATERNAL AGE

The impact of paternal age on fertility has been the subject of continued debate and the topic of two reviews.[5,6] As do their female counterparts, men experience decreased gonadal function with advancing age. Testosterone production begins to decrease around the age of 40.[7] A male at age 75 has about half of the circulating free testosterone compared to a male in his twenties.[8] Semen parameters also change with aging – there is a decrease in the semen volume, motility, and normal morphology. In a review of prior studies[5,6] it has been suggested that the aging male has reduced fertility that begins in his late thirties and early forties. Despite these changes, the reduction in a man's fertility is subtle and in some men may be insignificant. While a woman's fertility drops precipitously in the fourth decade,

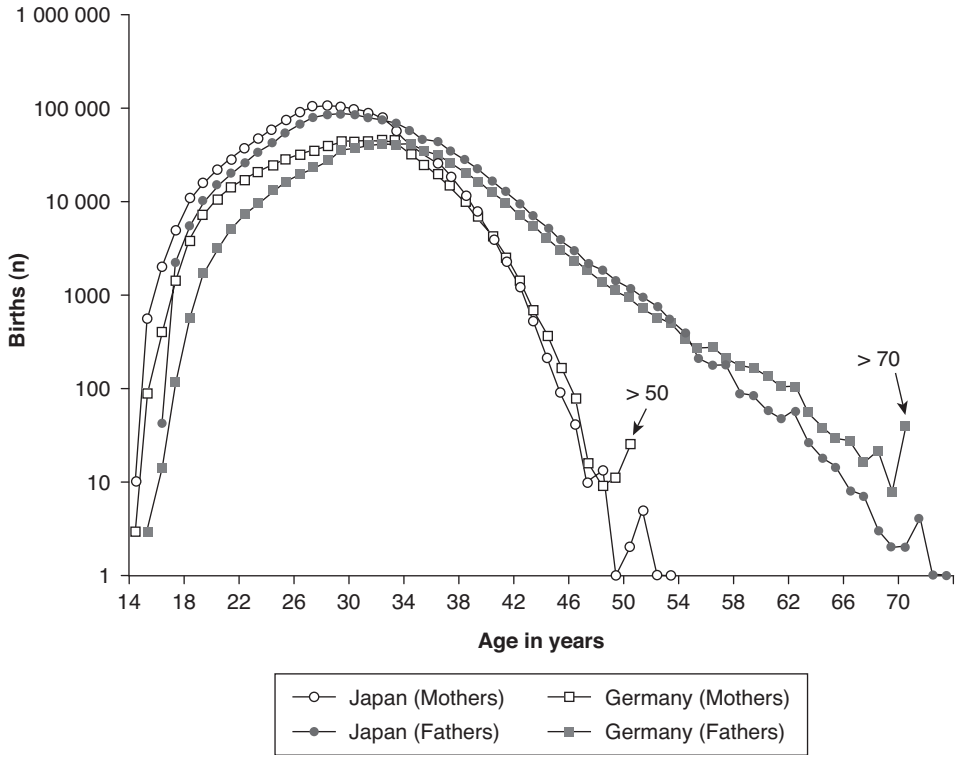

Figure 2.2 Maternal and paternal age at the time of birth of offspring born in Germany (2001; $n = 550\,659$) and in Japan (2002; $n = 1\,135\,222$). Reprinted from Kühnert B, Nieschlag E. Reproductive functions of the ageing male. Hum Reprod Update 2004; 10(4): 327–39. © European Society of Human Reproduction and Embryology. Reproduced by permission of Oxford University Press/Human Reproduction

men can maintain their fertility into their sixties and even later. A significant number of pregnancies are fathered by men over the age of 50 in Japan and Germany (Figure 2.2). The oldest father on record is 94 years of age.[9]

The rate of aneuploidy in oocytes increases with a woman's age and is the cause of most pregnancy losses. Aneuploidy or disomy in sperm may explain some pregnancy losses. The rate of aneuploidy in sperm is 2% and there is no evidence to support an increased rate of aneuploidy involving autosomes in men with advanced age.[10] However, there are data to support an increased risk of disomy involving the sex chromosomes with advanced paternal age.[11]

TIMING OF INTERCOURSE

The establishment of pregnancy is dependent on properly timed intercourse around the time of ovulation. Our patients are always asking about the optimal

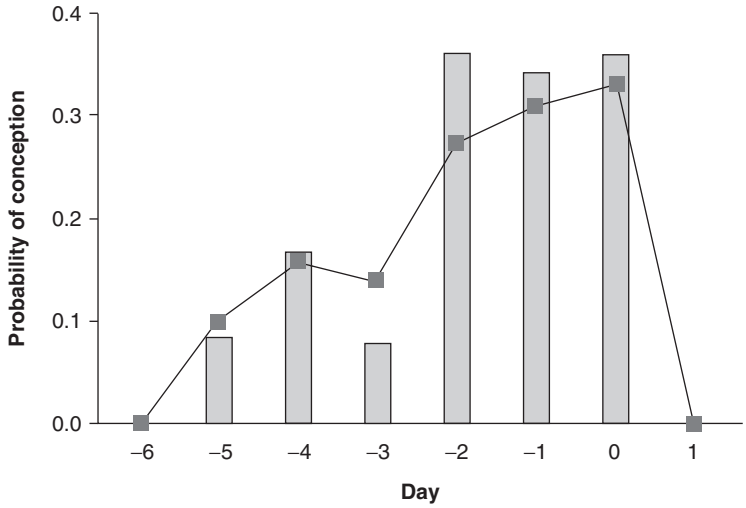

Figure 2.3 The conception rates for 129 menstrual cycles were recorded when intercourse occurred on a single day. The day of ovulation is day 0. No pregnancies resulted when intercourse took place 7 or more days prior to ovulation or after ovulation. The solid line is an estimate by the model for all 625 cycles. Reprinted with permission from Wilcox AJ, Weinberg CR, Baird DD. Timing of sexual intercourse in relation to ovulation. N Engl J Med 1995; 23: 1517–21. Copyright © 1995 Massachusetts Medical Society. All rights reserved

time and frequency of intercourse to maximize their chances. A previous study by Wilcox et al helps to shed light on this issue.[12] The investigators followed 221 women who were attempting pregnancy. All women kept track of the days they had intercourse and collected daily urine samples which were then analyzed to determine the day of ovulation. Conception only occurred when intercourse occurred in a 6 day window that ended with the day of ovulation. The investigators confirmed that the greatest chance of pregnancy was when intercourse occurred beginning 2 days prior to ovulation (Figure 2.3). However some pregnancies occurred when a single act of intercourse took place 5 days before ovulation. No pregnancies were achieved if intercourse only took place after ovulation occurred. The investigators also looked at how the frequency of intercourse impacted on conception. The greatest chance of pregnancy was when intercourse occurred 2–3 times during the 6 day time frame. Of interest is that lower pregnancy rates were noted when the frequency of intercourse was 4–6 times during the fertile period.

DURATION OF ATTEMPTING PREGNANCY

The monthly fecundity rate in the general population has been estimated to be between 15 and 20%, which is influenced by age. A study by Schwartz and

Mayaux reported on the cumulative pregnancy rates in 2193 women undergoing donor insemination.[13] The cumulative pregnancy rates after 12 months in the <31, 31–35, and >35 age groups were 73, 61, and 54%, respectively.[13] Between 78 and 85% of pregnancies that are achieved occur in the first 6 months of trying.[14] Taking this into consideration, if a couple has failed to achieve pregnancy after 6 months it seems justified to perform an infertility evaluation and even consider treatment – especially if the woman is over the age of 35. An evaluation may be indicated sooner if there is an obvious or known cause of the infertility (i.e. anovulation, blockage of the Fallopian tubes, etc.).

OTHER FACTORS THAT IMPACT ON FERTILITY

Previous contraception

From the most recent National Survey of Family Growth the contraceptive agents used by US women were as follows: oral contraceptives 53.2%, barrier methods 32%, injectables 9.2%, and intrauterine devices (IUDs) 2.8%.[15] The IUD was a popular method of contraception in the 1970s but one IUD in particular, the Dalkon shield, was linked to a higher risk of pelvic inflammatory disease (PID), which increases the chance of tubal factor infertility. The design of the Dalkon shield was the problem and it was subsequently taken off the market and the popularity for the IUD waned, but it continues to be an effective and safe method of contraception. A meta-analysis concluded that the risk of PID after insertion of an IUD is low, but is more prevalent during the first month after insertion, when there is a 6 fold increase.[16] The IUD is considered an option for women who have a low risk for sexually transmitted diseases.

The impact of other contraceptive agents on future fertility has been a topic of debate. Hassan and Killick reported on the results of a survey of 2841 women who presented to antenatal clinic.[17] They analyzed in the study population the time to pregnancy (TTP) for different contraceptive agents that were discontinued. They concluded that TTP was affected by the type of contraception that was previously used. The TTP for the condom, oral contraceptives, IUD, and injection was 4.6, 7.6, 7.5, and 13.6 months, respectively. The TTP results were also affected by the length of use of the oral contraceptive agents and the injectable progestational agent. For women who used oral contraceptives the TTP was increased to 8.9 months if it was used for >4 years. For those women who used the injectable contraceptive agents the TTP for <1, 1–2, and 2–4 years was 4.5, 11.2, and 19.1 months, respectively.

Occupational hazards

Chemical exposures can either result from an environmental exposure or more likely exposure in the workplace. The Occupational Safety and Health Administration (OSHA) regulates the workplace to insure safety for all employees.

Table 2.1 Chemical agents that have been shown to alter sperm production

Lead	Dibromochloropropane (DBCP)
Carbaryl	Toluenediamine
Dinitrotoluene	Ethylene dibromide
Welding	Ethylene glycol monoethyl ether
Perchloroethylene	Kepone
Bromine vapor	2,4–Dichlorophenoxy acetic acid

Their primary focus is on potential exposures as they relate to general health but they have identified a number of agents that impact on reproductive health, as well. It is well established that exposure to nitrous oxide (N_2O) is associated with reduced fertility and spontaneous abortion.[18] Since dentists are less likely to have scavenging equipment in their offices, dental hygienists may be at particular risk.[19] Exposure to other work related chemicals (e.g. cadmium, mercury, and dry cleaning chemicals) has also been reported to decrease fertility in women.

The male is more susceptible to environmental toxins since spermatogenesis is an ongoing and dynamic process. The first report of an occupationally related spermatotoxin appeared in the mid-1970s.[20] It showed that men who worked at factories which produced dibromochloropropane (DBCP, a pesticide) had an increased incidence of infertility – the severity being dependent on the dose and length of exposure. Since this report was released, other spermatotoxins have been identified that are listed in Table 2.1.

Diet

There are no data to suggest that any particular diet per se can impact on fertility. However, the consequences of an inadequate diet with extremes of body weight can alter ovarian function and predispose women to infertility. Women with a BMI < 19 or body fat contact < 22% are at risk for hypothalamic dysfunction. At the other extreme, women with increased body weight may have associated polycystic ovarian syndrome which can cause ovulatory dysfunction. There is growing evidence that increased body weight itself may reduce fertility aside from its impact on ovulatory function. In a study published by Boston IVF, Ryley et al performed a retrospective study of over 6000 IVF cycles.[21] The conclusion was that, with advanced body weight, there is a statistically significant drop in implantation and pregnancy rates.

Lifestyle habits

There are many lifestyle habits that can impact our general health and there is reason to believe that they may also impact on fertility.

Smoking

Of all of the lifestyle issues smoking is the most significant. Smoking is a confirmed reproductive toxin. The deleterious effects of smoking during pregnancy are well established. Several published studies have demonstrated that smoking in women is associated with decreased fertility.[22,23] Smoking reduces a woman's chances of conceiving by almost half. Smoking can alter ovarian function in a number of ways.[24] The chemicals in smoke stimulate the hepatic metabolism of steroid hormones, thereby reducing their levels in the blood stream. *In vitro* studies have demonstrated that the chemicals in smoke alter the enzymes that are necessary for ovarian hormone production. Finally, women who smoke generally go through an earlier menopause by 1–2 years, suggesting that the chemicals in smoke may be directly toxic to the ovaries. It is not known whether this is due to a direct action on the ovaries or indirectly through an alteration of the blood flow to the ovary. The published data are compelling enough to advise all women who smoke to stop to improve their fertility.

Caffeine

Caffeine use has been associated with an increased risk of pregnancy loss.[25] There have been several reports linking a woman's caffeine intake to decreased fertility when controlling for other factors.[26,27] A dose-dependent relationship has been confirmed which suggests that any amount of caffeine consumption could be detrimental to fertility.

Alcohol

The ill-effects of alcohol on pregnancy are well established. However, the influence of alcohol on fertility has not been well studied. In 1998 two separate studies were published that examined the impact of alcohol on the establishment of pregnancy.[28,29] Both studies arrived at the same conclusion that alcohol, in a dose-dependent fashion, reduced the chance of a conception in the study populations. There are no published data that suggest that moderate alcohol use affects male reproduction.

A study by Hassan and Killick lends further support that a healthy lifestyle improves fertility.[30] The investigators looked at the combined effects of lifestyle issues on the establishment of a pregnancy. Over 2000 women who presented for prenatal care were asked about lifestyle issues and then the investigators determined the time to pregnancy (TTP). The investigators confirmed that the TTP was delayed if the woman or her partner smoked, the partner consumed >20 units of alcohol per week, caffeine intake was >6 drinks per day, and the woman's BMI was >25 kg/m^2. Since many couples had multiple factors the authors calculated the cumulative pregnancy rate when more than one factor was present (Figure 2.4).

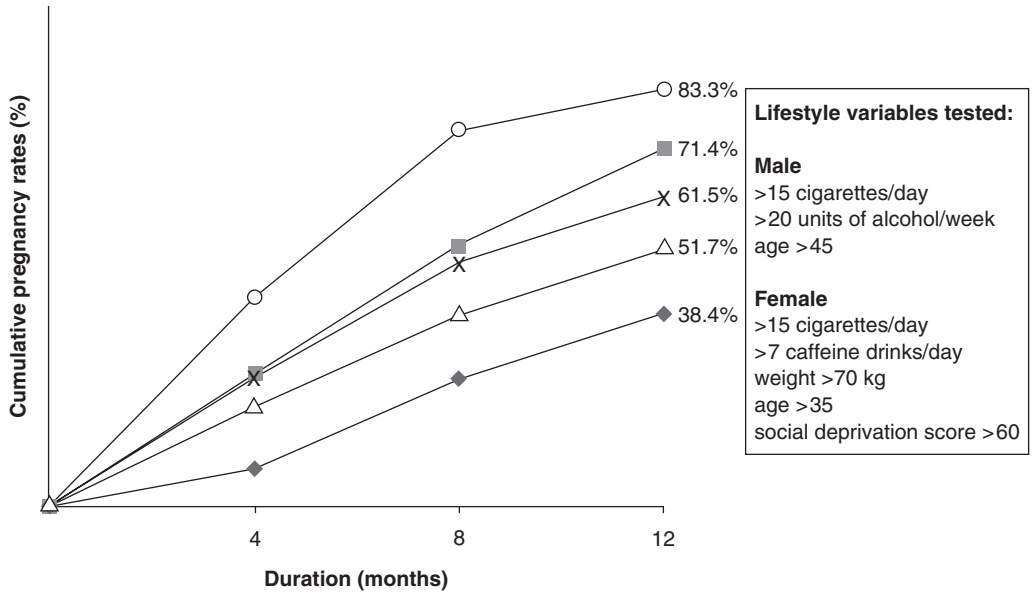

Figure 2.4 The effect of increasing numbers of lifestyle issues on the cumulative pregnancy rates within 1 year for a pregnant population. The lifestyle variables are presented in the box adjacent to the graph. Each line is the cumulative pregnancy rate for subgroups with different numbers of negative lifestyle variables: ○ No negative variables; ■ 1 negative variable; X 2 negative variables; Δ 3 negative variables; ♦ 4 or more negative variables. Reprinted from Hassan MAM, Killick SR. Negative lifestyle is associated with a significant reduction in fecundity. Fertil Steril 2004; 81: 384–92. With permission from the American Society for Reproductive Medicine

Stress and anxiety

There continues to be an ongoing debate about the role of stress in infertility. Lingering questions continue: Is stress a cause of infertility? Can stress decrease a woman's chance of pregnancy while undergoing treatment? For those patients who are stressed, what interventions are effective? There is no doubt that most patients who are seen at fertility clinics are stressed. For some patients the stress and/or anxiety preceded their desire for pregnancy, whereas for others it worsened or developed as a reaction to the disappointment of their situation. The stress associated with infertility is intense and is similar to the stress associated with a serious medical condition, such as cancer or HIV. It has been reported that up to 40% of infertile women have anxiety and/or depression.[31] This is significant when one considers the 3% incidence of anxiety/depression in the general population.

Does the stress prevent a patient from achieving pregnancy? Many of us have first hand stories about the patient who conceives after a relaxing vacation, or the woman who has battled years of infertility and proceeds with a successful adoption, then is surprised to learn she has achieved pregnancy on her own. These

situations no doubt raise suspicion. While it may be difficult to prove that stress is a cause of infertility there are data to suggest that it may reduce the chance of success with treatment. In a recent review most of the published studies examining this issue confirmed that anxiety and stress reduced a patient's chance of success with treatment.[32] In a recent publication[33] the largest investigation to date reported on a prospective study that involved 818 couples who were screened with a stress inventory at the start of treatment and then 12 months later treatment outcomes were determined. After controlling for female age and years of infertility the authors concluded that female and male stress affected the outcome of the treatment.

There are different interventions we can offer our patients to counter the stress. Those that offer cognitive-behavioral intervention seem to be the most effective in decreasing anxiety and improving success rates.[34,35] While significant progress has been made, further research is needed to provide a better understanding of the role of stress.

REFERENCES

1. Faddy MJ, Gosden RG, Gougeon A et al. Accelerated disappearance of ovarian follicles in mid-life: implications for forecasting menopause. Hum Reprod 1992; 7: 1342–6.
2. Johnson J, Canning J, Kaneko T et al. Germline stem cells and follicular renewal in the postnatal mammalian ovary. Nature 2004; 428: 145–50.
3. Munne S, Alikani M, Tomkin G et al. Embryo morphology, developmental rates and maternal age are correlated with chromosome abnormalities. Fertil Steril 1995; 64: 382–91.
4. Hook EB, Cross PK, Schreinemachers DM. Chromosomal abnormality rates at amniocentesis and in live-born infants. J Am Med Assoc 1983; 249: 2034–8.
5. Kidd SA, Eskenzazi B, Wyrobek AJ. Effects of male age on semen quality and fertility: a review of the literature. Fertil Steril 2001; 75: 237–48.
6. Kühnert B, Nieschlag E. Reproductive functions of the ageing male. Hum Reprod Update 2004; 10(4): 327–39.
7. Vermeulen A. Androgens in the aging male. J Clin Endocrinol Metab 1991; 73: 221–4.
8. Goemaere S, Van Pottelbergh I, Zmierczak H et al. Inverse association between bone turnover rate and bone mineral density in community-dwelling men >70 years of age: no major role of sex steroid status. Bone 2001; 29: 286–91.
9. Seymour FI, Duffy C, Koerner A. A case of authenticated fertility in a man, aged 94. J Am Med Assoc 1935; 105: 1423–4.
10. Luetjens CM, Rolf C, Gassner P et al. Sperm aneuploidy rates in younger and older men. Hum Reprod 2002; 17: 1826–32.
11. Lowe X, Eskenazi B, Nelson DO et al. Frequency of XY sperm increases with age in fathers of boys with Klinefelters syndrome. Am J Hum Genet 2001; 69: 1046–54.
12. Wilcox AJ, Weinberg CR, Baird DD. Timing of sexual intercourse in relation to ovulation. N Engl J Med 1995; 23: 1517–21.
13. Schwartz D, Mayaux MJ. Female fecundity as a function of age: results of artificial insemination of 2193 nulliparous women with azoospermic husbands. Federation CECOS. N Engl J Med 1982; 306(7): 404–6.
14. Ford WCL, North K, Taylor H et al. Increasing paternal age is associated with delayed conception in a large population of fertile couples: evidence for declining fecundity in older men. Hum Reprod 2000; 15: 1703–8.

15. Fertility, family planning and reproductive health of U.S. women: data from the 2002 National Survey of Family Growth. http: //www.cdc.gov/nchs/nsfg.htm.
16. Grimes DA, Schulz KF. Antibiotic prophylaxis for intrauterine contraceptive device insertion (Cochrane Review). In: The Cochrane Library, Issue 3. Chichester, UK: John Wiley & Sons, 2004.
17. Hassan MAM, Killick SR. Is previous use of hormonal contraception associated with a detrimental effect on subsequent fecundity? Hum Reprod 2004; 19: 344–51.
18. Cohen EN, Gift HC, Brown BW et al. Occupational disease in dentistry and chronic exposure to trace anesthetic gases. J Am Dent Assoc 1980; 101: 21–31.
19. Rowland AS, Baird DD, Weinber CR et al. Reduced fertility among women employed as dental assistants exposed to high levels of nitrous oxide. N Engl J Med 1992; 327(14): 993–7.
20. Cohen EN, Bellville JW, Brown BW Jr. Anesthesia, pregnancy and miscarriage: a study of operating room nurses and anesthetists. Anesthesiology 1971; 35: 343–7.
21. Ryley DA, Bayer SR, Eaton A et al. Influence of body mass index (BMI) on the outcome of 6827 IVF cycles. Fertil Steril 2004; 82: S38–S39.
22. De Mouzon J, Spira A, Schwartz D. A prospective study of the relation between smoking and fertility. Int J Epidemiol 1988; 17: 378–84.
23. Bolumar F, Olsen J, Boldsen J. Smoking reduces fecundity: a European multicenter study on infertility and subfecundity. European Study Group on Infertility Subfecundity. Am J Epidemiol 1996; 143: 578–87.
24. Smoking and Women's Health. Education Bulletin, Number 240. American College of Obstetricians & Gynecologists, 1997.
25. Tolstrup JS, Kjaer SK, Munk C et al. Does caffeine and alcohol intake before pregnancy predict the occurrence of spontaneous abortion? Hum Reprod 2003; 18: 2704–10.
26. Hatch EE, Bracken MB. Association of delayed conceptions with caffeine consumption. Am J Epidemiol 1993; 38: 1082–92.
27. Bolumar F, Olsen J, Rebagliato M, Bisanti L. Caffeine intake and delayed conception: a European multicenter study on infertility and subfecundity. European Study Group on Infertility Subfecundity. Am J Epidemiol 1997; 145: 324–34.
28. Jensen TK, Hjollund NHI, Henriksen TB et al. Does moderate alcohol consumption affect fertility? Follow up study among couples planning first pregnancy. Br Med J 1998; 317: 505–10.
29. Hakim RB, Gray RH, Zacur H. Alcohol and caffeine consumption and decreased fertility. Fertil Steril 1998; 70: 632–7.
30. Hassan MAM, Killick SR. Negative lifestyle is associated with a significant reduction in fecundity. Fertil Steril 2004; 81: 384–92.
31. Chen TH, Chang SP, Tsai CF, Juang KD. Prevalence of depressive and anxiety disorders in an assisted reproductive technique clinic. Hum Reprod 2004; 19: 2313–18.
32. Domar AD. Infertility and the mind/body connection. The Female Patient 2005; 30: 24–8.
33. Boivin J, Schmidt L. Infertility-related stress in men and women predicts treatment outcome 1 year later. Fertil Steril 2005; 83(6): 1745–52.
34. Tuschen-Caffier B, Florin I, Karuse W, Pook M. Cognitive-behavioral therapy for idiopathic infertile couples. Psychother Psychosom 1999; 68: 15–21.
35. Domar AD, Clapp D, Slawsby EA et al. Impact of group psychological interventions on pregnancy rates in infertile women. Fertil Steril 2000; 73: 805–11.

3.

The infertility workup

Steven R Bayer and Michael M Alper

INTRODUCTION

A complete infertility workup is a prerequisite before a treatment plan can be developed. The workup has changed dramatically over the years. In the past, the testing could span several months and entailed numerous tests that in retrospect were unreliable and are now considered unnecessary. Presently the workup is streamlined, focused, and can be completed within a month so that treatment can be started expeditiously. This chapter will review our approach to the workup of the infertile couple.

OBJECTIVES OF THE INITIAL INTERVIEW

Since infertility is a problem that affects the couple, it is important that both partners are present for the initial interview and when decisions are made regarding treatment. Like any doctor–patient relationship it is important to establish good rapport but this is even more critical when one is caring for the infertile couple. As a result of the psychologic component that accompanies this diagnosis, patients with infertility require a much more demanding relationship than is typically required with other gynecologic patients. The initial consultation is an extremely important encounter and an adequate amount of time (30–60 min) should be spent with the couple. There are several objectives of the initial interview, which are described below.

Determine the necessity of an evaluation

The first step is to make sure that an evaluation is indicated. The physician must determine whether the couple has had well timed intercourse and whether they have been trying for a sufficient duration of time. Although the classic definition of infertility is the lack of pregnancy after 1 year of unprotected intercourse, it is appropriate to initiate an evaluation after 6 months of infertility, or sooner if the woman is older (> 35 years of age), or when there is an obvious cause of the infertility (ovulatory dysfunction, known tubal disease, endometriosis, etc.). In fact,

about 75% of couples will achieve pregnancy after 6 months of unprotected intercourse and this only increases to 85% by 12 months. So, inability to conceive by 6 months is a 'red flag'.

Educate the couple

It is important to educate the couple on normal reproductive function. For many couples the last time they had formal instruction on reproduction was in high school during sex education classes and much of their current knowledge may not be factual. Diagrams may be helpful in achieving the education process. A basic knowledge of the normal reproductive process helps the couple better understand the various causes of infertility, the rationale of the evaluation, and the treatment that may be recommended. It is also important to emphasize to the couple that our reproductive systems are inefficient and even in optimal situations a normal fertile couple can only expect a 15–20% chance of pregnancy per month. This will help them put treatment success rates in the right perspective.

Identify risk factors

Another objective of the initial interview is to identify risk factors that may explain the infertility and provide focus to the workup. A history of irregular menstrual cycles is suggestive of an ovulatory problem. Previous use of an IUD, a history of a tubal pregnancy, or a pelvic infection can raise suspicion of a tubal factor. Complaints of worsening dysmenorrhea or dyspareunia may suggest the presence of endometriosis. Previous cryosurgery, conization, or the Loop Electrosurgical Excision Procedure (LEEP) of the cervix increases the chance of a cervical factor.

Preconceptional care

An important part of the initial consultation is a discussion on preconceptional care. This involves a review of medical, environmental, nutritional, social, and genetic issues that may impact on fertility and complicate the outcome of a pregnancy. In some cases, the particular issue of concern must be investigated before proceeding with any treatment. An in-depth discussion of preconceptional care appears in Chapter 4 of this book.

Psychological assessment

At some point during the initial interview the couple should be queried about how they are dealing with the stress of their plight. Patients always put on their best faces when in front of the physician, but when they are asked about the stress many times it becomes quite apparent that it is significant. It should be

emphasized that all couples experience stress to some degree and those that say they don't are most likely in denial. For many couples infertility may be the most stressful situation that they have had to deal with in their lives. The clinician should have mental health professionals that the couple can be referred to. In some cases a referral may be indicated early in the process, even before the testing is initiated.

Treatment plan

At the end of the consultation, a plan for evaluation should be discussed with the couple. The couple should have a good understanding about the scope of the evaluation and the rationale for the tests that have been selected. Since most patients will be unable to absorb and remember all that was discussed, written material should be given to the couple describing the tests that will be performed. Finally, the couple should be given an estimate of the length of time to complete the evaluation and when to schedule a follow-up appointment to discuss the results and begin discussions about treatment.

CAUSES OF INFERTILITY

The objective of the infertility evaluation is to identify specific cause(s) of the infertility, which will allow the clinician to administer the appropriate treatment (Figure 3.1). In the past, the infertility evaluation involved performing several tests including the semen analysis, hysterosalpingogram (HSG), postcoital test, endometrial biopsy, and a laparoscopy. During the course of the evaluation it was not uncommon that the postcoital test and endometrial biopsy were repeated multiple times; however, published studies have confirmed that the postcoital test and endometrial biopsy are unreliable and do not differentiate between fertile and infertile populations. Similarly, it was also common practice to perform a laparoscopy routinely before any therapy was started. However, we now realize that, in most cases, the findings at the time of the laparoscopy do not change the course of recommended treatment. To this end, the infertility evaluation has been redefined and is now more efficient, informative, and cost-effective (Table 3.1). A discussion of the various causes of infertility and the current infertility evaluation is presented. The reader is also referred to Chapter 5 where clinical algorithms are presented.

Ovarian function

One of the first steps in the infertility evaluation is to assess ovarian function. Significant information can be obtained from the menstrual history including the age at menarche, frequency of menstrual cycles in the present and past, and the duration of menstrual flow. Important aspects of ovarian function related to fertility are discussed below.

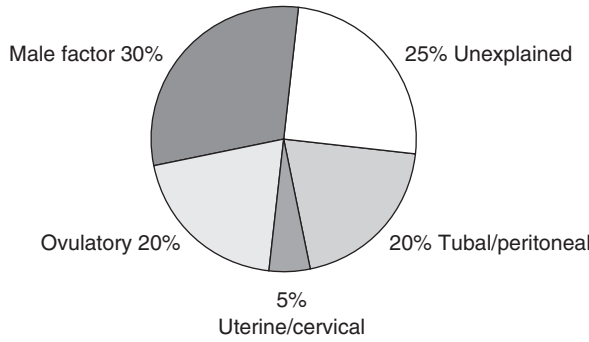

Figure 3.1 Causes of infertility

Table 3.1 The present day infertility evaluation

Semen analysis
Cycle day 3 FSH/estradiol
Hysterosalpingogram (HSG)
Preconceptional care
Laparoscopy (optional)

Determination of whether ovulation is occurring

If a woman is having regular menstrual cycles that are 23–39 days in length then she is most likely ovulating. This is further supported if the bleeding is preceded by premenstrual symptoms (i.e. water weight gain, breast tenderness, and mood changes). If there is any doubt about a woman's ovulatory status, then a simple inexpensive test is to have her keep a daily record of her temperature (BBT, basal body temperature record). The progesterone that is secreted by the corpus luteum during the luteal phase acts on the temperature regulating center in the hypothalamus, causing an increase in the basal temperature from 0.5 to 1.0° F. Previously women were instructed to take temperature readings upon wakening; however, the temperature can be taken at other times of the day as long as it is done on a consistent basis. Another way to confirm ovulation is with the ovulation predictor kits that are widely available. Finally, a serum progesterone level greater than 3 ng/ml is yet another confirmatory test that ovulation has taken place.

Assessment of ovarian reserve

During a woman's lifetime, the maximum number of oocytes (approximately 6–7 million) residing in the follicles is present *in utero* at 20 weeks of gestation.

From that time forward and throughout a woman's lifetime there is a continuum of ovarian follicular development that occurs and if the follicle at its critical stage of development is not rescued by a threshold level of follicle stimulating hormone (FSH) (which only occurs during the early follicular phase) it undergoes atresia. The decrease in the number of oocytes is significant – at birth the number is decreased to 1–2 million and at puberty to 600 000–700 000. Less than 0.01% of eggs a woman is endowed with ever have a chance of ovulating. Ultimately, there is total depletion of the oocytes and menopause occurs. It must be realized that menopause is not an abrupt process but represents an end-point of a transitional process that spans several years. One of the first changes that a woman can notice as she approaches menopause is a gradual shortening of the menstrual cycle, which is the result of a shorter follicular phase. In addition, early follicular phase FSH and estradiol levels also can identify women who are starting to approach the menopausal transition. Assessment of ovarian reserve is an important part of the infertility workup and there are several ways to accomplish it, as described below.

1. ***Basal FSH and estradiol*** The most common and easiest means of testing ovarian reserve is measurement of FSH and estradiol levels between cycle days 2 and 4. To interpret the FSH level, an estradiol level must also be done since an elevated estradiol through negative feedback can suppress the FSH level to the normal range. If the FSH level is >10 mIU/ml or the estradiol is >70 pg/ml then it can be concluded that the woman has reduced ovarian reserve (Table 3.2). There can be cycle to cycle variation in the FSH and estradiol levels but a single elevation is predictive of reduced ovarian reserve.
2. ***Clomiphene citrate challenge test (CCCT)*** The CCCT is a dynamic test used to examine ovarian reserve. Clomiphene citrate is a weak estrogen agonist/antagonist that binds to estrogen receptors in the hypothalamus which results in the release of FSH and luteinizing hormone (LH) from pituitary gonadotrophs. The test is performed as follows:
   - Cycle day 3 FSH and estradiol levels;
   - Clomiphene citrate 100 mg daily between cycle days 5–9;
   - Cycle day 10 FSH level.

If either one of the FSH levels is greater than 10 mIU/ml or the day 3 estradiol is greater than 70 pg/ml, it can be concluded that the ovarian reserve is reduced. The CCCT can be more informative since 75% of women with reduced ovarian reserve have a normal cycle day 3 hormone assessment. We generally use this test in all women over the age of 40 and younger women when indicated (family history of premature ovarian failure, previous ovarian surgery, and short menstrual cycles).

3. ***Antral follicle count (AFC)*** Assessment of the AFC by vaginal ultrasound has evolved into another test to evaluate ovarian reserve and was reviewed in a recent publication.[1] A vaginal ultrasound is performed on cycle day 3 and the number of antral follicles is determined. The definition of an antral follicle

Table 3.2 Interpretation of cycle day 3 hormone levels

Follicle stimulating hormone level (mIU/ml)*	*Estradiol level† (pg/ml)*	*Ovarian reserve*
> 10	< 70	reduced
> 10	> 70	reduced
2–10	> 70	reduced
2–10	< 70	normal

*Normal FSH level 2–10 mIU/ml; †normal estradiol level < 70 pg/ml

has not been standardized. Some investigators have considered an antral follicle to be between 2 and 5 mm, while others have used the maximum diameter up to 10 mm. If a center uses this method then it must be standardized and correlated with their outcome. Hendriks et al[1] published a meta-analysis on the AFC and confirmed that AFC is superior to the cycle day 3 FSH level in predicting ovarian response. However, neither test was good at predicting failure to establish a pregnancy.

4. ***Exogenous FSH ovarian reserve test (EFORT)*** This test was described by Fanchin et al.[2] The test is performed as follows: on cycle day 3 FSH and estradiol are checked and the patient is given a single injection of FSH 300IU. On cycle day 4 the estradiol level is measured. The authors defined normal ovarian reserve as an FSH level <11 mIU/mL and estradiol >30 pg/ml. This test has not been extensively investigated and it is not widely used in the clinical setting.

How do we counsel the woman who has reduced ovarian reserve? In the past as we were getting a handle on the concept of ovarian reserve it was not uncommon that a patient with an FSH level over a certain threshold was not allowed to undergo treatment with IVF. However, an elevated FSH level in the 42-year-old woman with unexplained infertility means something different than an elevated FSH level in the 25-year-old woman. A publication by Abdalla and Thum helps to put this into better perspective.[3] The investigators reported on 2057 patients who underwent their first IVF cycle. The policy in their clinic was that all women with regular menstrual cycles were considered candidates for IVF treatment. There were several conclusions from their study:

1. An elevated FSH level (irrespective of age) was associated with a reduced pregnancy rate.
2. The fertilization rate was not affected by the FSH level.
3. The chance of a pregnancy loss was dependent on age not the FSH level.
4. An elevated FSH level is indicative of oocyte number not quality.
5. A younger woman with an elevated FSH had a significantly higher chance of a successful pregnancy as compared to the older woman with a normal FSH level (21.2% vs 12.1%).

Ovarian reserve testing is an important part of the infertility evaluation but the results of the testing should not be used solely in the determination of whether to allow a patient to undergo treatment. While this information is helpful in the counseling of patients there are other factors including age, previous response to ovarian stimulation, and prior outcome of treatment that must be taken into consideration.

Evaluation of the woman with ovulatory dysfunction

Ovulatory dysfunction is present in a woman who has menstrual cycles that are out of the normal range (25–35 days). The initial workup should include measurement of thyroid stimulating hormone (TSH), prolactin, and cycle day 3 FSH and estradiol levels. Prolactin levels fluctuate throughout the day, reaching a nadir in the morning, and tend to be higher in the luteal phase. Therefore, it is important that the prolactin determination be performed on a morning follicular phase blood sample. If the woman has symptoms of hyperandrogenism, then additional testing is indicated. This should include a determination of testosterone, dehydroepiandrosterone sulfate (DHEAS), and 17-hydroxyprogesterone (17-OHP) levels. The 17-OHP determination should also be performed on a morning follicular phase blood sample. There is substantial evidence that insulin resistance is a cause of polycystic ovarian syndrome (PCOS). There is no reliable way to diagnose insulin resistance. Some have used the glucose to insulin ratio or simply the insulin level to gauge the degree of insulin resistance. Insulin resistance can lead to glucose intolerance. Therefore, patients with PCOS should have a fasting glucose or 2-hour glucose tolerance test. The clinical presentation and the laboratory studies will help to determine the cause of the ovulatory dysfunction, which can be varied and secondary to hypothalamic dysfunction (reduced weight), chronic anovulation (polycystic ovarian disease), and impending ovarian failure. For an overview of the workup of ovulatory dysfunction, refer to clinical algorithms in Chapter 5 and a discussion on ovulation induction in Chapter 6.

Luteal phase deficiency

In the past, there was a belief that luteal phase deficiency was a cause of infertility and recurrent miscarriages. It was theorized that some women may be ovulating and having regular menstrual cycles, but the progesterone secreted during the luteal phase is insufficient to mature the endometrium for implantation or unable to support a pregnancy. There were two approaches to evaluate the adequacy of the luteal phase. The first was to measure a mid-luteal phase progesterone level. A progesterone level below 10 ng/ml was suggestive of a progesterone deficiency. The major difficulty with using progesterone levels in this fashion is that progesterone is secreted in pulses every 2–3 hours, which will interfere with the interpretation of a single level.[4] The more popular technique to assess the adequacy of the luteal phase was an endometrial biopsy performed late

in the luteal phase. It was thought that the endometrial biopsy represented a bioassay of all of the progesterone that was secreted during the luteal phase. Progesterone causes day-by-day changes in the endometrium that can be appreciated histologically. A luteal phase deficiency was established if there was at least a 3-day lag between the histologic date of the endometrial biopsy and the chronologic date of the menstrual cycle (established retrospectively with the knowledge of the onset of the next menses and assuming a 14-day luteal phase). From a theoretic standpoint this makes good sense, but there are problems with the endometrial biopsy for assessment of the luteal phase, including:

1. Uncertainty when the menstrual period begins, which would interfere with the establishment of the chronologic day.
2. Inter-observer variation in the pathologic interpretation of the biopsy.
3. The false premise that the luteal phase is 14 days in length, when it can actually range between 13 and 16 days.

Coutifaris and co-workers shed more light on the use of the endometrial biopsy for infertility testing.[5] The study was a prospective multicenter study that involved 847 subjects, both fertile and infertile. A total of 42.2% of the fertile women and 32.7% of the infertile women tested had an out of phase biopsy (>2 days out of phase). Paradoxically, the fertile group had a greater chance of having an abnormal test result. Other studies have also suggested that the endometrial biopsy is an invalid test.[6–8] After reviewing the published studies it was concluded that the assessment of the luteal phase should not be a part of the infertility evaluation.

Cervical factor infertility

The cervix plays an important role in reproduction. It provides the passageway for sperm, allowing them access into the uterine cavity and ultimately the fallopian tubes. The ability of the sperm to gain access to the upper tract is influenced by the cervical mucus that is present in the cervical canal. The estradiol that is produced by the preovulatory follicle increases the quantity and consistency of mucus produced by the endocervical glands. Estradiol increases the water content of the mucus, that reaches a peak of 95–98% at mid-cycle. In the days that precede ovulation, a thin, watery mucus spills out of the cervical canal and covers the portio of the cervix and upper vagina. Some women notice this change in the cervical mucus, whereas others do not. If intercourse occurs during this time period the sperm are able to penetrate the mucus and survive for up to 3 days or more. In contrast, during the early follicular phase when the estradiol levels are low, or in the luteal phase when any estrogenic affect is counteracted by progesterone, the cervical mucus is thick and tenacious. If intercourse occurs at these times the sperm are unable to penetrate this poor quality mucus and die in the vagina within a few hours because of its acidic environment.

Impaired sperm penetration of the cervical mucus following intercourse can prevent the establishment of pregnancy. The etiology of this condition is varied and can be secondary to faulty coital technique, inadequate cervical mucus production, or poor quality sperm. Less than 5% of infertile couples will have a cervical factor as the cause of their infertility (excluding couples with a contributory male factor). A previous history of LEEP or ablative surgery to the cervix can put the woman at risk for a cervical factor. It is also important to ask couples about the use of lubricants during intercourse. Some over the counter lubricants can impair sperm motility. An alternative is vegetable oil, which does not impair sperm function.

The postcoital test

The postcoital test is the diagnostic test that has been used to assess the functional capacity of the cervix as it relates to fertility. The postcoital test is an evaluation of the quality of the cervical mucus and a determination of the number of sperm that have penetrated the mucus. There has been controversy about the test in part because it has never been standardized. Further, published data have confirmed that the postcoital test is unreliable and does not differentiate between fertile and infertile couples.[9]

It is our opinion that the postcoital test should not be part of the routine evaluation. However, an examination of the cervical mucus during the preovulatory period may be indicated in the woman who has had a destructive procedure performed on the cervix, which may compromise cervical mucus production.

Male factor infertility

Male factor infertility is identified in approximately 30% of infertile couples. At the initial consultation, it is important that an in-depth medical history is obtained from the male partner. Previous surgery for repair of an inguinal hernia could have resulted in inadvertent injury to the vas deferens, which courses through the inguinal canal. A history of cryptorchidism can be associated with altered testicular function. Chronic illnesses (i.e. chronic renal disease, thyroid dysfunction, diabetes mellitus, and malnourished states) can also impair normal spermatogenesis. A neuropathy can complicate diabetes and can result in the development of impotence or retrograde ejaculation. A medication history is also important. Sulfasalizine may be prescribed for ulcerative colitis and can cause a decrease in sperm concentration and motility, which will resolve after the medication is discontinued. The antimitotic activity of colchicine, a medication prescribed for gout, can also decrease sperm production. Some medications that are used to treat hypertension and mood disorders have sympathetic or parasympathetic actions that can interfere with erectile function and/or ejaculation. Male body builders should be questioned about the use of anabolic steroids and other oral hormonal agents that can result in significant oligospermia and in some cases

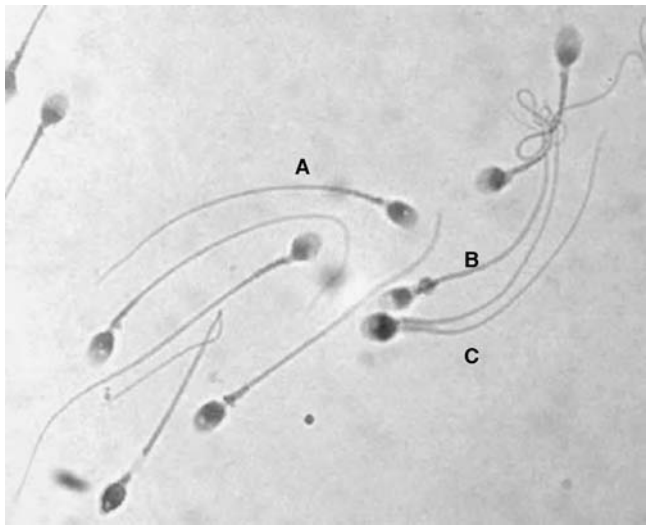

Figure 3.2 A standard part of the semen analysis is an assessment of the morphology or shape of the sperm. Note: a spermatozoon with normal morphology (A), and spermatozoa with abnormal morphology including one with a mid-piece defect (B) and one with two tails (C)

azoospermia, which are reversible. Other medications that can impact on male reproduction include the following: cimetidine, spironolactone, isoniazid, calcium channel blockers, and chemotherapeutic drugs. Recreational drugs such as alcohol, tobacco, and marijuana, if taken in excess, can also be detrimental. Spermatogenesis is a temperature sensitive process and the scrotal temperature is generally 2–3°F lower than core body temperature. Hot tubs, saunas, or a febrile illness can increase the temperature of the testes and can impair sperm production. Finally, the male should be questioned regarding chemical exposure at the workplace. Exposure to insecticides, pesticides, lead, and organic solvents, among others, has been shown to impact on male fertility.

The semen analysis has been the standard test for the evaluation of the male partner. The male partner is instructed to abstain from ejaculation for 2 days prior to performance of the test. The specimen is produced by masturbation. Depending on the laboratory facility the specimen can be produced on site. If the couple lives within 45 minutes of the laboratory then the sample can be produced at home and then transported to the laboratory for the analysis. During transport, it is important that the sample is kept at body temperature. The normal parameters of the semen analysis are shown in Table 3.3.

An important assessment of the semen analysis is a determination of the percentage of sperm with normal morphology (Figure 3.2). The World Health Organization (WHO) classification system has been used to evaluate sperm morphology and a sample is considered normal if ≥40% of the sperm have

Table 3.3 Normal parameters of semen analysis

Volume	2–5 cc
Sperm count	> 20 million sperm/cc
Motility	> 50%
Morphology	> 4% normal forms (by Tygerberg or Krüger classification) > 40% normal forms (by World Health Organization criteria)
Liquefaction time	15–30 min

normal morphology. Presently, the Tygerberg classification (also called the Krüger classification) is widely used and is a more critical assessment of sperm morphology. By this classification, it is considered normal if > 4% of the sperm have normal morphology. It must be realized that the assessment of the morphology is subjective on the part of the laboratory technician and variations in interpretation may occur from lab to lab. Since a semen analysis is a specialized test, it is important to select an experienced laboratory to perform the test. The reliability of the interpretation of a semen sample will be proportional to the number of specimens that are handled by any particular laboratory.

If the semen analysis is normal then no further workup of the male partner is indicated. If the semen analysis is abnormal then a repeat sample should be obtained 2–4 weeks later. There is day-to-day variability of the semen parameters. Further, an abnormal semen analysis might be explained by a stressful event (i.e. febrile illness) that occurred 2–3 months prior to the time of the initial semen analysis. This is the amount of time it takes for mature sperm to develop. If the repeat semen analysis is abnormal, then a referral to a urologist is indicated for further evaluation. One important reason for a referral is that a presenting sign of testicular cancer may be an abnormal semen analysis.[10,11] On exam by the urologist a varicocele may be identified. A varicocele is a dilated scrotal vein, which can be identified in up to 40% of infertile males but can also be present in 15% of normal fertile males.[12] There are several theories that have been proposed to explain the association between a varicocele and male infertility. The most accepted theory is that the dilated testicular vein raises the temperature of the testes, which alters sperm production. However, there continues to be controversy about the association of a varicocele and infertility, and the benefits of surgical correction. The reported pregnancy rates following surgical ligation of a varicocele are between 30 and 50%. However, a meta-analysis of pertinent studies failed to demonstrate any improvement in male fertility following a varicocele ligation.[13]

Laboratory studies (FSH, LH, testosterone, and prolactin) may help to rule out an endocrinopathy, which could explain significantly impaired spermatogenesis. If the gonadotropins (FSH, LH) are depressed or undetectable, this may suggest the presence of either Kallman's syndrome or hypothalamic dysfunction, which can be corrected with FSH and human chorionic gonadotropin (hCG) injections. An elevated FSH level suggests the presence of testicular failure that may be secondary

to Kleinfelter's syndrome (47,XXY), Sertoli only-cell syndrome, previous mumps orchitis, or prior cancer treatment. A karyotype is indicated in cases of azoospermia (associated with an elevated FSH) and severe oligospermia when the sperm concentration is less than 5 000 000 sperm/cc. An abnormal karyotype is identified in 10–15% of men with non-obstructive azoospermia and 5% of men with severe oligospermia.[14] Microdeletion studies of the Y chromosome should also be performed on males with severe oligospermia and are identified in 10–15% of men in this group.[15] Understanding the underlying genetic basis for oligospermia is important for genetic counseling purposes. Genetic testing in men with severe oligospermia is indicated and should be a prerequisite prior to proceeding with IVF and intracytoplasmic sperm injection (ICSI). An abnormal genetic test should trigger a referral to a genetics counselor. Hyperprolactinemia is uncommon in the male but can be associated with impotence. In the male with azoospermia and normal gonadotropins, one must consider either the presence of an obstructed outflow tract or the congenital absence of the vas deferens as the cause. Often the diagnosis can be made on physical examination, but a testicular biopsy with a vasogram may be helpful. While a physical examination and laboratory evaluation are helpful to evaluate the male with abnormal semen parameters, the majority of cases remain unexplained.

It is important to realize that the semen analysis is a quantitative assessment of the semen sample. Unfortunately, we do not have a test that provides a qualitative assessment of sperm function short of *in vitro* fertilization or pregnancy itself. Several years ago the hamster penetration assay was touted as a qualitative test of sperm function, but numerous studies have disproved its reliability and we do not feel that it has any use in the evaluation of male infertility.

Tubal factor infertility

Tubal factor infertility is present in approximately 20% of infertile women. Risk factors include a previous ectopic pregnancy, ruptured appendix, previous use of an IUD, or a past history of pelvic inflammatory disease. Even so, the majority of women who are found to have a tubal factor do not have any risk factor. These cases are most likely the result of an asymptomatic pelvic infection.

The HSG is the standard test to assess tubal patency (Figures 3.3 and 3.4). This test is performed early in the follicular phase after the cessation of menstrual flow. It is safer to use a water-based medium for the examination. Absolute contraindications for performing the test are suspicion of pregnancy and active pelvic infection. If a patient states that her previous menses was lighter than normal or delayed, then a pregnancy test should be done prior to the X-ray. A complication following an HSG is an infection, which has an incidence of 1–3%.[16] For this reason, prophylactic antibiotics (i.e. metronidazole, doxycycline) should be considered for women who have a history of a sexually transmitted disease or a pelvic infection, or who are diagnosed with a hydrosalpinx at the time of the HSG. If the woman has a known iodine allergy, the test

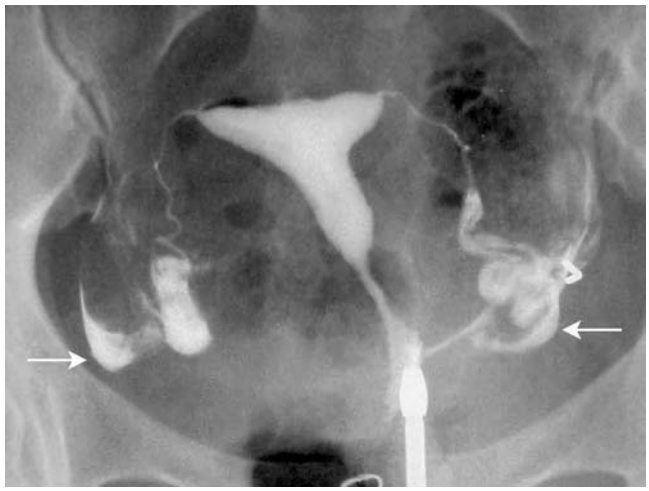

Figure 3.3 Normal hysterosalpingogram (HSG). This HSG demonstrates a uterine cavity that has a normal shape and there are no filling defects noted within the cavity. Both Fallopian tubes have filled and the arrows point to dye that has exited the ends of both tubes into the abdominal cavity

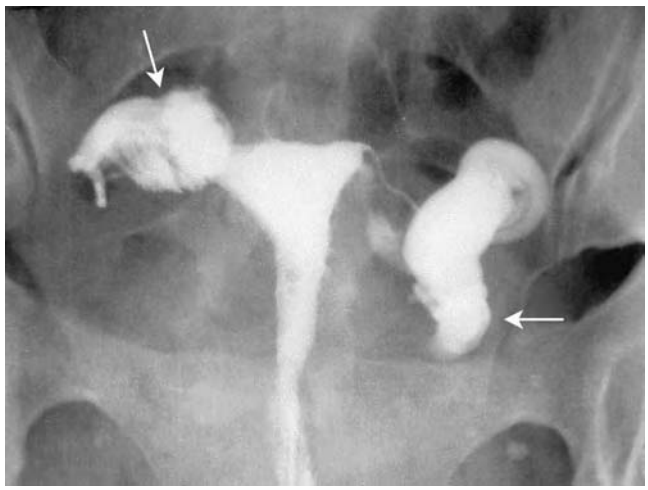

Figure 3.4 Distal tubal obstruction. In this X-ray both Fallopian tubes are filled but their distal ends are dilated and no dye is seen escaping into the abdominal cavity. The ends of the tubes are indicated by the arrows. This finding is most likely the result of a pelvic infection

should be reconsidered. If the allergy is mild, the test can be performed with a contrast medium that contains non-ionic iodine, which reduces the chance of an allergic reaction. If the woman has a more significant iodine allergy, the clinician should consult with the radiologist before performing the test. It may be

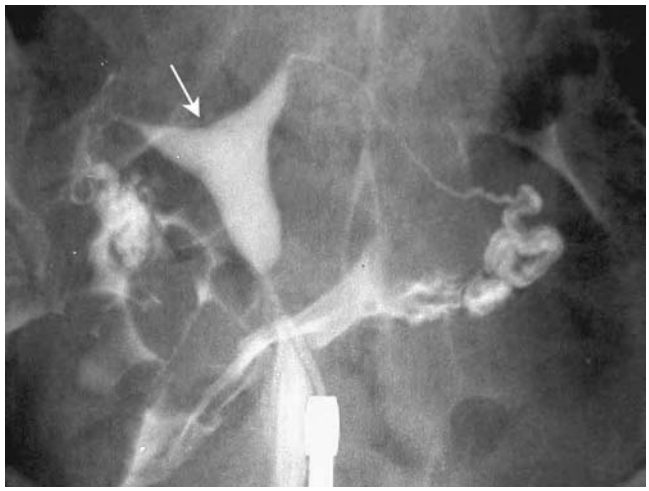

Figure 3.5 Arcuate uterus. In this otherwise normal study a depression can be seen indenting the superior aspect of the uterine cavity (see arrow). This is compatible with an arcuate uterus and is considered a normal variant. No additional workup is indicated. For comparison, a normal uterine cavity can be seen in Figures 3.3 and 3.4

recommended to pretreat the patient with steroids or antihistamines prior to the procedure. Another alternative is to use gadolinium contrast, which is used for MRI. Adequate visualization is appreciated with gadolinium, but it is significantly more expensive than iodine contrast agents.[17]

In addition to assessing tubal patency, the HSG allows examination of the uterine cavity (Figures 3.5–3.10). If a balloon catheter is used for the HSG, the balloon should be deflated at the end of the contrast injection to better visualize the endometrial cavity. We routinely attach a tenaculum to the anterior cervix for traction and inject the dye through a cannula with a plastic cone-shaped tip that is abutted against the external cervical os. Retraction of the tenaculum caudad straightens out the uterus and allows a better examination of the cavity. If the dye is injected slowly and if a non-steroidal anti-inflammatory drug (e.g., ibuprofen 600 mg) is given one hour prior to the procedure, the HSG can be performed with minimal discomfort and often painlessly, contrary to popular belief.

Besides being a diagnostic tool, the HSG has been shown to be of therapeutic benefit as well. Approximately 30% of patients who have a normal HSG will conceive over the following 6 months.[18,19] Initially, this was thought to be only a characteristic of the oil-based contrast medium. A prospective randomized study demonstrated comparable pregnancy rates over a 6-month period in patients who had tubal patency confirmed using either a water- or an oil-based contrast medium.[18] In an effort to explain the therapeutic benefit of the HSG, some have suggested that the injection of dye may dislodge intratubal mucus plugs, stimulate the tubal cilia, or break up intratubal adhesions.

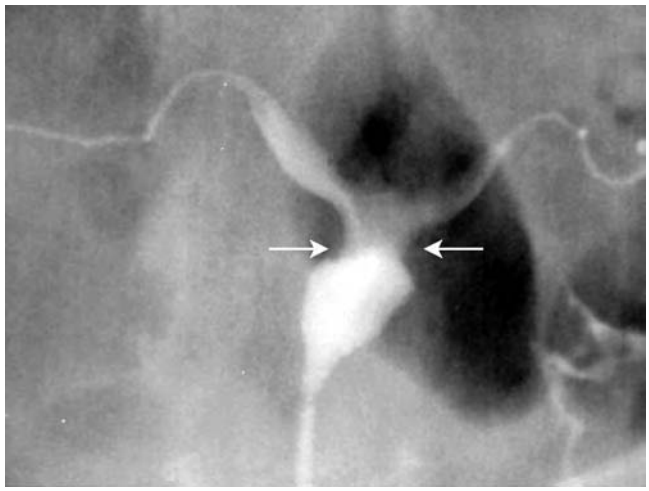

Figure 3.6 A diethylstilbestrol (DES) uterus. The shape of this uterine cavity is compatible with previous DES exposure that causes impingement of the lateral walls as indicated by the arrows. The prominent uterine horns create a bicornuate shape, as well. Overall the uterine cavity has a 'T-shape' which is classic for previous DES exposure

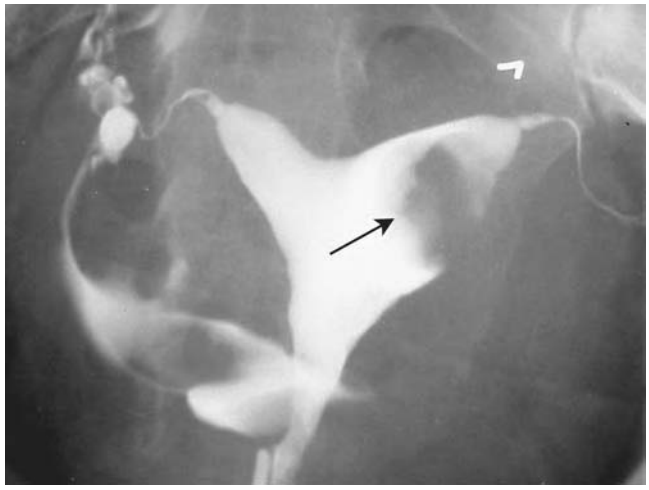

Figure 3.7 Submucosal fibroid. This hysterosalpingogram demonstrates a large filling defect in the left uterine horn, which was later found to be a submucosal fibroid. Also note the depression in the superior aspect of the cavity which is an arcuate deformity

When is a laparoscopy indicated?

A laparoscopy is the most invasive of the infertility tests and, for this reason, is generally performed in selected cases after the completion of the workup.

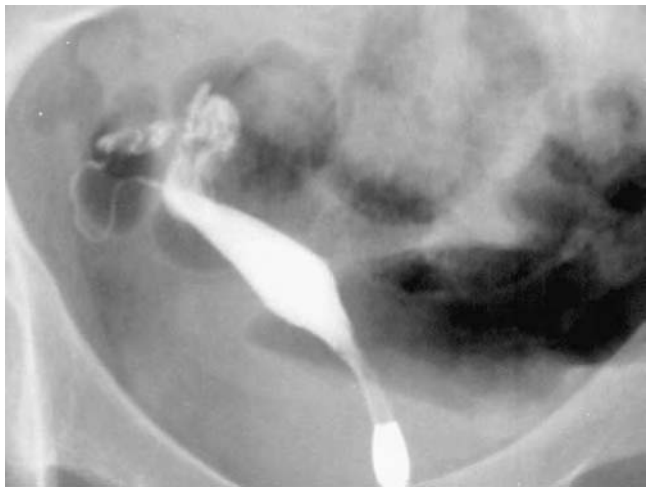

Figure 3.8 Unicornuate uterus. During this X-ray only the right horn of the uterine cavity filled. This is compatible with a unicornuate uterus. A unicornuate uterus increases the risk of premature labor and fetal malpresentations. It can be accompanied by renal abnormalities

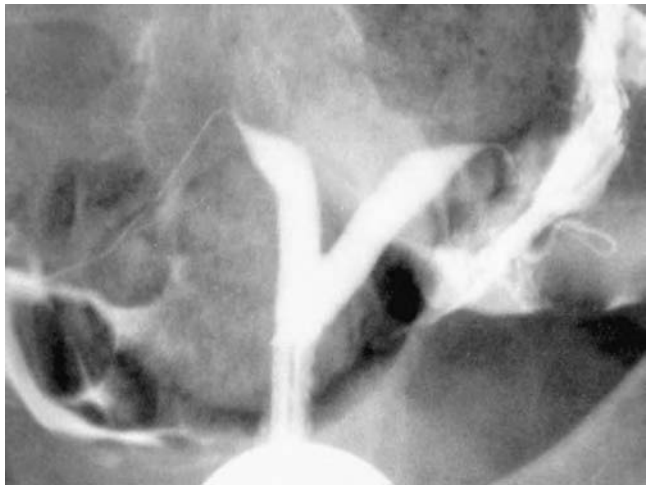

Figure 3.9 Uterine septum. This X-ray demonstrates a division in the uterine cavity, which was confirmed to be a uterine septum

In the past, it was considered a routine part of the infertility evaluation, but presently we counsel our patients on the risks and benefits of the procedure and perform it on an individual basis. There are some women who choose to have a laparoscopy during the initial part of the evaluation while others choose never to

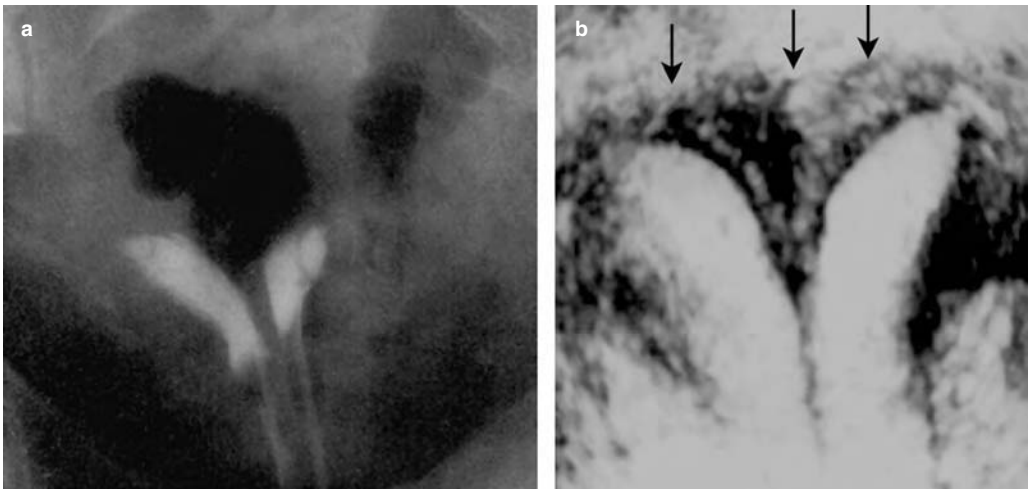

Figure 3.10 ***Is the uterine anomaly a septate or bicornuate uterus?*** Panel (a) shows a uterine duplication anomaly confirmed by an HSG. Two separate cervices were cannulated and two separate uterine horns were noted. Panel (b) shows a three-dimensional ultrasound image of the uterus on the same patient. The black arrows note the border of the outer extent of the myometrium of the uterine fundus. The conclusion – ***this anomaly is a uterine septum***

have the surgery performed and proceed with treatment. A laparoscopy may be more seriously considered for the patient who has a history of a pelvic infection, signs or symptoms compatible with endometriosis, or abnormal findings on the HSG. It is important that the findings at the time of surgery are clearly documented not only with an accurate operative note, but drawings, pictures, and video recordings are also helpful. At the time of the laparoscopy, the surgeon must have the necessary tools available to treat any conditions that are encountered. If endometriosis is identified the patient should be properly staged. Staging sheets can be obtained by contacting the American Society of Reproductive Medicine in Birmingham, Alabama (see Chapter 19) or obtaining a copy of the article entitled 'Revised American Society for Reproductive Medicine classification of endometriosis' (Fertil Steril 1997; 67: 817–21). There is no documented evidence that medical treatment of endometriosis enhances fertility. There are some published data suggesting that surgical treatment may enhance fertility.[20–22] Another indication to perform a laparoscopy is when distal tubal obstruction is identified. If the patient cannot afford IVF, then correction of the obstruction (often covered by insurance companies) might be considered; however the patient should be counseled that the overall success rate is no higher than 20%. Alternatively, if the patient plans to undergo IVF treatment, then a salpingectomy should be performed since evidence suggests that a hydrosalpix will reduce the chance of pregnancy by 50%.[23] The mechanism by which a hydrosalpinx reduces IVF implantation is likely related to the adverse affect of the tubal fluid on the endometrium or embryo.

Uterine factor infertility

Dysfunction in the uterus can prevent the establishment of a pregnancy. Further evaluation of the uterine cavity should be considered for any woman who has abnormal bleeding, an abnormal cavity noted on the HSG, or a history of repeated miscarriages. Uterine fibroids are a common finding and occur in approximately 15–20% of women over the age of 35. In the majority of cases, the fibroids do not produce symptoms or impact on fertility. Fibroids can be located and attached to the outside of the uterus (subserosal), in the uterine wall (intramural), and in the cavity (submucosal). It is the submucosal fibroids that can have the greatest impact on fertility. The management of uterine fibroids has changed dramatically over the years. In the past it was standard to recommend that asymptomatic fibroids 2 cm or larger be removed. However, the approach has changed since there is a great deal of controversy concerning the role of fibroids on fertility and complicating pregnancy.[24,25] Unfortunately most published studies looking at the effectiveness of a myomectomy are retrospective in design and prospective randomized studies are lacking. Specific reasons to consider surgical removal of the fibroids include size (5 cm or larger), location within the cavity, association with menorrhagia, or distortion of the uterine cavity on the HSG.

The HSG provides a good examination of the cavity but the examination can be somewhat limited. When the clinician is suspicious of an abnormality in the cavity, then further testing may be indicated with a diagnostic hysteroscopy or a sonohysterogram (SHG). We have found that the SHG is an excellent test to evaluate the cavity. This test can be performed in the office if the clinician has access to a vaginal ultrasound. To perform the test, a small catheter is inserted into the cavity and a syringe filled with saline is attached. Then the vaginal ultrasound is inserted. After the uterus is identified saline is injected into the cavity. A normal cavity has sharp borders (Figure 3.11). Any structure seen within the cavity is considered abnormal and could represent a polyp or fibroid (Figure 3.12). In this circumstance, a hysteroscopic examination would be indicated.

CONCLUSIONS

The causes of infertility can be varied and the infertility evaluation will provide a better understanding of the potential causes. Up to 25% of couples will have a combination of factors. Therefore, it is important that a complete evaluation is performed and the evaluation is not halted after a single abnormal test is encountered. After the evaluation is completed, the couple should be seen in consultation to discuss the results and formulate a treatment plan.

ADDITIONAL RESOURCES

American Society for Reproductive Medicine. Optimal Evaluation of the Infertile Female. A Practice Committee Report; A Committee Opinion. Birmingham, ALA: American Society for Reproductive Medicine, 2003.

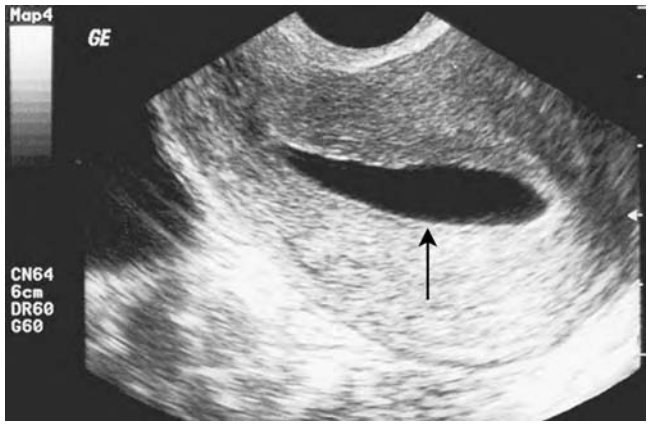

Figure 3.11 Sonohysterogram (normal cavity). This is a longitudinal image of the uterus taken at the time of a sonohysterogram. The black area (arrow) is the image of the saline that has been injected into the uterine cavity. Note that the borders of the uterine cavity are sharp and no masses are noted to be entering into the cavity. This study confirms a normal uterine cavity

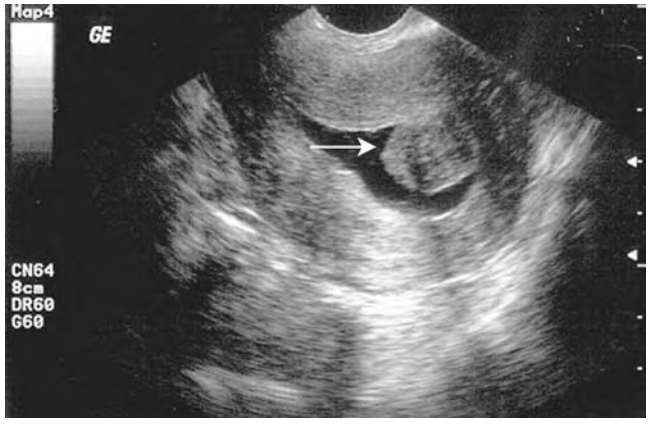

Figure 3.12 Sonohysterogram (abnormal cavity). In this image the injected fluid in the cavity (appearing black) outlines an intracavitary mass, which was later confirmed to be a uterine fibroid

Adamson D, Chang RJ, DeCherney AH et al. A model for initial care of the infertile couple. J Reprod Med 2001; 46(Suppl 4): 409–26.

REFERENCES

1. Hendriks DJ, Mol BWJ, Bancsi LF et al. Antral follicle count in the prediction of poor ovarian response and pregnancy after in vitro fertilization: a meta-analysis and comparison with basal follicle-stimulating hormone level. Fertil Steril 2005; 83: 291–301.
2. Fanchin R, de Ziegler D, Olivennes F et al. Exogenous follicle stimulating hormone ovarian reserve test (EFFORT): a simple and reliable screening test for detecting 'poor responders' in in-vitro fertilization. Hum Reprod 1994; 9: 1607–11.

3. Abdalla H, Thum MY. An elevated basal FSH reflects a quantitative rather than a qualitative decline of the ovarian reserve. Hum Reprod 2004; 19: 893–8.
4. Rossmanith WG, Laughlin GA, Mortola JF et al. Pulsatile cosecretion of estradiol and progesterone by the midluteal phase corpus luteum: temporal link to luteinizing hormone pulses. J Clin Endocrinol Metab 1990; 70: 990–5.
5. Coutifaris C, Mayers ER, Guzick DS et al. Histological dating of timed endometrial biopsy tissue is not related to fertility status. Fertil Steril 2004; 82: 1264–72.
6. Shoup D, Mishell DR Jr, Lacarra M et al. Correlation of endometrial maturation with four methods of estimating day of ovulation. Obstet Gynecol 1989; 73: 88–92.
7. Li T-C, Dockery P, Rogers AW, Cooke ID. How precise is histologic dating of endometrium using the standard dating criteria? Fertil Steril 1989; 51: 759–63.
8. Batista MC, Cartledge TP, Merino MJ et al. Midluteal phase endometrial biopsy does not accurately predict luteal function. Fertil Steril 1993; 59: 294–300.
9. Grimes DA. Validity of the postcoital test. Am J Obstet Gynecol 1995; 172: 1327.
10. Tal R, Holland R, Belenky A et al. Incidental testicular tumors in infertile men. Fertil Steril 2004; 82: 469–71.
11. Simon SD, Lee RD, Mulhall JP. Should all infertile males undergo urologic evaluation before assisted reproductive technologies? Two cases of testicular cancer presenting with infertility. Fertil Steril 2001; 75: 1226–7.
12. Nagler HM, Luntz, RK, Martinis FG. Varicocele. In: Lipshultz LI, Howards SS, eds. Infertility in the Male. St. Louis: Mosby Year Book, 1997: 336–59.
13. Evers JL, Collins JA. Surgery or embolization for varicocele in subfertile men. Cochrane Database Syst Rev 2005; 4.
14. DeBraekeleer M, Dao TN. Cytogenetic studies in male infertility: a review. Hum Reprod 1991; 6: 245–50.
15. Pryor JL, Kent-First M, Muallem A et al. Microdeletions in the Y chromosome of infertile men. N Engl J Med 1997; 336: 534–9.
16. Stumpf PG, March CM. Febrile morbidity following hystersalpingography: identification of risk factors and recommendations for prophylaxis. Fertil Steril 1980; 33: 487–92.
17. Noorhasan D, Heard MJ. Gadolinium radiologic contrast is a useful alternative for hysterosalpingography in patients with iodine allergy. Fertil Steril 2005; 84: 1744.
18. Alper MM, Garner PR, Spence JE, Quarrington AM. Pregnancy rates after hysterosalpingography with oil- and water-soluble contrast media. Obstet Gynecol 1986; 68: 6–9.
19. Schwabe MG, Shapiro SS, Haning RV. Hysterosalpingography with oil contrast medium enhances fertility in patients with infertility of unknown etiology. Fertil Steril 1983; 40: 604–6.
20. Marcoux S, Maheux R, Bérubé S. Laparoscopic surgery in infertile women with minimal or mild endometriosis. Canadian Collaborative Group on Endometriosis. N Engl J Med 1997; 337: 217–22.
21. Parazzini F. Ablation of lesions or no treatment in minimal-mild endometriosis in infertile women: a randomized trial. Gruppo Italiano per lo Studio dell; Endometriosi. Hum Reprod 1999; 14: 1332–4.
22. Schenken RS. Modern concepts of endometriosis. Classification and its consequences for therapy. J Reprod Med 1998; 43: 269–75.
23. The Practice Committee of the American Society for Reproductive Medicine. Salpingectomy for hydrosalpinx prior to in vitro fertilization. Fertil Steril 2004; 82: S117–19.
24. Hurst BS, Matthews ML, Marshburn PB. Laparoscopic myomectomy for symptomatic uterine myomas. Fertil Steril 2005; 83: 1–23.
25. The Practice Committee of the American Society for Reproductive Medicine Educational Bulletin. Myomas and reproductive function. Fertil Steril 2004; 82 Suppl 1: S111–16.

4.

Getting the patient ready for a pregnancy

Steven R Bayer

The ultimate goal of treatment of the infertile couple goes beyond just simply helping them achieve a pregnancy, but rather it should be the establishment of a pregnancy that ends with a healthy mother and a healthy baby. In some cases, the woman has a medical condition, is taking a medication, has a genetic risk, or is exposed to an environmental toxin that could jeopardize her health and/or the health of her unborn child during pregnancy. To this end, preconceptional care is a prerequisite before treating the infertile couple (or any couple contemplating a pregnancy). Preconceptional care is an assessment of the medical, social, genetic, environmental, and occupational factors that can impact on fertility and the health of a pregnancy (Figure 4.1). In this chapter, a comprehensive summary and framework for preconceptional care is presented.

LIFESTYLE HABITS

A social history with an assessment of lifestyle habits is an important part of the medical history that should be obtained from the male and female partners. The use of tobacco, alcohol, and recreational drugs should be ascertained and the couples appropriately counseled. These habits may not only be harmful during pregnancy but could also impair conception.

Smoking

Smoking is one of the major public health-care issues that continues to challenge the medical community. According to the Centers for Disease Control and Prevention (CDC) there is an encouraging downward trend of smoking in the United States. However, approximately 20% of women in the reproductive age group continue to smoke.[1] The impact of smoking on general health is well known. There are substantial data to support that smoking compromises reproductive health and, therefore, is considered a reproductive toxin.[2] Women who

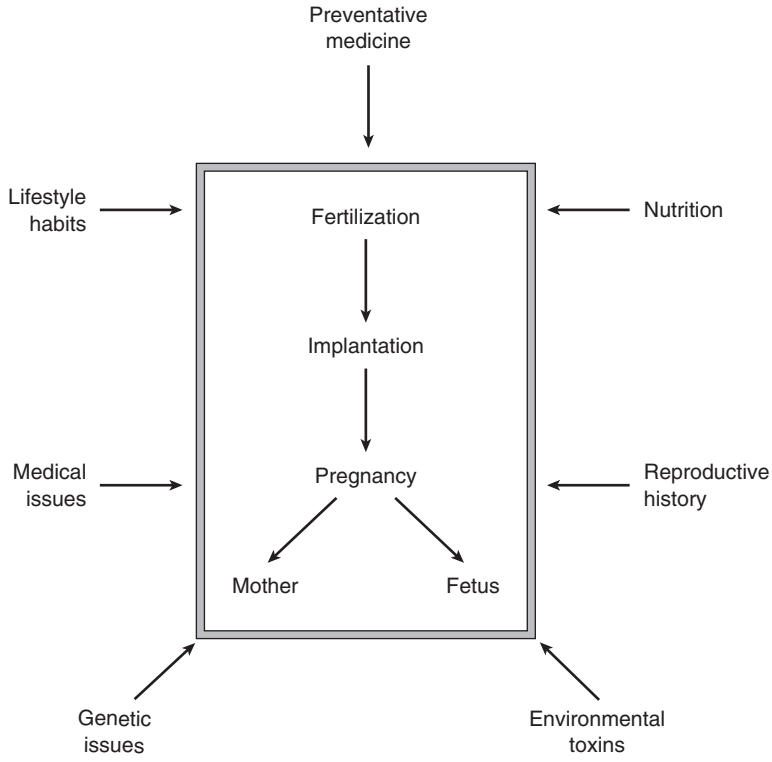

Figure 4.1 Factors that can impact on fertility and pregnancy

smoke are at greater risk of having infertility, a spontaneous abortion, and a tubal pregnancy. During pregnancy maternal smoking increases the chances of abruptio placenta, premature rupture of the membranes, and impaired fetal growth. Maternal smoking during pregnancy also increases the chance of the sudden infant death syndrome (SIDS). Smoking may also be mutagenic, causing damage to DNA and chromosomes. Maternal smoking increases the risk of trisomy 21.[3,4] It is clear that any woman who smokes and is contemplating a pregnancy should be strongly encouraged to stop. Smoking is a strong addiction and referral for active intervention may be necessary.

Alcohol

Alcohol use during pregnancy increases the risk of several complications and the one complication of most concern is *fetal alcohol syndrome*, which is associated with altered fetal growth, dysmorphic features, and mental retardation. The risk of fetal alcohol syndrome is related to the degree and timing of alcohol intake, but no level of alcohol intake is considered safe. Previous studies have demonstrated that maternal alcohol intake can decrease the chances of

conception.[5,6] Therefore, any woman who is trying for a pregnancy should limit alcohol intake and avoid it altogether once pregnancy is established. Finally, heavy alcohol intake may suggest an addiction and a history of other drug use should be ascertained. In some cases, referral for counseling may be indicated before the couple attempts a pregnancy.

Recreational drug use

The use of recreational drugs is absolutely contraindicated while a couple is attempting to conceive and during pregnancy. Males who use marijuana on a regular basis have lower serum testosterone levels and decreased sperm counts. Other drugs used by the mother, such as cocaine and heroin, may lead to a severe neonatal withdrawal reaction. Further, the use of intravenous drugs increases the risk of human immunodeficiency virus (HIV) and hepatitis infections.

NUTRITION

There is no doubt that our general health is influenced by what we eat, how much we eat, and how much energy we expend with activity and exercise. In addition, nutrition impacts on reproductive health and can influence the establishment and maintenance of a pregnancy. There is growing concern about the increased incidence of obesity (body mass index (BMI) > 30) in the United States. There is evidence to suggest that we are in the midst of an epidemic of this problem. The incidence of obesity doubled between 1980 and 2000 (Figure 4.2). In 2002, obesity affected 30% of the US population or 60 million persons.[7] While there may be a genetic explanation in some, most cases of obesity are preventable and result from a sedentary lifestyle and an unhealthy diet. If the trend does not change, obesity may become one of the leading causes of death.

In response to the growing obesity problem, the US Department of Agriculture has recently revised the Food Guide Pyramid (http://www.mypyramid.gov/). The major differences in the current recommendations include reduced consumption of carbohydrates and increased physical activity. As a general recommendation, women should be encouraged to maintain a balanced diet of grains, vegetables, fruits, meats, and dairy products. Foods with a high content of fats, oils, and carbohydrates should be used sparingly. In addition to a well-balanced diet, caloric intake should be limited to maintain a normal body weight.

Body weight

Extremes of body weight can be associated with altered ovarian function. It is well established that a threshold body weight and fat content are necessary to maintain normal ovarian function. If the body weight is reduced below the 10th percentile for a particular height (BMI < 18) or the body fat content is reduced to less than 22%, then altered menstrual function and ovulatory dysfunction

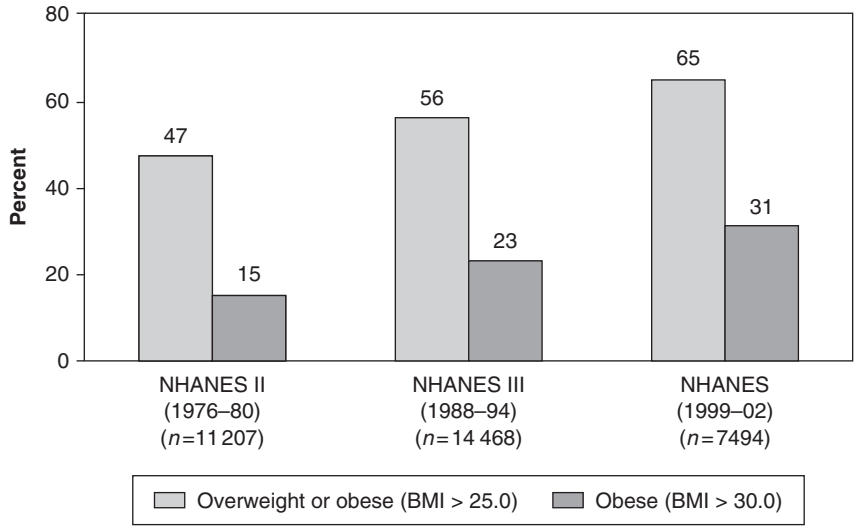

Figure 4.2 Age-adjusted prevalence of overweight and obesity among US adults, age 20–74 years from the National Health and Nutrition Examination Survey (NHANES), United States, 1999–2002. http://www.cdc.gov/nchs/products/pubs/pubd/hestats/obese/obse99.htm

can develop.[8] This explains the high incidence of amenorrhea in some female athletes (e.g. marathon runners, ballet dancers) and women who diet excessively. Alternatively, increased body weight can also be associated with ovulatory dysfunction. A major concern about increased body weight is the increased incidence of complications that may occur during pregnancy, including spontaneous abortion, gestational diabetes, hypertension, thromboembolism, congenital anomalies, and stillbirth.[9,10] Women who are overweight tend to have babies with macrosomia, which increases the chance of shoulder dystocia and the need for a Cesarean section. A Cesarean section that is performed on a woman who is overweight is associated with a higher incidence of anesthetic and surgical complications. Obesity is responsible for 18% of maternal mortalities and 80% of anesthesia related mortalities.[11] Guidelines have been published that provide a strategy for the clinician in dealing with obesity in the adult population.[12,13]

Assessing the body habitus

The BMI or the Quetelet's index is a determination of whether an individual's weight is appropriate. It is a calculation that takes into account the weight and height ($703 \times$ weight [lbs]/height^2[inches^2]). A reference table to calculate the BMI is provided in Chapter 20. For easy calculation a BMI calculator can be downloaded to your computer desktop (http://www.nhlbisupport.com/bmi).

The BMI is a quantitative measure that helps to put into perspective the individual's weight. A woman is considered *normal* if the BMI is 18.5–24.9, *overweight*

if the BMI is 25–29.9, and *obese* if the BMI is > 30. The obesity is further classified into Class I, II, and III for a BMI of 30–34.9, 35–39.9, and > 40, respectively.[11]

Caffeine intake

Several publications have suggested a dose-dependent relationship between caffeine intake and reduced fertility. Further, caffeine intake during pregnancy is associated with an increased chance of a spontaneous abortion and a low birth weight.[14] Therefore, it is reasonable to suggest to women who are attempting pregnancy to discontinue their caffeine intake altogether, or at least, limit their intake to one caffeinated beverage a day. This advice should also be followed during pregnancy. The quantity of caffeine in beverages is variable. The average amount in a cup of coffee, tea, and a can of soda is approximately 100, 50, and 50 mg, respectively. Men experience no fertility risk from caffeine intake. Interestingly, sperm exposed to caffeine-like drugs in the laboratory have actually been shown to display enhanced motility.

Vitamin supplementation

Women who take folic acid prior to pregnancy reduce their chance of having a baby with a neural tube defect. Neural tube defects are abnormal developments of the spine and skull. The most common types of neural tube defects are anencephaly and spina bifida. In the United States, the occurrence of neural tube defects is 1–2 per 1000 deliveries. Previous studies have reported that women who supplemented their daily diet with 0.4 mg of folic acid experienced a 40–100% reduction in the frequency of neural tube defects.[15–18] Some studies have suggested that folic acid may prevent the development of other birth defects including cardiac, renal, cleft lip/palate, and limb abnormalities.[19,20] It is now recommended that all women of child bearing age who are capable of becoming pregnant should consume 0.4 mg of folic acid per day. This can be accomplished either through dietary supplementation or by taking an over-the-counter multivitamin preparation, which contains 0.4 mg of folic acid.

Women who are overweight (BMI > 30) have an increased chance of having a baby with a neural tube defect.[21] In this population, it is prudent to prescribe a daily supplement of 1.0 mg of folic acid or a prenatal vitamin, which also contains 1.0 mg of folic acid. It is recommended that a woman who has had a previous pregnancy complicated by a neural tube defect or a family history of this defect should be treated with 4.0 mg of folic acid daily.[22–24]

While vitamin supplementation is helpful, excessive vitamin intake can prove to be harmful to the developing fetus. Published data have confirmed that excessive intake of vitamin A increases the chance of congenital anomalies involving craniofacial, cardiac, thymus, and central nervous system organ systems.[25] Isotretinoin (Accutane®), a derivative of vitamin A, is used to treat severe acne. In women who take this drug orally during pregnancy there is a 25% chance of

congenital anomalies.[26] Prenatal vitamins and over-the-counter multivitamins contain 5000–8000 IU of vitamin A, which is a safe dose. However, daily intake of vitamin A should not exceed 10 000 IU. Excessive intake of animal liver, a food that is rich in vitamin A, should also be avoided. Supplementation with β-carotene, a precursor of vitamin A, is not associated with a toxic effect.

Recommendations for folic acid supplementation to prevent neural tube defects (NTD)*

- *Routine* – 0.4 mg daily (a multivitamin)
- *Obesity (BMI >30)* – 1.0 mg daily (a prenatal vitamin or a 1.0 mg folic acid tablet)
- *Previous history or family history of NTD* – 4.0 mg folic acid daily†

*For adequate prevention of an NTD the folic acid supplement should be started 1 month before conception and continued during pregnancy.

†This level of intake can be achieved either by taking four 1.0 mg tablets of folic acid or three 1.0 mg folic acid tablets plus a prenatal vitamin. To achieve this level of supplementation more that one multivitamin (or prenatal vitamin) should ***not*** be taken on a daily basis. This will increase the intake of vitamin A over the safe level, which could increase the chance of birth defects.

Herbal remedies

Over the past several years, there has been an increase in the use of alternative medical therapies including herbal remedies. Herbal remedies are advertised as 'natural' but many have strong medicinal qualities. However, one must exercise caution in their use since there are very few published studies analyzing the effectiveness and safety of these agents, especially during pregnancy.[27] In a previous study, three commonly used herbs including St John's Wort, *Echinacea purpura*, and *Ginkgo biloba* were demonstrated to be detrimental to egg and sperm function.[28] It is important to ask patients about the use of all medications, including herbal remedies. Many patients do not view herbal or over-the-counter medications as 'true' medications. Until published studies confirm the safety of herbal remedies, women should be encouraged to discontinue these agents before and after pregnancy is established.

ROUTINE GYNECOLOGIC CARE

Every woman should have a yearly blood pressure check, physical examination, pelvic examination, and Pap smear. The American Cancer Society current recommendations are that every woman should have yearly mammograms beginning at age 40. Earlier screening may be indicated if there is a family history of breast cancer.

LABORATORY TESTING

Routine laboratory studies are an essential part of preconceptional care. In essence, the same tests that are routine for any pregnant woman should also be performed on the woman who is contemplating a pregnancy. The tests that we recommend are presented below. A complete blood count may identify a woman who has anemia or some other abnormality that needs attention. A blood type and screen may uncover the presence of an antibody that could increase the chance of isoimmunization. In addition, knowledge of the blood type is also advantageous when a patient is experiencing bleeding during the early part of pregnancy and the clinician needs to know whether anti-D immunoglobulin (RhoGAM®) is indicated.

Thyroid function should be assessed with a serum TSH determination. Thyroid dysfunction is present in 3–10% of women. Since thyroid disorders can be genetic, any woman who has a family history of thyroid dysfunction should be screened with a TSH level along with thyroid peroxidase antibodies. Despite a normal TSH level, if a woman has positive thyroid antibodies she is at risk for thyroid dysfunction in the future, especially during pregnancy. Borderline hypothyroidism during the early stage of pregnancy has been reported to impact on fetal neuropsychologic development.[29,30] A previous study confirmed that 85% of patients receiving treatment for hypothyroidism required an increase in thyroid replacement during the first trimester of pregnancy, so close vigilance is indicated.[31] During the postpartum period thyroid antibodies can further alter thyroid function and place the woman at increased risk of postpartum depression.

Certain infections during pregnancy can pose a health risk to the mother and/or fetus. During childhood it is public policy to administer immunizations that provide protection against many of these infections. Despite these efforts, a segment of the population remains at risk because of failure to receive the vaccine or failure to convert to immunity following a vaccination. Determining the immune status to certain infections including rubella, varicella, and hepatitis should be considered a routine part of preconceptional care. Screening for other infectious diseases may be indicated depending on the clinical circumstances.

Preconceptional blood work

- TSH
- CBC
- Blood type & screen
- RPR
- Antibody screens for:
  - Rubella
  - Varicella
  - Hepatitis
  - HIV
- Genetic screening (if indicated)

Rubella (German measles)

Rubella is a self-limited viral infection that is associated with a characteristic rash. A maternal infection during the first trimester of pregnancy can result in fetal death or cause severe damage to the fetal cardiac, neurologic, ophthalmologic, and auditory organs. A major concern of a rubella infection is that almost one-third of infections are asymptomatic. In the past, rubella was an endemic infection that affected our population. Since the introduction of the rubella vaccine in 1969, there has been a significant reduction in rubella infections and babies born with congenital rubella syndrome. However, one in nine women is not immune to rubella.[32] Screening for rubella immune status should be routinely performed on any woman who is contemplating pregnancy. Those women who are non-immune should be encouraged to receive the vaccine. The rubella vaccine is a live-attenuated virus and the current CDC recommendations are that a woman should avoid pregnancy for 1 month after receiving the vaccine.

Varicella (chicken pox)

Varicella is a highly contagious viral infection that is caused by a herpes virus. Most individuals experience a memorable varicella infection during their childhood, which confers lifelong immunity. A non-immune individual can acquire the infection after exposure to an individual who has a primary varicella infection or herpes zoster (a latent form of varicella). Symptoms of an infection include malaise, fever, and the development of characteristic vesicular lesions. Approximately 5% of individuals are non-immune to varicella.[33] There are concerns about a primary varicella infection that develops in an adult. Up to 20% of adults, who acquire a primary varicella infection, will develop a concomitant pneumonia, which is fatal in 40% of cases.[34] If a pregnant woman develops the infection during the first trimester there is an increased risk of congenital anomalies.[33] Immunity to varicella can be assessed by blood testing. A varicella vaccine is available and should be offered to non-immune individuals. The vaccine is administered in two doses 4–8 weeks apart. It is recommended that pregnancy be avoided during the vaccination period and until 1 month after the last injection.

Hepatitis screening

There are six types of viral hepatitis (A, B, C, D, E, and G). The severity and risk for vertical transmission varies depending on the type. Any woman who has been diagnosed with hepatitis in the past should receive counseling about the risks during pregnancy. Screening for hepatitis B and C is recommended for all pregnant women and those contemplating a pregnancy. While those with documented immunity to hepatitis pose no risk to the fetus, chronic carrier states do exist that can be associated with liver dysfunction and vertical transmission of

the infection to the fetus. Women who have chronic active hepatitis B should be appropriately counseled. Individuals who work with blood products or who are at high risk for a hepatitis B infection should be offered immunization. For additional information on this topic the reader is referred to a review on this topic.[35]

HIV testing

An HIV infection can lead to acquired immunodeficiency syndrome (AIDS). This viral infection targets and debilitates the immune system. Initially, the disease was found primarily in homosexual men, but the infection has been confirmed in the heterosexual population as well. Many people who do not know that they are infected can infect others, mainly through sexual contact. Of concern, is that an asymptomatic woman who is infected with the virus can pass the infection to her unborn child. HIV testing should be performed on all couples trying to conceive.

MEDICAL HISTORY

An important aspect of preconceptional care is an in-depth medical history to identify medical problems that could complicate a pregnancy. A medical condition or the medications used to treat the condition can have an impact on the establishment and health of a pregnancy. Another concern is that the pregnancy can worsen the medical condition and impact on the health of the mother. In some cases, obtaining medical clearance may be indicated from the treating physician or a high-risk obstetrician before initiating treatment. Some of the more common medical problems that can be encountered are discussed below.

Diabetes mellitus

Diabetes mellitus is a commonly encountered medical problem during pregnancy. It has been estimated that approximately 6% of the general population and 3% of pregnant women have diabetes. Diabetes is associated with an increased incidence of congenital anomalies, which is directly related to the control of the diabetes prior to conception. A blood glucose level gives the clinician an idea of the glucose control at that point in time. The hemoglobin (Hgb) A1C level is an indicator of how well the diabetes has been controlled over the previous 3–4 months. If the Hgb A1C is in the normal range then the incidence of congenital anomalies approaches the incidence in the general population. In addition to the increased risk of congenital anomalies, poorly controlled diabetes during pregnancy is associated with increased fetal and maternal wastage. Therefore, the objective in the diabetic woman is to establish tight control of glucose levels prior to conception. Vascular disease can complicate diabetes and

warrants an assessment of renal function and an ophthalmologic examination (to rule out a retinopathy) prior to pregnancy.

Screening for diabetes should be considered in any woman who is overweight (BMI > 27), has documented insulin resistance, hypertension, chronic anovulation (PCO), a previous pregnancy complicated by gestational diabetes or macrosomia, or a family history of diabetes. Screening for diabetes can be accomplished by a fasting plasma glucose test or the 75 g oral glucose tolerance test (which includes a fasting plasma glucose test and a 2-hour glucose determination). The American Diabetes Association interpretation of the glucose tolerance test is given in Table 4.1. Patients diagnosed with diabetes should be referred for further evaluation and treatment.

Hypertension

Chronic hypertension is a commonly encountered medical problem and, if left untreated, can cause irreparable damage to the kidneys and heart. Women with chronic hypertension should have baseline renal studies performed prior to conceiving. Hypertension places a woman at increased risk of superimposed pre-eclampsia during pregnancy, even if it is well controlled. Presently, there are many types of medications that control hypertension. The adverse effects of any medication should be investigated to assess whether there are any adverse effects on the fetus. As a general guideline, methyldopa and labetalol are considered safe to take during pregnancy. Angiotensin-converting enzyme inhibitors (ACE inhibitors) and angiotensin II receptor antagonists are contraindicated during pregnancy.

Advanced maternal age

Current technology has increased the ability for women well over the age of 40 years to achieve a pregnancy with egg donation. However, older women are at increased risk for complications during pregnancy as compared to their younger counterparts. With advancing age, every woman is at increased risk of developing diabetes mellitus, chronic hypertension, and coronary artery disease, which can complicate a pregnancy. Therefore, it is prudent that every woman over the age of

Table 4.1 The 2006 American Diabetes Association (ADA) threshold glucose values for a 2-hour glucose tolerance test.

Time	*Normal*	*Borderline*	*Diabetes mellitus*
Fasting	< 100 mg/dl	100–125 mg/dl	≥ 126 mg/dl
2 hours	< 140 mg/dl	140–199 mg/dl	≥ 200 mg/dl

40 undergo a medical evaluation prior to undergoing treatment to assess her medical fitness for a pregnancy.

Medication use

All medications that a woman is taking should be investigated for potential detrimental effects on a pregnancy. The Food and Drug Administration (FDA) has placed medications into several categories based on animal and human studies that have investigated the harmful effects during pregnancy:

FDA drug categories for fetal toxicity

Category	Description
A	Adequate, well-controlled studies in pregnant women have not shown an increased risk of fetal abnormalities.
B	Animal studies have revealed no evidence of harm to the fetus; however, there are no adequate and well-controlled studies in pregnant women. **or** Animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus.
C	Animal studies have shown an adverse effect and there are no adequate and well-controlled studies in pregnant women. **or** No animal studies have been conducted and there are no adequate and well-controlled studies in pregnant women.
D	Studies, adequate well-controlled or observational, in pregnant women have demonstrated a risk to the fetus. However, the benefits of therapy may outweigh the potential risk.
X	Studies, adequate well-controlled or observational, in animals or pregnant women have demonstrated positive evidence of fetal abnormalities. The use of the product is contraindicated in women who are or may become pregnant.

It is clear that if a pregnant woman is taking a category X medication that it should be discontinued. However, if a medication falls into one of the other categories, continuation of the medication during pregnancy may be considered if benefits outweigh the risks. Consultation with a specialist is important and the decision to continue the medication is dependent on several factors. If the medical condition is not life-threatening or of significant importance, then

serious consideration should be given to discontinuing the medication. In other situations, not treating the medical condition may put the mother or fetus at risk. In this situation, the clinician must try to select a medication that is effective in treating the condition and yet minimizes the risk to the fetus. For any medical therapy, if the benefits of treating the medical condition clearly outweigh the risks to the fetus then the medication should be continued.

There are several resources to find information about the safety of any medication during pregnancy. The Physician's Desk Reference (PDR) is a good resource. Pharmacists have access to information that may be helpful. In addition, there are several internet resources, including:

- US National Library of Medicine and the National Institute of Health: www.nlm.nih.gov/medlineplus/druginfo/drug_Wa.html
- The Pregnancy and Environmental Hotline: www.thegenesisfund.org
- REPRORISK® system can be purchased from Micromedix, Inc (www.micromedex.com). This system embodies several other teratology data bases including REPROTEST®, REPROTOX®, Shapard's catalog of Teratogentic Agents, and TERIS (Teratogen Information System)
- www.perinatology.com/exposures/druglist3.htm

REPRODUCTIVE HISTORY

A reproductive history is an important part of preconceptional care and the details of previous pregnancies should be obtained. If a woman has had a previous pregnancy with complications, she could be at increased risk for the recurrence of these complications with a future pregnancy. Therefore, any pregnancy with an abnormal outcome should be investigated before attempting pregnancy. The correction of an underlying problem may improve the outcome of a future pregnancy. Some of the more common issues concerning the reproductive history are discussed below.

Recurrent miscarriages

If a couple has experienced two or more miscarriages, then an evaluation is indicated. A survey of lifestyle issues and environmental factors may give insight into the pregnancy losses. The workup includes serum karyotypes on both the female and male partner to rule out chromosomal anomalies. A balanced translocation can be present in up to 6–8% of couples. A menstrual history is important to determine whether ovulatory dysfunction may be a contributing factor. The female partner should have an assessment of TSH level, glucose, lupus anticoagulant, and anticardiolipin antibodies. An assessment of the uterine cavity should also be performed to rule out an anatomic reason for the pregnancy losses, such as uterine fibroids, Müllerian defects, and DES changes. An examination of the uterine cavity can be accomplished by a hysterosalpingogram, sonohysterogram, or a hysteroscopy.

Previous stillborn or infant born with congenital anomalies

In most cases, when a previous pregnancy has resulted in a stillbirth or a baby with birth defects, testing has been performed on the fetus and the couple has undergone counseling. However, if there is uncertainty about the depth or scope of the workup, then the couple should be referred to a high-risk obstetrician for a consultation to determine the risk with a future pregnancy.

History of premature labor

The causes of premature labor are varied and can be secondary to premature rupture of the membranes, an abnormal uterine cavity (secondary to uterine fibroids, a Müllerian defect, and *in utero* DES exposure), chorioamnionitis, or an incompetent cervix. A history of premature labor places a woman at increased risk of a similar occurrence with a future pregnancy. A pregnancy complicated with premature labor and a malpresentation increases the likelihood of an underlying Müllerian anomaly, which has an incidence of 2–3% in the general population. A vaginal ultrasound and a hysterosalpingogram will help to determine whether there is any abnormality of the uterine cavity. Painless dilatation prior to the delivery suggests the diagnosis of incompetent cervix. These women should be counseled on the benefits of a cervical cerclage with a future pregnancy. Finally, a multiple pregnancy should be avoided in women with a previous history of premature labor.

Gestational diabetes

A woman who has been diagnosed with gestational diabetes during a pregnancy is at increased risk of recurrence during a future pregnancy. In addition, these women are at increased risk of developing adult onset diabetes during their lifetime (approximately 2–4% chance per year). For this reason, women with a history of gestational diabetes should be screened for glucose intolerance with a fasting blood glucose or a 2-hour glucose tolerance test. If diabetes is diagnosed then referral to a medical endocrinologist or a high-risk obstetrician would be in order prior to attempting pregnancy. Adequate control of diabetes before conception decreases the chance of congenital anomalies and complications during the pregnancy.

Severe pre-eclampsia

Pre-eclampsia complicates 6–8% of all pregnancies. In most cases, pre-eclampsia occurs during the first pregnancy and does not recur. However, severe pre-eclampsia with onset during the second trimester may recur in 10–15% of future pregnancies. It may be increased to a greater degree if there are any underlying risk factors including diabetes, renal dysfunction, chronic hypertension, or a thrombophilia. Women with a history of severe pre-eclampsia may benefit from a referral to a high-risk obstetrician for counseling.

OCCUPATIONAL HISTORY

There is increased awareness about the impact of environmental toxic exposures on general and reproductive health. Toxic exposures at the workplace can put some individuals at considerable risk. The Occupational Safety and Health Administration (OSHA), a federal agency of the Department of Labor, was established in 1970 and has monitored safety in the workplace. One of the three categories of hazardous substances monitored by the OSHA is reproductive toxins. Reproductive toxins are categorized as mutagens, teratogens, fertility toxins, and toxins transferred at lactation. It has been estimated that 17% of working women are exposed to known teratogens in the workplace.[36] The following is a discussion of some occupational risks that may pose a risk to reproduction.

Exposure to anesthetic gases

It is well documented that women who are exposed to anesthetic gases (i.e. operating room personnel, dental hygienists) are at increased risk for infertility, spontaneous abortion, and congenital anomalies.[37–39] Of interest is that paternal exposure may also be of consequence. Women who were impregnated by men who were exposed to anesthetic gases were found to be at greater risk of a having a pregnancy complicated by a spontaneous abortion and congenital anomalies.[39]

Exposure to beauty salon chemicals

Beauty salon workers work in a complex environment and are exposed to many chemicals in hair dyes, permanent solutions, and bleaches. Furthermore, nail sculpturing also involves exposure to volatile chemicals that can be inhaled. A previous study concluded that beauty salon workers have an increased risk of miscarriage and infertility.[40] The risk was influenced by the number of hours worked per week, the use of formaldehyde disinfectants, the practice of using gloves during hair treatments, and whether nail sculpturing was done in the salon.

Exposure to video display terminals

Many jobs require long hours in front of a video display terminal (VDT), or computer monitor. The theoretic concern over a VDT is that it creates an electromagnetic field. It is reassuring that studies have failed to associate VDT exposure with an increased risk of a spontaneous abortion and infertility.[41,42]

Organic solvents

All women should be asked about exposure to organic solvents. Organic solvents include aliphatic and aromatic hydrocarbons, phenols, trichloroethylene, xylene,

vinyl chloride, and acetone. Women at greatest risk for exposure to these chemicals are those who work in the health-care profession, and the clothing and textile industries. However, women in other professions may be unknowingly exposed to these agents, as well. In a previous prospective study, women who were exposed to organic solvents during the first trimester were followed throughout the pregnancy.[43] When compared to a control group there was no statistical difference in the rate of a spontaneous abortion and minor malformations. However, the group exposed to organic solvents had a statistically higher incidence of major malformations when compared to controls (12% vs 1%, $p < 0.001$).

Exposure to spermatotoxins

From a fertility standpoint, males are more susceptible to toxins since sperm production is an ongoing process. The first report of an occupationally related spermatotoxin appeared in the mid-1970s.[44] It showed that men who worked at factories which produced DBCP (a pesticide) had an increased incidence of infertility – the severity being dependent on the dose and length of exposure. Since this report was released, other spermatotoxins have been discovered, including kepone, ethylene glycol ethers, carbon disulfide, naphthyl methylcarbamate, ethylene dibromide, organic solvents, and lead.

Recommendation

As part of preconceptional care it is important to assess whether either the male or female partner is exposed to any toxin in the workplace that may prove detrimental. All employers must provide material safety data sheets (MSDS) of all chemicals that are present in the workplace. Any potential risk is dependent on the specific toxin, length of time of exposure, and degree of exposure. If there is concern about an exposure, a consultation with a specialist in occupational medicine will help to clarify the risk.

GENETIC COUNSELING AND SCREENING

As our knowledge in the field of genetics grows, increased responsibility will rest with those who counsel and prepare couples for pregnancy. A genetic history should be part of every evaluation of the infertile couple. There is no consensus as to the scope and breadth of the genetic history. Ideally, every couple contemplating pregnancy would be evaluated by a geneticist or genetic counselor to determine their genetic risks. This obviously is not practical, but a thorough assessment of genetic risk and counseling is indicated.

It is important that any practitioner who is providing genetic counseling has an understanding of the disease process, its inheritance, and the limitations of the screening tests that are currently available. In addition, it is of the utmost importance that the clinician stays abreast of new clinical developments and screening tests that become available. In some cases, referral to a genetic counselor is indicated. Recommendations for genetic counseling and position statements concerning testing have been published by the American College of Obstetrics and Gynecology (www.acog.com) and the American College of Medical Genetics (www.acmg.net). An overview of some of the more common genetics issues follows.

Ancestral backgrounds

An important aspect of the genetic history is an exploration of the ancestral backgrounds of both partners. Historically, individuals of a specific ethnic population are more likely to reproduce with others from the same population. This gives an opportunity for the propagation and higher prevalence rate of certain genetic disorders within these populations. Autosomal recessive diseases are most common. In this inheritance pattern, carriers are asymptomatic for the disease and both partners must be carriers to be at risk (one in four chance) of having a child that could be affected by the disease. Some of the commonly inherited conditions and indicated testing are discussed below. Many of these diseases can result in early death or significant morbidity. If an individual does not have an at-risk ancestral background but does have a family history of the disease, he/she should undergo screening (Table 4.2). It is also important that any individual who is identified to be a carrier of a genetic disease should be instructed to tell his/her siblings so that they too can undergo screening.

Screening for chromosomal anomalies

In some situations, a chromosomal analysis may be indicated. The following are some indications in which a karyotype of the male and female partners may be indicated.

Recurrent miscarriages

Couples with two or more miscarriages have a 5–8% chance of having a balanced translocation.[45,46] This chromosomal abnormality may explain the repeated miscarriages. While this chromosomal abnormality may put a couple at risk for a miscarriage, most gametes that are produced in affected individuals are chromosomally normal. If a viable pregnancy is established when one of the partners has a balanced translocation there is concern that the fetus may have a chromosomal imbalance that would increase the risk of congenital anomalies. In these cases, the couple may consider genetic testing with chorionic villus sampling or a genetic amniocentesis.

Table 4.2 Genetic testing based on ancestral backgrounds

Ancestral 'group' or country of origin	*Disease*	*Screening test*
Caucasian, Native American	cystic fibrosis*	DNA testing
French Canadian, Cajun	Tay-Sachs	assessment of hexosaminadase enzyme activity or DNA testing
Jewish†	Canavan disease	DNA testing
	cystic fibrosis*	DNA testing
	familial dysautonomia	DNA testing
	Tay-Sachs	hexosaminadase enzyme activity or DNA testing
African, Asian, Cambodia, Caribbean, Central America, India, Indonesia, Laos, Malaysia, Mediterranean, Middle Eastern, Pakistan, Thailand, Turkey, Vietnam	Hemoglobinopathies	CBC, Hgb electrophoresis

*It is impractical to screen for all cystic fibrosis mutations since over 1000 mutations have been identified. Therefore, the clinician must realize the limitations of the screening and counsel couples accordingly. For instance, the detection rate of cystic fibrosis carriers in the Caucasian, Native American, and Jewish populations is 90, 94, and 97%, respectively

†Recommendations from the American College of Obstetricians and Gynecologists (ACOG). Committee Opinion; Number 298, August 2004

History of Down's syndrome

If a first-degree relative was diagnosed with Down's syndrome, then it should be ascertained whether that affected individual underwent chromosomal testing. Approximately 90% of cases of Down's syndrome are trisomy 21, which is a sporadic event. The remaining 10% are the result of a translocation. Of these, half are inherited and the other half occur *de novo*. Therefore, if there is uncertainty about the etiology or the result of the chromosomal analysis of the affected individual with Down's syndrome then a karyotype should be offered.

History of stillbirth, congenital anomalies

In situations when a couple gives birth to a stillborn infant or an infant with a congenital anomaly, the chromosomal makeup of the fetus is usually tested. If this testing was not done or was inconclusive then chromosomal testing of the couple should be offered.

Severe male factor infertility

In males with azoospermia or severe oligospermia (< 5 million sperm/cc) there is a 5–15% chance of chromosomal anomalies and 3–15% of microdeletions in the Y chromosome.[47–49]

Fragile X screening

Mental retardation can be caused by many factors including environmental, social, genetic, and unknown factors. The most commonly inherited type of mental retardation is Fragile X syndrome, which affects 1 in 1200 males and 1 in 2500 females. Fragile X syndrome is the result of expansion of a repeat section on the long arm of the X chromosome. The degree of mental retardation can be borderline to severe and is related to the number of repeats within the mutation allele. Fragile X is associated with specific findings including a long thin facies with prominent jaws, autistic features, and speech and language difficulties. Fragile X syndrome has an atypical inheritance. From one-third to one-half of females who carry the full mutation have Fragile X syndrome. If a woman is a carrier of a premutation, then she will not be affected by Fragile X syndrome, but she is at increased risk of premature ovarian failure (prior to the age of 40). The premutation is identified in 2% and 14% of women with isolated and familial premature ovarian failure, respectively.[50] Fragile X screening should be considered for couples with a family history of unexplained mental retardation, autism, or premature ovarian failure.

Maternal age counseling

Advanced maternal age is associated with an increased incidence of postfertilization chromosomal abnormalities in the embryo. This explains why increased maternal age is associated with an increased incidence of infertility, pregnancy loss, and fetal chromosomal abnormalities. While most pregnancies complicated by a chromosomal anomaly result in a miscarriage, others will progress to term, resulting in a delivery. The incidence of fetal chromosomal abnormalities in relation to maternal age is shown in Table 4.3. Once pregnancy is achieved, the risk of a fetal chromosomal abnormality can be evaluated with triple serum screening of AFP, hCG, and estriol levels. For those at risk, prenatal genetic testing can be performed with a genetic amniocentesis or chorionic villus sampling.

Paternal age counseling

There is evidence that advanced paternal age can also pose a risk to the fetus. The increase in risk is not based upon chromosomal abnormalities, but in the transmission of new genetic mutations. In contrast to oogenesis, spermatogenesis is an ongoing process that continues throughout a man's life, beginning at puberty. The increased frequency of divisions within the spermatocytes increases the chance of errors that can result in a new mutation. These new mutations can result in the passage of an autosomal dominant disorder to an offspring or an X-linked recessive disorder to a grandson which is called the 'grandfather effect'. The incidence of the inheritance of an autosomal dominant condition is 1 in 5000–10 000 deliveries. While the paternal age effect on the occurrence of any specific autosomal dominant condition may be low, the combined effect on

Table 4.3 Chromosomal abnormalities in liveborn infants and maternal age*

Maternal age (years)	*Risk for Down's syndrome*	*Total risk for chromosomal anomalies*†
20	1/1667	1/526
21	1/1667	1/526
22	1/1429	1/500
23	1/1429	1/500
24	1/1250	1/476
25	1/1250	1/476
26	1/1176	1/476
27	1/1111	1/455
28	1/1053	1/435
29	1/1000	1/417
30	1/952	1/385
31	1/909	1/385
32	1/769	1/322
33	1/602	1/286
34	1/485	1/238
35	1/378	1/192
36	1/289	1/156
37	1/224	1/127
38	1/173	1/102
39	1/136	1/83
40	1/106	1/66
41	1/82	1/53
42	1/63	1/42
43	1/49	1/33
44	1/38	1/26
45	1/30	1/21
46	1/23	1/16
47	1/18	1/13
48	1/14	1/10
49	1/11	1/8

*The data presented above were modified from Hook DB, Cross PK, Schreinemachers DM. Chromosomal abnormality rates at amniocentesis and in live-born infants. J Am Med Assoc 1983; 249: 2034–8, and Hook EB. Rates of chromosomal abnormalities at different maternal ages. Obstet Gynecol 1981; 58: 282–5

†The other chromosomal anomalies that are increased with maternal age in addition to 47,+21 (Down's syndrome) are 47,+18, and 47,+13, 47,XYY (Klinefelter's syndrome), 47,XYY, and 47,XXX. The incidence of 47,XXX for women between the ages of 20 and 32 years is not available

all autosomal dominant conditions can be significant. While advanced paternal age increases the risk of these new mutations, testing for all of these autosomal dominant and X-linked disorders is not possible. Further, there is no consensus as to the definition of advanced paternal age. It has been estimated that one-third of new autosomal dominant mutations are the result of advanced paternal age (> 40). It seems prudent to suggest that men complete their families by age 40.

Even though there is no easy way to screen for all of these genetic conditions *in utero*, at the very least, couples should be made aware of the potential risk and given the opportunity to meet with a genetic counselor.

CONCLUSION

Any couple who is interested in pregnancy should have a thorough evaluation to identify factors that may put the woman at risk for a complicated pregnancy. Depending on the situation, further workup or counseling may be indicated before the couple attempts pregnancy.

REFERENCES

1. Cigarette smoking among adults – United States, 2004. MMWR 2005; 54(44): 1121–4.
2. Smoking and infertility. The Practice Committee of the American Society for Reproductive Medicine. Fertil Steril 2004; 81: 1181–6.
3. Zenzes MT. Smoking and reproduction: gene damage to human gametes and embryos. Hum Reprod Update 2000; 6: 122–31.
4. Yang Q, Sherman SL, Hassold TJ et al. Risk factor for trisomy 21: maternal cigarette smoking and oral contraceptive use in a population-based case-control study. Genet Med 1999; 1: 80–8.
5. Eggert J, Holger T, Engfeldt P. Effects of alcohol consumption on female fertility during an 18-year period. Fertil Steril 2004; 81: 379–83.
6. Klonoff-Cohen H, Lam-Kruglick P, Gonzalez C. Effects of maternal and paternal alcohol consumption on the success rates of in vitro fertilization and gamete intrafallopian transfer. Fertil Steril 2003; 79: 330–9.
7. Prevalence of Overweight and Obesity Among Adults: United States, 1999–2002; http://www.cdc.gov/nchs/products/pubs/pubd/hestats/obese/obse99.htm.
8. Falsetti L, Pasinetti E, Mazzani MD, Gastaldi A. Weight loss and menstrual cycle: clinical and endocrinological evaluation. Gynecol Endocrinol 1992; 6: 49–56.
9. Watkins ML, Rasmussen SA, Honein MA. Maternal obesity and risk for birth defects. Pediatrics 2003; 111: 1152–8.
10. Nohr EA, Bech BH, Davies MJ et al. Prepregnancy obesity fetal death: a study within the Danish national birth control. Obstet Gynecol 2005; 106: 250–9.
11. Endler GC, Mariona FG, Sokol RJ et al. Anesthesia-related maternal mortality in Michigan, 1972–1984. Am J Obstet Gynecol 1988; 159: 187–93.
12. The practical guide: Identification, evaluation and treatment of overweight and obesity in adults. National Heart Lung and Blood Institute and North American Association for the study of obesity. Bethesda (MD): National Institutes of Health, 2000; www.nhlbi.nih.gov/guidelines/obesity/practgde.htm.
13. The American College of Obstetricians and Gynecologists. Committee opinion; obesity in pregnancy 2005; Number 315.
14. Signorello LB, McLaughlin JK. Maternal caffeine consumption and spontaneous abortion: a review of the epidemiologic evidence. Epidemiology 2004; 15: 229–39.
15. Mulinare J, Cordero JF, Erickson JD, Berry RT. Periconceptional use of multivitamins and the occurrence of NTDs. J Am Med Assoc 1988; 260: 3141–5.
16. Bower C, Stanley FJ. Dietary folate as a risk factor for NTDs: evidence from a case control study in Western Australia. Med J Aust 1989; 150: 613–19.
17. Miles JL, Rhoads GG, Simpson JL et al. The absence of a relationship between the periconceptional use of vitamins and NTDs. N Engl J Med 1989; 321: 430–5.

18. Milunsky A, Jick H, Jick SS et al. Multivitamin/folic acid supplementation in early pregnancy reduces the prevalence of NTDs. J Am Med Assoc 1989; 262: 2847–52.
19. Hall JG, Solehdin F. Folate and its various ramifications. Adv Pediatr 1998; 45: 1–35.
20. McDonald SD, Ferguson S, Tam L et al. The prevention of congenital anomalies with periconceptional folic acid supplementation. J Obstet Gynaecol Can 2003; 25: 115–121.
21. Shaw GM, Velie EM, Schaffer D. Risk of neural tube defect-affected pregnancies among obese women. J Am Med Assoc 1996; 275: 1093–6.
22. MRC Vitamin Study Research Group. Prevention of NTDs: results of the Medical Research Council Vitamin study. Lancet 1991; 338: 131.
23. Smithells RW, Nevin NC, Sellers MJ et al. Further experience of vitamin supplementation for the prevention of NTD recurrences. Lancet 1983; 1: 1027.
24. Vergel RG, Sanchez LR, Heredero BL et al. Primary prevention of NTDs with folic acid supplementation: Cuban experience. Prenat Diagn 1990; 10: 149.
25. Rothman KJ, Moore LL, Singer MR et al. Teratogenicity of high vitamin A intake. N Engl J Med 1995; 333: 1369–73.
26. Lammer EJ, Hayes AM, Schunior A, Holmes LB. Unusually high risk for adverse outcomes of pregnancy following fetal isotretinoin exposure. Am J Hum Genet 1988; 43: A58.
27. Donald M. Marcus, Wayne R. Snodgrass. Do no harm: avoidance of herbal medicines during pregnancy. Obstet Gynecol 2005; 105: 1119–22.
28. Ondrizek RR, Chan PJ, Patton WC, King A. An alternative medicine study of herbal effects on the penetration of zona-free hamster oocytes and the integrity of sperm deoxyribonucleic acid. Fertil Steril 1999; 71: 517–22.
29. Morreale de Escobar G, Obregon MJ, Escobar del Rey F. Is neuropsychological development related to maternal hypothyroidism or to maternal hypothyroxinemia? J Clin Endocrinol Metab 200; 85: 3975–87.
30. Haddow JE, Palomaki GE, Allan WC et al. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. N Engl J Med 1999; 342: 549–555.
31. Alexander EK, Marqusee E, Lawrence J et al. Timing and magnitude of increases in levothyroxine requirements during pregnancy in women with hypothyroidism. N Engl J Med 2004; 351: 241–9.
32. Bayer SR, Turksoy RN, Emmi AM, Reindollar RH. Rubella susceptibility of an infertile population. Fertil Steril 1991; 56: 145–6.
33. Reid KC, Grizzard TA, Poland GA. Adult immunizations: recommendations for practice. Mayo Clin 1999; 74: 377–84.
34. Rodrigues J, Niederman MS. Pneumonia complicating pregnancy. Clin Chest Med 1992; 13: 679–91.
35. The Practice Committee of the American Society for Reproductive Medicine. Hepatitis and reproduction. Fertil Steril 2004; 82: 1754–64.
36. Makuc D, Lalich N. Employment characteristics of mothers during pregnancy. Health United States and Prevention Profile 1983. National Center for Health Statistics, DHSS Publication No (PHS) 841232. Washington, DC: US Government Printing Office, December 1983: 25–32.
37. Cohen EN, Bellville JW, Brown BW Jr. Anesthesia, pregnancy and miscarriage: a study of operating room nurses and anesthetists. Anesthesiology 1971; 35: 343–7.
38. Rowland AS, Baird DD, Weinberg CR et al. Reduced fertility among women employed as dental assistants exposed to high levels of nitrous oxide. N Engl J Med 1992; 327: 993–7.
39. Guirguis SS, Pelmear PL, Roy ML, Wong L. Health effects associated with exposure to anesthetic gases in Ontario hospital personnel. Br J Int Med 1990; 47: 490–7.
40. John EM, Savitz DA, Shy DM. Spontaneous abortions among cosmetologists. Epidemiology 1994; 5: 147–55.
41. Brent RL, Gordon WE, Bennett WR, Beckman DA. Reproductive and teratologic effects of electromagnetic fields. Reprod Toxicol 1993; 7: 535–80.

42. Parazzini F, Luchini L, La Vecchia C, Crosignani PG. Video display terminal use during pregnancy and reproductive outcome: a meta-analysis. J Epidemiol Community Health 1993; 47: 265–8.
43. Khattak S, K-Moghtader G, McMartin K et al. Pregnancy outcome following gestational exposure to organic solvents: a prospective controlled study. J Am Med Assoc 1999; 281: 1106–9.
44. Whorton D, Krauss RM, Marshall S et al. Infertility in male pesticide workers. Lancet 1977; 2: 1259–61.
45. Plouffe L, White EW, Tho ST et al. Etiological factors of recurrent abortion and subsequent reproductive performance of couples: have we made any progress in the past 10 years? Am J Obstet Gynecol 1992; 167: 313.
46. Harger JH, Archer DF, Marchese SG et al. Etiology of recurrent pregnancy losses and outcome of subsequent pregnancies. Obstet Gynecol 1983; 62: 574.
47. DeBraekeler M, Dao TN. Cytogenetic studies in male infertility: a review. Hum Reprod 1991; 6: 245–50.
48. Pryor JL, Kent-First M, Muallem A et al. Microdeletions in the Y chromosome of infertile men. N Engl J Med 1997; 336: 534–9.
49. Kent First MG, Kol S, Muallem A et al. The incidence and possible relevance of Y-linked microdeletions in babies born after intracytoplasmic sperm injection and their infertile fathers. Mol Hum Reprod 1996; 2: 943–50.
50. Sherman SL. Premature ovarian failure in the fragile X syndrome. Am J Genet 2000; 97: 189–194.

5.

Clinical algorithms

Michael M Alper

This chapter contains clinical algorithms which will aid the physician in the day to day management of the infertile couple. Each infertile couple presents with a different set of circumstances and the scope of the testing and recommended treatment will vary accordingly. The clinical algorithms are general guidelines regarding patient care and other circumstances, including patient choice, may dictate another course of management other than that presented.

The following clinical algorithms are presented:

Infertility evaluation
Unexplained infertility
Reduced ovarian reserve
Ovulatory dysfunction
Uterine factor
Tubal/peritoneal factor
Male factor

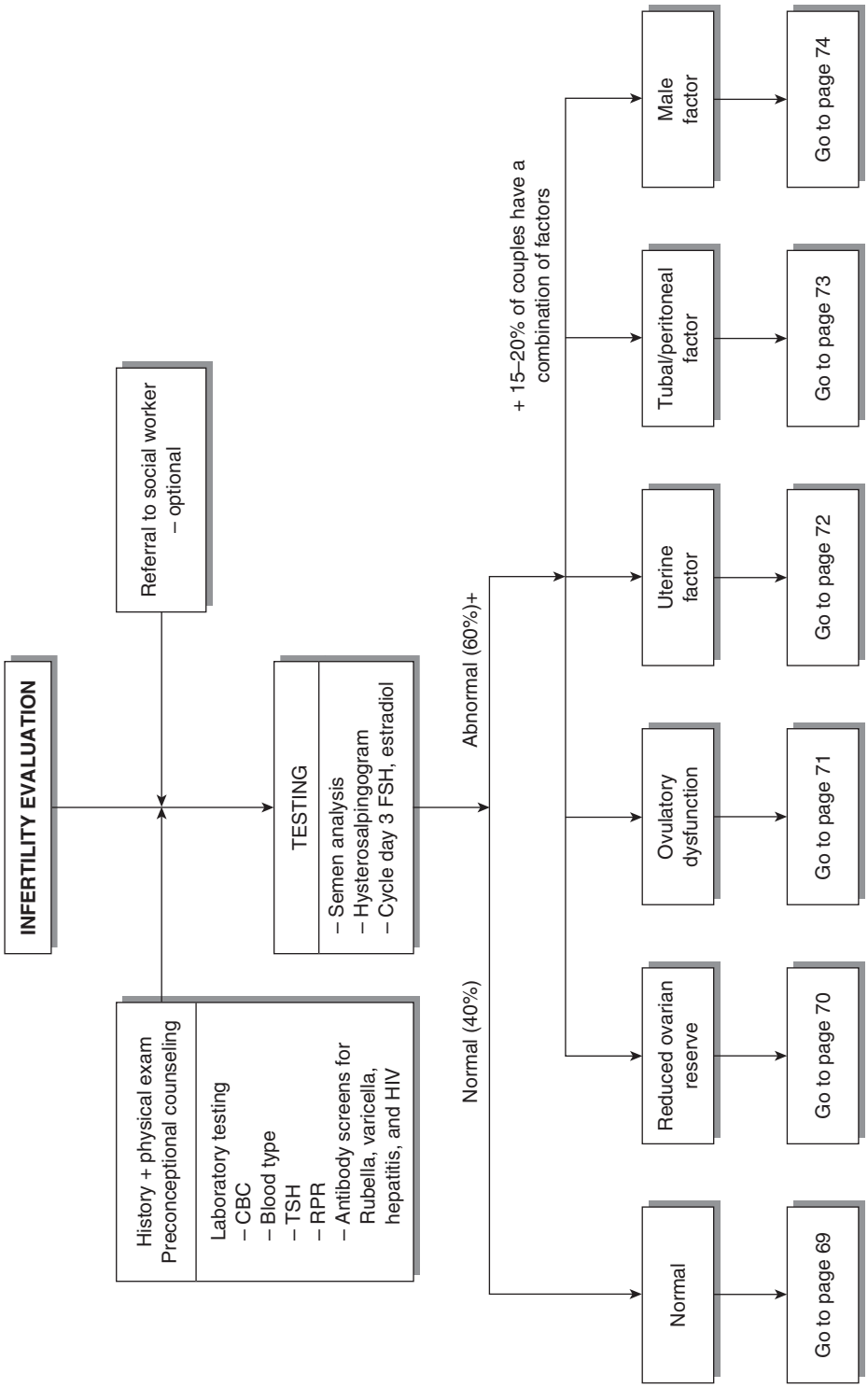

Figure 5.1 Infertility evaluation

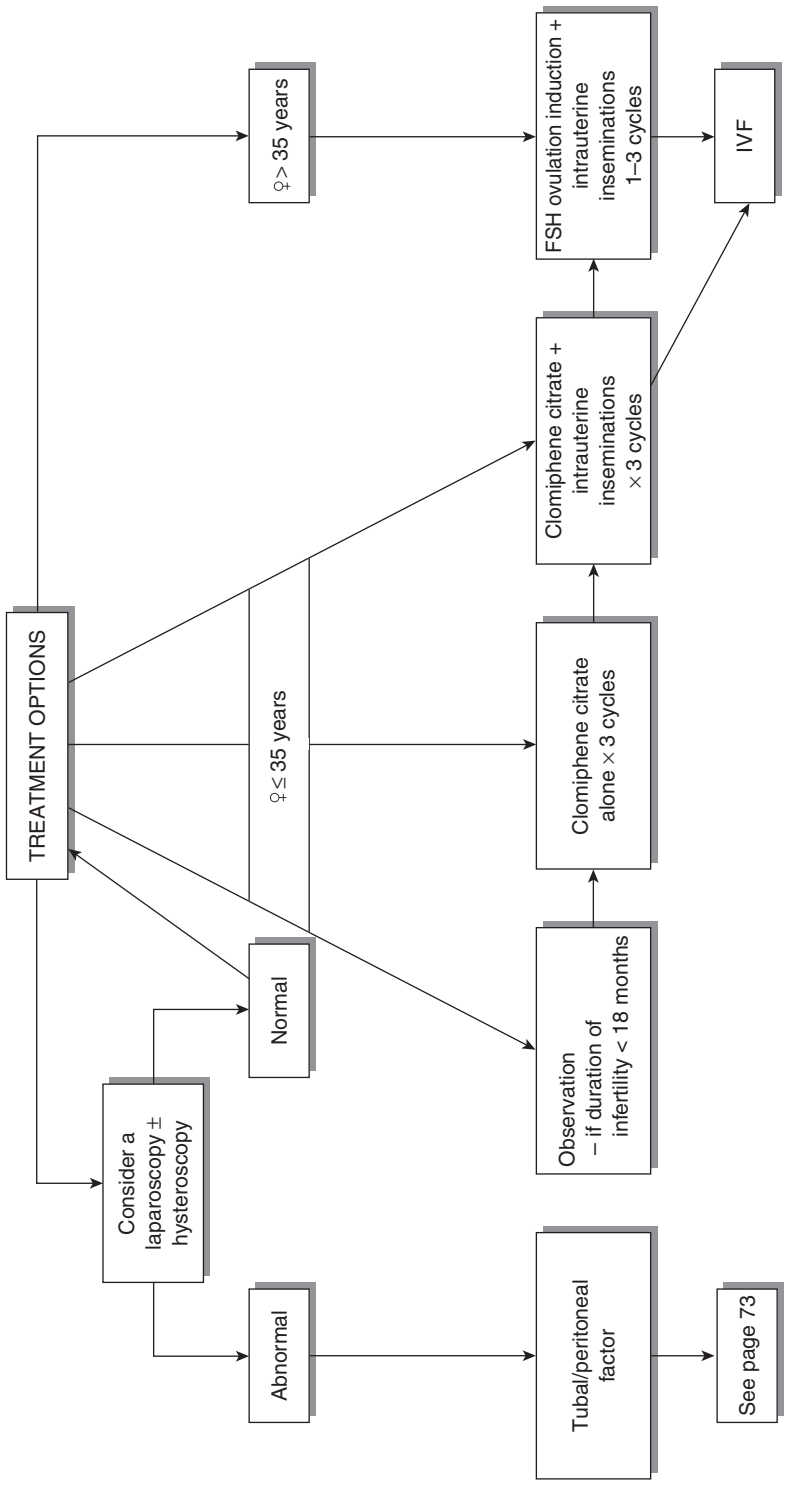

Figure 5.2 Unexplained infertility

DIAGNOSIS:

The diagnosis of reduced ovarian reserve is supported by any of the following:

1. Cycle day 3 FSH > 10 mIU/ml or estradiol > 70 pg/ml
2. Abnormal clomiphene challenge test

   To perform:
   - Cycle day 3 FSH, estradiol levels
   - Cloimphene citrate 100 mg cycle days 5–9
   - Cycle day 10 FSH level

   If any of the FSH levels are > 10 mIU/ml or the estradiol is > 70 pg/ml the test is considered abnormal
3. Documented poor response to aggressive ovulation induction

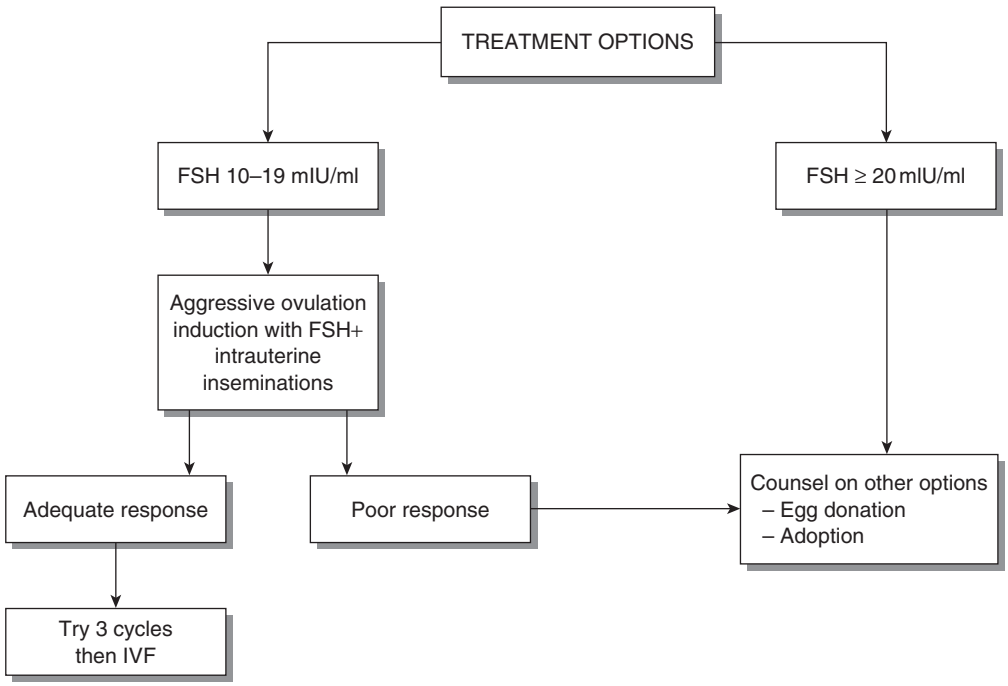

Figure 5.3 Reduced ovarian reserve

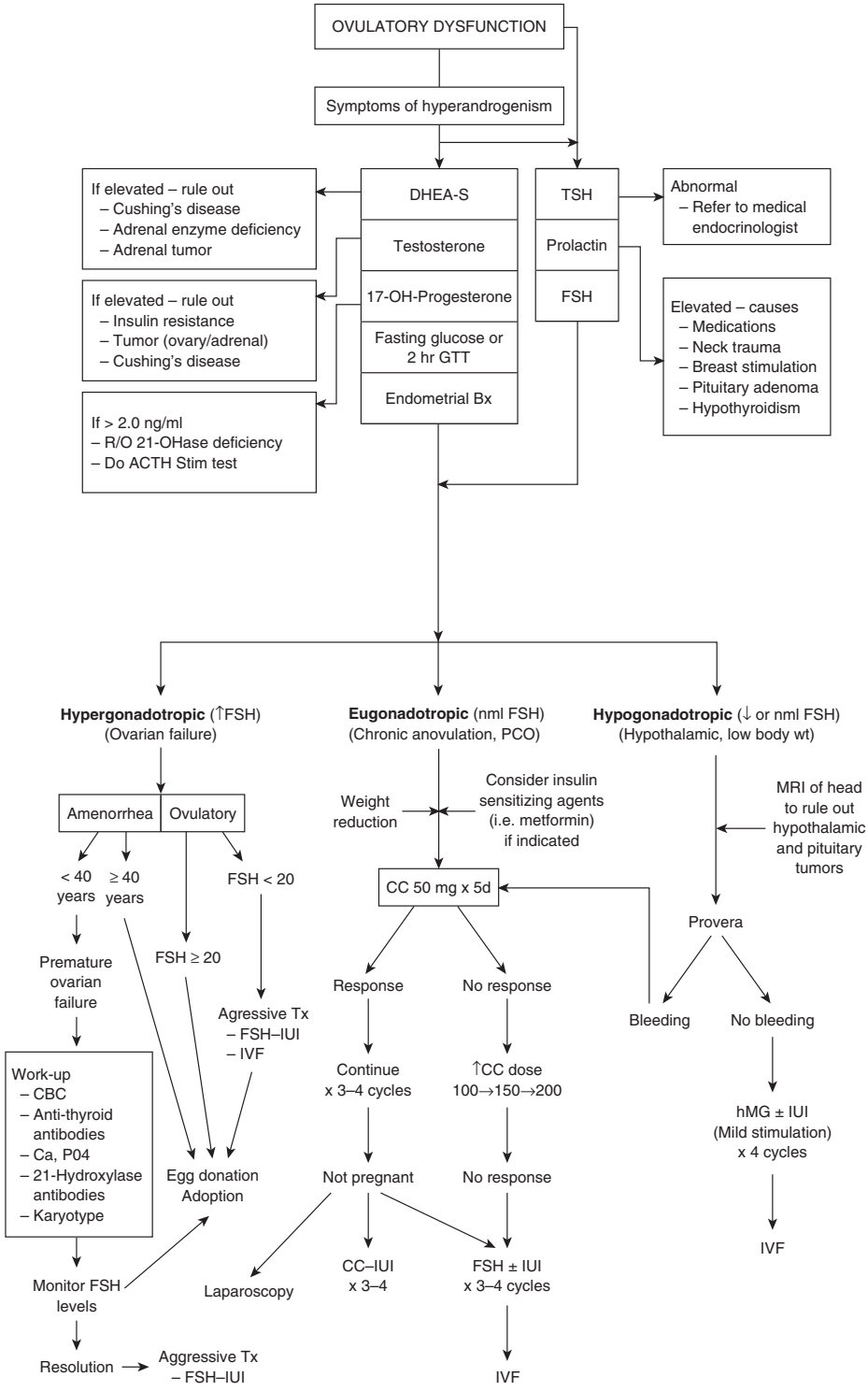

Figure 5.4 Ovulatory dysfunction

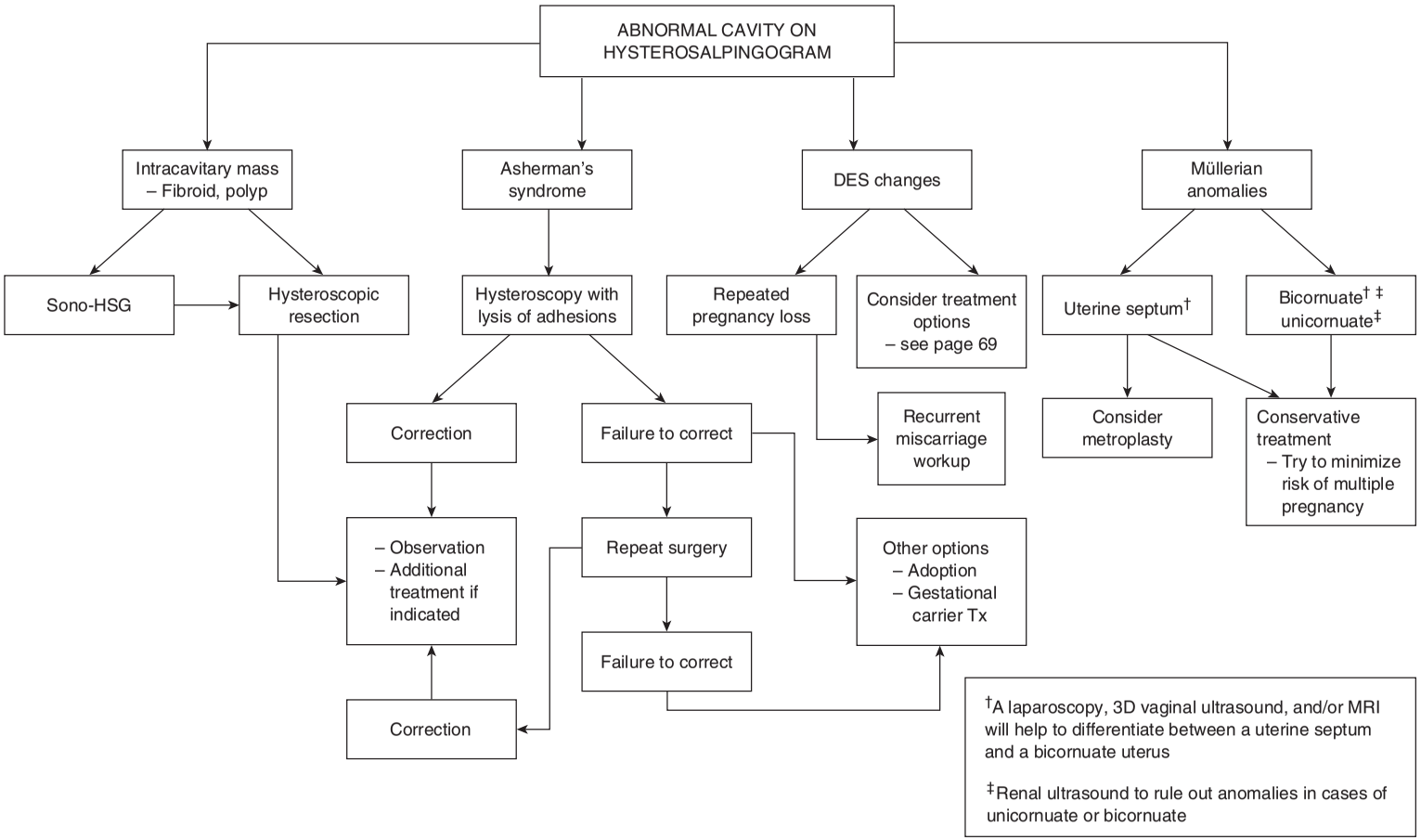

Figure 5.5 Uterine factor

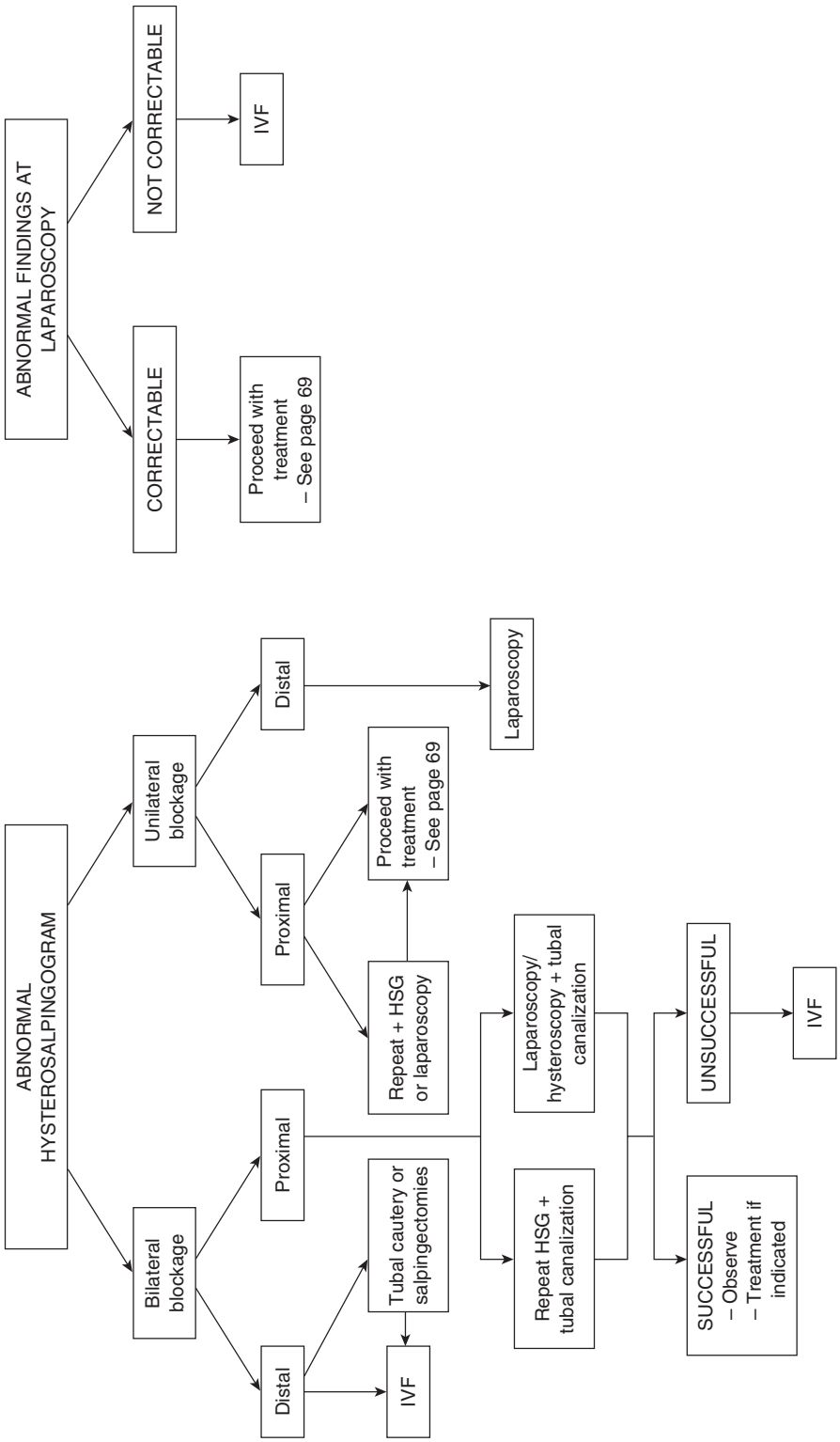

Figure 5.6 Tubal/peritoneal factor

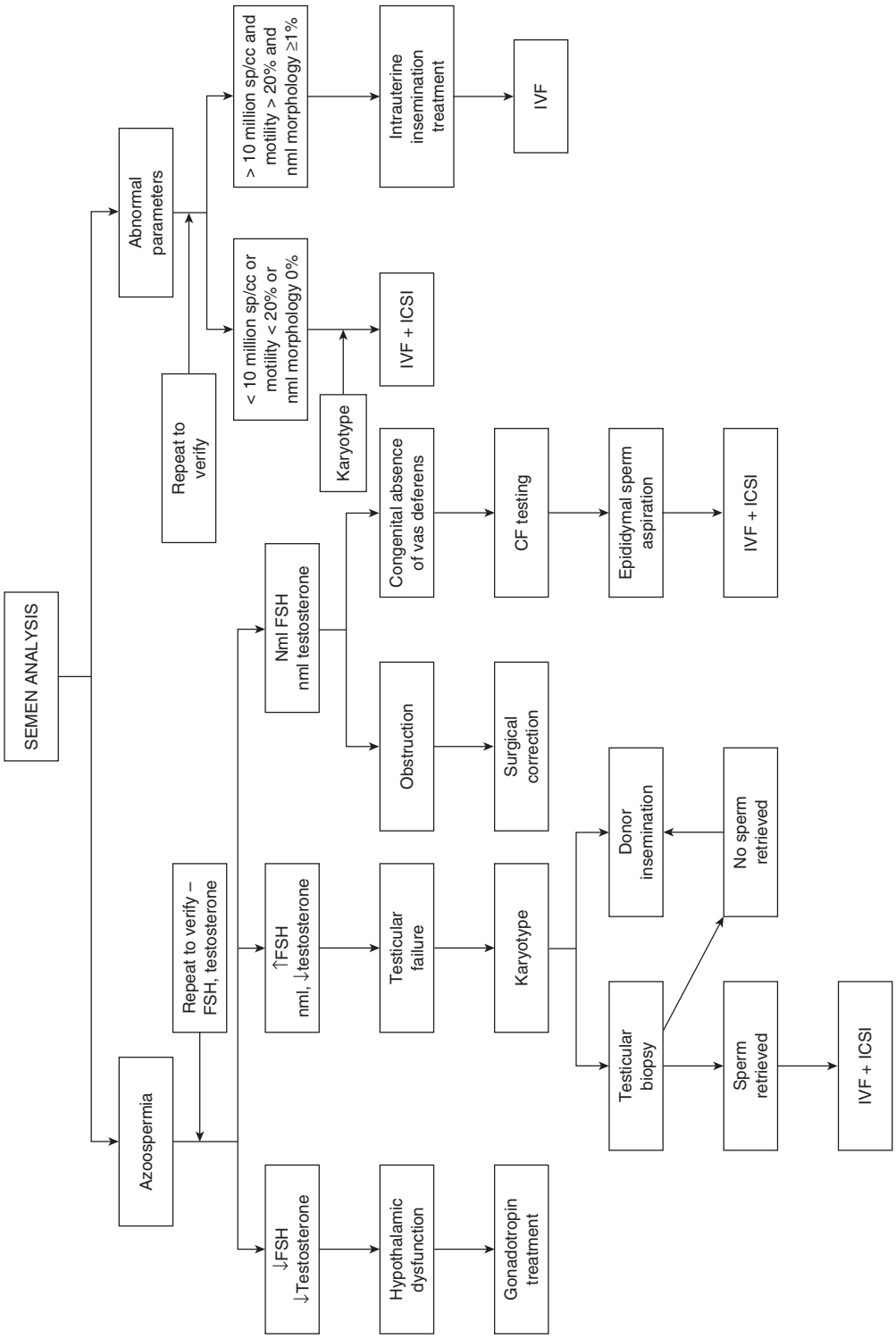

Figure 5.7 Male factor

6.

Treatment options I: ovulation induction

Selwyn P Oskowitz

Approximately 20% of infertile patients present with underlying ovulatory dysfunction as a major contributing factor to their infertility. Compared to other etiologies, ovulatory problems are often the easiest to correct. However, before any treatment is started, it is important to delineate the underlying cause of the ovulatory dysfunction (refer to the clinical algorithms in Chapter 5). The causes of ovulatory dysfunction are varied and can be categorized into *hypergonadotropic* (ovarian failure), *eugonadotropic* (chronic anovulation), and *hypogonadotropic* (hypothalamic, weight-related) states. Women who have ovarian failure or are perimenopausal generally do not respond favorably to medical treatment. There are many different medications, both oral and injectable, that can be used as part of ovarian stimulation. The choice of medication depends on the clinical presentation and the goal of the specified treatment. This chapter will review the current approach to ovulation induction.

Definition of terms

Ovulation induction (OI) is the term for the stimulation of ovulation in the anovulatory patient. The aim is to stimulate the growth of a single follicle with the release of its egg.
Superovulation (SO) is the term for stimulating the growth of multiple follicles with the release of eggs from each follicle. SO is an integral part of intrauterine insemination and IVF treatments.

CLOMIPHENE CITRATE

Clomiphene citrate (CC) was first introduced over 40 years ago and is the most commonly prescribed medication for the infertile woman. It can be prescribed

for different reasons, but its primary indication is for the correction of ovulatory dysfunction. When compared to other ovulation induction agents, CC is inexpensive, easy to administer, and does not require intense monitoring as is required with other ovulation induction agents. CC is the treatment of choice for those patients with PCOS (but some advocate pretreatment with metformin). Those patients with hypothalamic dysfunction who fail to have withdrawal bleeding following a progesterone challenge will not respond to CC. Failure to bleed from progesterone indicates a low estrogen state which counters the effectiveness of CC.

Pharmacology

CC is a triphenylethylene derivative that is related to tamoxifen and diethylstilbestrol. CC exists in two isomeric forms, zuclomiphene and enclomiphene citrate. The pharmacologic effect of this medication is from the zuclomiphene citrate isomer. The two available agents, under the trade names of Serophene® and Clomid®, contain equal amounts of these two isomers. CC is a weak estrogen agonist and binds to hypothalamic estrogen receptors, which decreases the replenishment of these receptors. The hypothalamus responds to the *pseudo*-hypoestrogenic state by increasing GnRH release, which, in turn, increases the secretion of FSH and LH from the anterior pituitary. CC has a half-life of 5 days and can be detected in the blood up to 6–8 weeks after administration. Despite the long half-life of clomiphene citrate, there are no reported increases in congenital anomalies that can be attributed to the use of this medication.

Side-effects

Since CC is a synthetic hormonal agent, side-effects are common but are not dose-related. Many of the side-effects that result are related to the pseudo-hypoestrogenic state that is created. The more common side-effects include vasomotor symptoms (10%), abdominal discomfort (6%), breast discomfort (2%), nausea/vomiting (2%), visual symptoms (2%), and headaches (1%). The use of ovulation induction agents, especially CC, may result in more significant pain associated with ovulation. Patients should also be made aware that the medication can commonly cause emotional irritability. While most women are able to deal with these side-effects, others find them intolerable. Prolonged administration of CC, through its anti-estrogenic action, can diminish cervical mucus production and thin the endometrial lining.

Dosage and administration

CC is available in 50 mg tablets. The initial recommended dose of CC is 50 mg daily for 5 days starting on cycle days 3, 4, or 5 following either a spontaneous or progesterone-induced menstrual period. If the menstrual cycle is less than 32–33 days in length, then the current dose should be continued for three cycles.

Couples should be instructed to use an ovulation predictor kit or time intercourse around the predicted peri-ovulatory period. If the cycles are greater than 33 days, the dosage of the CC should be increased in a stepwise fashion to 100 mg for 5 days. If this dose is inadequate, then the dose should be increased to 150 mg. If pregnancy is not achieved despite three ovulatory cycles, then other factors should be ruled out. If no other factors are identified then intrauterine inseminations can be added to the CC treatment since CC may have an adverse affect on cervical mucus in 15% of cases. Although higher doses up to 200 or 250 mg per day may be attempted, the majority of pregnancies occur at dosages of 150 mg daily or less. If the patient with chronic anovulation does not respond to a dose of 150 mg daily, then our approach is to proceed with injectable gonadotropins.

Outcome

Proceeding in the stepwise fashion as described above, the percentages of patients that ovulate on the 50 mg, 100 mg, and 150 mg dosage regimens are 50%, 22%, and 12%, respectively.[1] However, despite these high ovulatory rates with CC treatment, only 40–50% of women will achieve pregnancy.[2]

Pregnancy rate

The pregnancy rate is 10% per ovulatory cycle. The multiple pregnancy rate is 8–10%, most are twins but there is a 1% chance of triplets.

Options for the CC failures

1. Increasing CC doses up to 250 mg per day. In clinical experience, doses beyond 150 mg per day are rarely effective.
2. Metformin – of those patients who fail to respond to CC alone, if they are pretreated with metformin 500 mg t.i.d. for 4–6 weeks prior to another course of CC, 90% will ovulate.[3]
3. Dexamethasone – 0.5 mg po q.d.
4. Injectable gonadotropins.

Clomiphene citrate and unexplained infertility

In clinical practice, CC is most commonly prescribed for the woman with unexplained infertility. A previous meta-analysis confirmed that CC in comparison to placebo increases the chance of pregnancy.[4] However, other published data are inconclusive concerning the benefits of CC used in this circumstance.[5,6] Nevertheless, some couples and clinicians feel that this is a reasonable treatment. As with any therapy, most pregnancies are achieved within the first few months

of treatment. Therefore, the duration of treatment should be limited to 3–4 months, after which the treatment plan should be reassessed.

Recommended dosage

Typically 100 mg administered between cycle days 3 and 7. Limit the duration of treatment to 3–4 months. Instruct couples to use an ovulation predictor kit or have intercourse every other day between cycle days 10 and 18.

Pregnancy rate

The pregnancy rate is 6% per cycle.

LETROZOLE

Letrozole is an aromatase inhibitor. Its trade name is Femara® and it is approved by the FDA for adjunctive of breast cancer but not approved for fertility treatment. The use of letrozole in the infertile population was the topic of a recent review.[7] By inhibiting the aromatase enzyme, letrozole causes a drop in estrogen levels which results in release of FSH by the pituitary gland. Unlike CC, letrozole does not have detrimental effects on the cervical mucus and endometrial lining. Letrozole is available in 2.5 mg tablets and it is taken once a day. The standard dose is 2.5 mg per day, and can be increased up to 7.5 mg a day for 5 days. Side-effects are nausea, dizziness, hot flashes, and headache. Risks include twins, 5–10%; triplets or more are rare. Ovarian hyperstimulation syndrome is theoretically possible.

> ***Note:*** A recent study reported an increased incidence of locomotor and cardiac malformations in babies conceived using letrozole.[8] Until additional published data are available this medication should be used with caution and the patient needs to be advised of the potential increased risk of malformations. All patients prior to taking this medication should have a serum pregnancy test.

OTHER MEDICATIONS THAT CAN BE USED WITH OR WITHOUT CLOMIPHENE CITRATE

In some women with ovulatory dysfunction, other medications may be considered which can be administered by themselves or in addition to clomiphene citrate.

Oral hypoglycemic agents

It is now believed that insulin resistance plays a central role in the pathogenesis of polycystic ovarian syndrome (PCOS). Insulin resistance is a condition in which the action of insulin is hampered either by a defective insulin receptor or a

postreceptor defect. With insulin resistance, higher circulating levels of insulin are necessary to maintain normal glucose homeostasis. Hyperinsulinism can explain many of the associated findings of PCOS. Insulin increases ovarian and adrenal androgen production, decreases the production of sex hormone binding globulin, and stimulates the pituitary secretion of LH. All of this leads to an androgenic milieu that interferes with the normal follicular development and ovulation. Insulin resistance is a metabolic disorder and ovulatory dysfunction is only one of its manifestations. Other abnormalities associated with insulin resistance include type II diabetes, hypertension, dyslipidemia, centripetal obesity, and an increased risk of cardiovascular disease.

Any woman who presents with ovulatory dysfunction and has symptoms of hyperandrogenism should be tested for serum androgens (DHEAS, 17-OH-progesterone, testosterone). In addition, she should have an assessment of glucose metabolism. The laboratory diagnosis of insulin resistance has been a subject of debate. Some have advocated measuring insulin levels or the glucose to insulin ratio.[9] However, these tests alone are not reliable; one does not have to substantiate the diagnosis on laboratory grounds but can do it on the clinical presentation alone. If the fasting blood sugar is greater than 100 mg/dl, glucose intolerance should be suspected and a 2-hour glucose tolerance test should be performed to rule out diabetes mellitus. Patients with insulin resistance are at greater risk for the development of gestational diabetes and type II diabetes. Many individuals with insulin resistance are also overweight. Exercise and a low carbohydrate diet should be stressed since weight loss will help to improve the insulin resistance and decrease the chance of developing diabetes.

Patients with adult-onset diabetes mellitus have been treated effectively with oral hypoglycemic agents, such as metformin. Metformin improves the actions of insulin in several ways. It increases the uptake of glucose into fat and muscle cells. In addition, it decreases intestinal absorption of glucose and reduces hepatic gluconeogenesis. There are published data that have confirmed that metformin improves the insulin resistance in patients with PCOS, which results in a correction of the ovulatory dysfunction.[3,10,11] This has been a significant breakthrough in the treatment of PCOS. Many women with PCOS respond poorly to CC and have to be treated with injectable gonadotropins to induce ovulation. In a meta-analysis it was concluded that metformin improved the rate of ovulation.[12] The ovulation rates were different between the metformin and placebo groups: 46 vs 26%. The rates of ovulation in those who took metformin + CC and CC alone were 76 vs 42%, respectively. While metformin may be effective by itself it may take up to 6 months to appreciate ovulatory cycles.[11,13]

Evaluation

Perform a standard workup for anovulation (see p. 71). Metformin treatment may be considered in any patient with signs of PCOS. Check a fasting glucose and if the fasting blood glucose is greater than 100 mg/dl, perform a 2-hour glucose tolerance

test to rule out diabetes. Renal studies (creatinine, BUN) and liver function tests (SGOT, SGPT) should also be obtained. One potential risk of metformin treatment is lactic acidosis. The incidence of this side-effect is increased in those patients with renal or hepatic dysfunction.

Recommended dosage

Metformin is available in 500 mg tablets. Initiation of metformin should be done in a gradual fashion to decrease the incidence of side-effects. One tablet (500 mg) should be taken daily for 1 week, then one tablet twice a day for 1 week, then one tablet three to four times a day (1500–2000 mg per day). The medication should be taken with meals.

Side-effects

Gastrointestinal symptoms, including nausea, vomiting, diarrhea, bloating, and flatulence, occur in 30% of patients who take metformin. These side-effects are usually temporary. Lactic acidosis is a serious metabolic disorder that may be increased in those with renal and/or hepatic dysfunction. There have been reports of metformin-induced lactic acidosis following the administration of intravenous iodine contrast agents, which can result in transient nephrotoxicity. Therefore metformin should be withheld 24 hours before and 48 hours after the performance of the X-ray procedure. Metformin is a schedule B drug but should be discontinued when pregnancy is established. Metformin does not cause hypoglycemia.

Clinical application

Long-term treatment In some cases, long-term treatment with metformin can be considered for up to 6–12 months. This is especially attractive treatment for obese women and for those women who want to avoid a multiple pregnancy associated with ovarian stimulation medications. For the patient with obesity, good nutrition and an exercise program should be stressed. Weight loss will increase the effectiveness of metformin. The patient should follow up with the physician periodically every 6–8 weeks. Monitoring for ovulation or with pregnancy tests should be performed to assess treatment efficacy.

Short-term treatment For those patients who want to move on quickly to treatment, a short course of metformin (4–8 weeks) can be used before moving on to CC. For those who have failed to respond to CC alone, pretreatment with metformin many times will improve their response when CC is tried again.

Dopaminergic agents

Hyperprolactinemia is a cause of ovulatory dysfunction. A serum prolactin assay should be obtained on any woman who presents with irregular or absent

menstrual periods and/or galactorrhea. It is important that the prolactin level is assessed on a blood sample drawn in the morning (around 10 o'clock) during the follicular phase of the menstrual cycle. At other times of the day, and in the luteal phase, physiologic elevations of prolactin can occur. If an elevated prolactin level is found, the assessment should be repeated for verification. If a woman is found to have persistent hyperprolactinemia then a cause should be determined. Hyperprolactinemia can be secondary to previous breast surgery, neck trauma, medication use, renal insufficiency, a pituitary tumor, and hypothyroidism. Any woman with unexplained hyperprolactinemia when associated with ovulatory dysfunction should have an MRI of the head to rule out a pituitary tumor.

Several dopaminergic agents are available to correct the hyperprolactinemia (e.g. bromocriptine, cabergoline). Many times, these agents are effective by themselves in correcting the ovulatory dysfunction. In a previous review reporting on 22 clinical trials, it was noted that 80% of women with hyperprolactinemia had restoration of their menstrual function.[14] On average, menstrual function returned 5–6 weeks after treatment was started. If the patient fails to develop normal ovulatory cycles despite the establishment of a normal prolactin level, then the clinician may consider adding CC or another ovulation induction agent to the treatment regimen.

Some patients have hyperprolactinemia despite normal menstrual cycles. There are different species of prolactin that circulate in the blood stream, some active others not. Most likely in these situations the majority of the circulating prolactin is the inactive variety, has no biological significance, and does not necessitate treatment.

Available agents and doses

- *Bromocriptine (Parlodel®)* Available in 2.5 mg tablets. Start with half a tablet (1.25 mg) q.h.s. for 1 week then increase up to one tablet (2.5 mg) q.h.s. Repeat the prolactin level in 2–3 weeks. If the prolactin level is increased the dose can be increased in an incremental fashion.
- *Cabergoline (Dostinex®)* Available in 0.5 mg tablets. Start with one tablet (0.5 mg) twice a week. The dose may be increased by 0.25 mg twice weekly to less than or equal to 1 mg twice a week, depending on the serum prolactin level. Do not increase the dose more often than every 4 weeks.

Side-effects The more common side-effects include gastrointestinal upset, fatigue, dizziness, and nasal stuffiness. For those with persistent gastrointestinal side-effects vaginal administration of the medication may be considered.

Dexamethasone

Dexamethasone can be considered for the anovulatory woman who fails to respond to increasing doses of CC or who is noted to have an elevated

dehydro-epiandrostenedione (DHEAS) level. An elevated DHEAS level may suggest an attenuated adrenal enzyme deficiency. Other causes include an adrenal tumor and Cushing's syndrome, which must be considered but are, nonetheless, rare. The administration of dexamethasone will decrease the adrenal androgen contribution to the pool of androgens. In some cases, this will be enough to improve the response to CC. Dexamethasone should be administered at night at a dose of 0.5 mg. One month after starting the dexamethasone, a morning cortisol level should be checked. A cortisol level less than 3 μg/dl suggests significant depression of cortisol synthesis by the adrenal gland, which could interfere with a stress response by the adrenal gland. In this circumstance, the dose or frequency of administration should be decreased. The use of dexamethasone should be avoided during pregnancy.

Gonadotropins

Gonadotropins are injectable medications that are effective in correcting ovulatory dysfunction. A list of current agents that are available appears in Chapter 8. The agent used depends on the clinical presentation. One must exercise caution when administering these agents to correct ovulatory dysfunction (as compared to their use in the context of superovulation) to minimize the risk of multiple pregnancy.

Hypothalamic dysfunction

Since these patients are deficient in FSH and LH, both of these hormones need to be replaced. Therefore, human menopausal gonadotropins (HMG) (Menopur®, Repronex®) must be administered or pure LH (Luveris®) can be added to pure FSH. It is important that low doses (75 IU) be administered initially and one is cautious in raising the dose.

1. Human choronic gonadotropin (HMG) 75 IU × 5–7 days then check estradiol (E2) and ultrasound (US).
   (a) If E2 < 50 increase by 37.5 IU × 3 days then repeat the E2/US. Increase HMG by no more than ½ amps every 3–4 days.
   (b) If E2 > 50 continue the same dose and repeat monitoring every 2–3 days.
2. Administer hCG when lead follicle is ≥16 mm.

Caution: These patients are at significant risk of a multiple pregnancy – the goal of the stimulation is 1–2 follicles. If more than 2 follicles ≥16 mm or if several secondary follicles are present >12 mm, consideration should be given to canceling the cycle

Polycystic ovarian disease

These patients are deficient in FSH and have elevated circulating levels of LH. Therefore, only FSH containing medications (Gonal F®, Bravelle®, Follistim®) are needed to correct the ovulatory dysfunction.

1. FSH 75 IU × 5 days then check E2 and ultrasound.
   (a) If E2 < 50 increase by 37.5 IU × 3 days then repeat the E2/US. Increase HMG by no more than ½ amp every 3–4 days.
   (b) If E2 > 50 continue the same dose and repeat monitoring every 2–3 days.
2. Administer hCG when lead follicle is ≥ 16 mm.

Caution: These patients are at risk of a multiple pregnancy and OHSS – the goal of the stimulation is 1–2 follicles. However, the success rate in the PCO population is lower that in those patients with hypothalamic dysfunction. If more than 3–4 follicles ≥ 16 m develop on ultrasound examination, or if several secondary follicles > 12 mm are present, then consideration should be given to canceling the cycle.

REFERENCES

1. Gysler M, March CM, Mishell DR, Bailey EJ. A decade's experience with an individualized clomiphene treatment regimen including its effect on the post-coital test. Fertil Steril 1982; 37: 161.
2. Garcia J, Jones GS, Wentz AC. The use of clomiphene citrate. Fertil Steril 1977; 28: 707.
3. Nestler JE, Jakubowicz DJ, Evans WS, Pasquali R. Effects of metformin on spontaneous and clomiphene-induced ovulation in the polycystic ovary syndrome. N Engl J Med 1998; 338: 1876–80.
4. Hughes E, Collins J, Vandekerckhove P. Clomiphene citrate for unexplained subfertility in women. Cochrane Database Syst Rev 2006; 1.
5. Hughes EG. The effectiveness of ovulation induction and intrauterine insemination in the treatment of persistent infertility: a meta-analysis. Hum Reprod 1997; 12: 1865–72.
6. Fujii S, Fukui A, Fukushi Y et al. The effects of clomiphene citrate on normally ovulatory women. Fertil Steril 1997; 68: 997–9.
7. Holzer H, Casper R, Tulandi T. A new era in ovulation induction. Fertil Steril 2006; 85: 277–84.
8. Biljan MM, Hemmings R, Brassard N. The outcome of 150 babies following the treatment with letrozole or letrozole and gonadotropins. Fertil Steril 2005; 84(Suppl 1); S95.
9. Legro RS, Finegood D, Dunaif A. A fasting glucose to insulin ratio is a useful measure of insulin sensitivity in women with polycystic ovary syndrome. J Clin Endocrinol Metab 1998; 83: 2694–8.
10. Velazquez EM, Acosta A, Mendoza SG. Menstrual cyclicity after metformin therapy in polycystic ovary syndrome. Obstet Gynecol 1997; 90: 392–5.
11. Velazquez EM, Mendoza SG, Hamer et al. Metformin therapy in polycystic ovary syndrome reduces hyperinsulinemia, insulin resistance, hyperandrogenemia, and systolic blood pressure, while facilitating normal menses and pregnancy. Metabolism 1994; 43: 647–54.
12. Lord JM, Flight IHK, Norman RJ. Metformin in polycystic ovary syndrome: systematic review and meta-analysis. BMJ 2003; 327: 951–7.

13. Ibanez L, Valls C, Ferrer A et al. Sensitization to insulin induces ovulation in nonobese adolescents with anovulatory hyperandrogenism. J Clin Endocrinol Metab 2001; 863: 595–8.
14. Cuellar FG. Bromocriptine mesylate (Parlodel) in the management of amenorrhea/galactorrhea associated with hyperprolactinemina. Obstet Gynecol 1980; 55: 278.

RECOMMENDED READING

ASRM Committee Opinions

- Use of clomiphene citrate in women. Fertil Steril 2003; 80: 1302–8.
- Use of insulin sensitizing agents in the treatment of polycystic ovarian syndrome. Fertil Steril 2004; 82: S181–3.

ACOG Technical Bulletins

- ACOG practice bulletin: Management of infertility caused by ovulatory disorders. Clinical Management Guidelines for the Obstetrician-Gynecologists. Number 34, February 2002.

7.

Treatment options II: intrauterine insemination

Steven R Bayer

Intrauterine insemination (IUI) was first introduced over 50 years ago and is one of the most commonly administered fertility treatments. It is a rationale treatment for infertility secondary to a cervical factor, mild male factor, and ejaculatory dysfunction, but the most common indication is unexplained infertility. It is also the best approach to therapeutic donor sperm insemination (TDI). In cases of TDI, a non-medicated or natural cycle is used initially but, for other indications, this approach has a low success rate. Therefore, the use of fertility medications to increase the development of multiple follicles is an important part of IUI treatment and has been shown to increase the chance of success. In addition, the success rate with ovulation induction plus IUI is higher than with ovulation induction alone. How does an IUI increase the chance of pregnancy? The explanation remains obscure, but may be the result of several factors. The sperm washing procedure may eliminate toxins or bacteria in the seminal plasma and has been shown to induce the acrosome reaction causing activation of the sperm. Performance of the IUI may bypass an impediment in the cervical mucus. In contrast to intercourse, the IUI results in a higher number of motile sperm that find their way into the uterine cavity. Finally, the IUI may overcome faulty coital technique on the part of the couple. Despite all of these theoretic benefits of IUI, the overall success of IUI treatment is low in comparison to IVF. Nevertheless, for many infertility patients IUI is their first introduction to treatment. This chapter will provide an overview of the treatment.

APPROACHES TO IUI TREATMENT

Natural cycle

A natural or non-medicated approach is most often used with TDI, but in the context of infertility this approach is associated with a low success rate. However, it might be the desire for the couple who wants to completely avoid medications

or a multiple pregnancy. This is not considered an option for a woman with ovulatory dysfunction.

Monitoring

The patient is instructed to start testing the urine with an ovulation predictor kit 3–4 days before the anticipated time of ovulation. For the woman who has cycles that are 28–30 days in length she is instructed to start testing her urine on day 11. When the ovulation predictor test turns positive she is instructed to come in the following day for the insemination.

Clomiphene citrate

Clomiphene citrate (CC) can be the initial medicated approach for women under the age of 35. For women over the age of 35, a more aggressive ovulation induction (e.g. gonadotropins) is the preferred approach. CC is the most widely prescribed fertility medication. For a detailed description of this medication please refer to Chapter 6. CC is administered at a dose of 100 mg for 5 days between cycle days 3 and 7.

Monitoring

The patient is instructed to use an ovulation predictor kit beginning on cycle day 11. When the test turns positive, a single insemination treatment is done the following day. In our experience, approximately 90% of patients will detect the LH surge between cycle days 11 and 15. An alternative is to perform vaginal ultrasound examinations beginning cycle day 12 and to administer human chorionic gonadotropin (hCG) (10 000 IU, or 250 µg of Ovidrel®) when the follicle reaches 18 mm – the insemination is scheduled 36 hours later. Whether the insemination is timed with ultrasound monitoring and an hCG trigger or the ovulation predictor kit there is no difference in success rates.[1] However, the advantage of doing ultrasound exams is that it provides valuable information about the ovarian response. If just a single follicle develops then there should be consideration to substituting FSH injections for the CC.

FSH injections

The use of FSH injections for ovulation induction as part of IUI treatment increases the success rate. For a detailed discussion on these medications the reader is referred to Chapter 8. The injections of FSH are started on day 3 and continued until mature follicles have developed. The initial dose will be dependent on many factors including previous response and age. In general, the first cycle of treatment requires more caution with the starting dose (75–150 U)

since it is unknown how the patient will respond to the medication. This is of less concern for the older patient over the age of 40, who most likely has some reduced ovarian reserve, and the starting dose may be increased to 150–225 U. The goal of the treatment may vary as well. For younger women, the goal is to obtain 2–5 mature follicles that are 16 mm or larger. If more than 5 mature follicles are present, and/or there are multiple follicles between 12 and 16 mm, then there is an increased risk of a multiple pregnancy. These cycles should be either cancelled or converted to an IVF treatment cycle. For the woman over the age of 40, the chance of a multiple pregnancy is reduced so these cycles are rarely cancelled if too many follicles develop.

Monitoring

A serum estradiol level determination and vaginal ultrasound exam are recommended 4–5 days after starting injections. If the estradiol level is > 400 pg/ml, then the dose is reduced by 75 U. The goal is to have the estradiol level increase by 50–100% every 2–3 days. The vaginal ultrasound will determine the number and size of the follicles. A mature follicle is between 16 and 20 mm in diameter. The goal of the treatment is to obtain 2–5 follicles that have reached this size or larger. The final goal of the treatment is to have a peak estradiol level between 500 and 2000 pg/ml at the time of the hCG administration. A single insemination is performed 36 hours after hCG administration.

PREPARATION OF THE SEMEN SAMPLE

A single insemination is typically performed. A semen sample is produced on the day of the IUI. It is preferable that the semen sample is produced on site, but it can be produced at home and then transported to the laboratory as long as it can be delivered within 60 minutes after production. The sample should be kept at body temperature. The sperm concentration and motility of the semen sample are assessed. The semen sample is then washed and prepared. Washing of the sample removes prostaglandins and bacteria and it also concentrates the sperm by removing the seminal plasma. For security reasons, we only accept sperm samples from the husband and not another party (including the wife). His identification is confirmed by examination of his driver's license. Our sperm washing procedure is as described below.

Process all specimens using sterile technique and practicing universal precautions. Latex gloves should be worn at all times, and facial protection should be used if the sample is not processed under a hood.

1. The semen sample is produced by masturbation into a labeled non-coated, sterile container after 2–3 days' abstinence. Lubricants should not be used to produce the sample.

2. Allow semen sample to liquefy for 20–60 minutes.
3. Measure volume with a 10 ml pipet.
4. Divide sample into two test tubes labeled 'pellet' with patient's name.
5. Add an equal volume of sperm wash to each of the tubes and mix well.
6. Remove any coagulates that may pellet to the bottom of the tubes.
7. If viscosity still exists, chrymotrypsin may be used.
8. Centrifuge for 10 minutes at 1200 rpm (300 × **g**).
9. Remove supernatant and place in labeled 'super' tube.
10. Resuspend the pellets in a total of 2 ml fresh sperm wash; the two pellet tubes should be combined at this step. The wash medium should not exceed 2 ml.
11. Centrifuge (second time) for 5 minutes at 1200 rpm (300 × **g**).
12. Remove supernatant.
13. Resuspend the pellet in a total of 0.5 ml sperm wash.
14. Mix thoroughly and count the sample.
15. Place washed sample on the 37° C warmer until ready to use.

Intrauterine inseminations

Our nurses are trained to perform the IUIs. If there is any difficulty with the insemination, then a physician is called to complete the procedure. Before the insemination, the patient's name is verified and she confirms that her name is on the tube containing the washed sperm sample. To perform the IUI treatments a speculum examination is performed and the cervix is visualized. The cervix is wiped with a large cotton tip applicator. The washed sperm sample is loaded into a catheter, which is inserted through the cervical canal and into the uterine cavity. Immediately following the IUI the patient is discharged and normal activity can be resumed. A pregnancy test is scheduled 14 days later.

One versus two inseminations

The decision to do one versus two inseminations has been the subject of ongoing debate. In a meta-analysis, Osuna et al reported on eight randomized controlled studies.[2] The pregnancy rate in two vs one insemination groups was 13.30 vs 10.2%, respectively. The odds ratio was 1.33 (95% CI 0.99, 1.73). However, two of the studies included used CC as a stimulatory agent. Both of these studies using CC confirmed a benefit of a second insemination. The explanation as to why a second insemination is needed with CC remains uncertain. When the CC studies were excluded the results did not confirm that the additional IUI improved the success. The data published to date do not provide conclusive evidence that a second insemination is necessary. From a theoretic standpoint a second insemination may not be necessary if one considers that sperm generally maintain their viability for 48–72 hours and the oocyte has a 12–24 hour window to be fertilized. One important factor is the type of ovulation induction that is used (Table 7.1).

Table 7.1 Success rates for conservative infertility treatment options

Treatment	*Success rate (per cycle) (%)*	*Multiple pregnancy rate (%)*
Obsevation	3–4	1
Non-medicated IUI	4	1
Clomiphence citrate	6	10
Clomiphence citrate–IUI	8–10	10
FSH	10	15–20
FSH–IUI	15–18	20–25

IUI, intrauterine insemination; FSH, follicle stimulating hormone injections

Table 7.2 The impact of age on success following intrauterine inseminations

Age	*Number of cycles*	*Live birth rate, % (95% CI)*
< 25	15	26.7 (4.3,49.4)
25–29	219	14.2 (9.6,18.8)
30–35	556	12.5 (9.8,15.2)
36–39	221	9.5 (5.6,13.4)
> 40	106	8.5 (3.2,13.8)

SUCCESS RATES

As with any fertility treatment several factors impact success. For those patients with unexplained infertility, the success rate is affected by the type of ovulation induction agent that is used and whether IUI is performed (Table 7.1). Another important factor that impacts on IUI success is the semen quality. Pregnancy rates are higher when the total motile sperm count is > 2 million, postwash motility is > 40%, and/or normal sperm morphology is > 4%.[3] However, interpretation of sperm morphology can vary from lab to lab. Age impacts on the chance of success and was the subject of one study.[4] The authors examined over 1000 cycles and reported the live birth rate in the different age groups to be as shown in Table 7.2.

COST ANALYSIS

Another factor that must be considered in the decision-making process is cost. Massachusetts has an insurance mandate that provides complete coverage for the costs of treatment. The disadvantage is that a certain number of IUI treatments must be completed before approval is given to move on to IVF treatment. Most patients throughout the country don't have insurance coverage and are therefore self-pay. The approximate costs of CC–IUI, FSH–IUI, and IVF including medications are $500, $2500, and $7000–10 000. When one

considers the overall success rates following the various treatments for some patients it makes sense to try CC–IUI and, if this proves unsuccessful, to move on to IVF.

REFERENCES

1. Lewis V, Queenan J, Hoeger K et al. Clomiphene citrate monitoring for intrauterine insemination timing: a randomized trial. Fertil Steril 2006; 85: 401–6.
2. Osuna C, Matorras R, Pijoan JL, Rodriguez-Escudero FJ. One versus two inseminations per cycle in intrauterine insemination with sperm from patients' husbands: a systematic review of the literature. Fertil Steril 2004; 82: 17–24.
3. Haebe J, Martin J, Tekepety F et al. Success of intrauterine insemination in women aged 40–42 years. Fertil Steril 2002; 78: 29–33.
4. Duran HE, Morshedi M, Kruger T, Oehninger S. Intrauterine insemination: a systematic review on determinants of success. Hum Reprod Update 2002; 8: 373–84.

8.

Treatment options III: *in vitro* fertilization

Michael M Alper

In vitro fertilization (IVF) is one of the most significant advances in the field of reproductive medicine. The first IVF baby Louise Brown, born in England in 1978, was the result of a decade of research by Drs Patrick Steptoe and Robert Edwards. Since that time, over 400 IVF units have been established in the US alone. An estimated one million babies have been born as a result of this technology. Initially IVF was developed for the woman with tubal disease but now it is the treatment of choice for other causes of infertility that are refractory to more conservative treatment. Since its introduction, all of the steps of IVF treatment have been improved upon, which has resulted in continuously rising success rates over the last 20 years (Figure 8.1). IVF is the most successful infertility treatment that can be offered. IVF has also provided a platform for the development of other treatments including egg donation, gestational surrogacy, and preimplantation diagnosis. This chapter will provide an overview of the IVF treatment.

The four steps of IVF will be reviewed:

1. Ovulation induction
2. Oocyte retrieval
3. Oocyte insemination
4. Embryo transfer.

OVULATION INDUCTION

IVF treatment initially utilized non-medicated or natural cycles. The timing of egg retrieval was based on the initiation of the endogenous LH surge. Overall the natural cycle was extremely inefficient and one of the first modifications that increased IVF success rates significantly was the use of gonadotropins to stimulate the growth of multiple ovarian follicles. This was a definite improvement, but

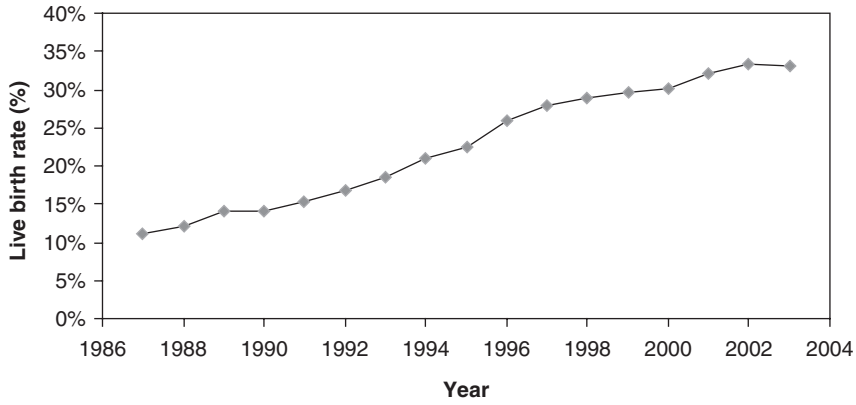

Figure 8.1 IVF treatment success rates have continued to increase. The live birth rate (per oocyte retrieval for all women treated during the calendar year) has increased 3.0 fold between 1987 and 2003. Data were obtained from the CDC/SART statistics that are published on an annual basis. The increase in the success rates has been paralleled by an increased number of ART procedures that have been performed in the United States. In 1987, a total of 8725 retrievals was performed and, in 2003, a total of 86 753 procedures was carried out

premature ovulation complicated approximately 30% of cycles, making timing of the egg retrieval a challenge and cancellation common. The next breakthrough was in the late 1980s when the GnRH agonist was introduced. The GnRH agonist eliminated any chance of a premature LH surge, resulting in more control of the cycle. The ovulation induction step is extremely important since the success rate is directly related to the number of oocytes that are retrieved, which in turn impacts on the number of embryos that are available for transfer. Over the years, there has been a change from using urinary gonadotropins to using those created by recombinant DNA technology. The newer gonadotropins are more purified and consistent, allowing subcutaneous injection. The medications used for ovulation induction are listed in Table 8.1. The ovulation induction protocols that are used today are described below.

Pituitary downregulation with a GnRH agonist

This is the most common protocol utilized by IVF programs. Daily injections of a GnRH agonist, Lupron®, results in 'downregulation' of pituitary GnRH receptors, which reduces pituitary FSH and LH release and prevents an LH surge. Generally, the GnRH agonist is administered for a period of 10–15 days before downregulation has occurred. The quickest way to achieve downregulation is to start the GnRH agonist in the mid-luteal phase (cycle day 21) of the preceding cycle. It can also be started in the early follicular phase with the onset of menses. After downregulation has occurred, the dose of the GnRH agonist is reduced and

Table 8.1 Fertility medications

- *Gonadotropin* – Gonadotropins are injectable medications used for ovulation induction for intrauterine insemination and IVF treatment. Two types of gonadotropins can be administered and are discussed below:
  1. *FSH (Gonal-F®, Follistim®, Bravelle®)* – These medications contain only FSH and are administered by subcutaneous injection. These are the most commonly prescribed medications for ovulation induction.
  2. *Human menopausal gonadotropins (Menopur®, Repronex®)* – These medications contain equal amounts of FSH and LH, and are administered on a daily basis by subcutaneous injections.
- *GnRH agonist (Lupron®)* – This is a synthetic hormone that is administered by subcutaneous injection. The administration of a GnRH agonist initially causes release of FSH and LH from the pituitary gland. However, with continued administration there is downregulation of the GnRH receptors, which minimizes release of FSH and LH by pituitary gonadotrophes and prevents an LH surge. GnRH agonists are administered with gonadotropes in women undergoing IVF treatment. The main benefit is that pretreatment with a GnRH agonist prevents an LH surge.
- *GnRH antagonists (Ganirelix, Cetrotide®)* – GnRH antagonists reversibly bind to GnRH receptors and prevent release of FSH and LH. The major benefit of the use of GnRH antagonists in conjunction with FSH is the suppression of the LH surge. In contrast to Lupron® the GnRH antagonists have an immediate action in prevention of an LH surge.
- *Human chorionic gonadotropin [hCG] (Profasi®, Pregnyl®, Ovidrel®, Novarel®)* – This medication contains the pregnancy hormone, hCG, which functions similarly to LH. LH is an important hormone that helps to mature the eggs to allow them to become fertilized and stimulates ovulation. The administration of hCG is necessary in women who are undergoing IUI (when gonadotropins are used) and during IVF treatment.
- *Progesterone supplements* – Progesterone supplements are used in women undergoing IVF treatment to help prepare the endometrium for implantation and support a pregnancy. Progesterone can be administered by intramuscular injection, vaginally, and orally. Progesterone supplements are not FDA approved for IVF treatment except for Crinone®, which is administered vaginally. However, the progesterone present in the supplements is the natural hormone and studies have confirmed there is no increased risk of congenital anomalies or health risks to women who take natural progesterone supplements during pregnancy.

ovulation induction is initiated with FSH injections. The dose of FSH required may vary from 150 to 450 U per day.

Microdose-Lupron

This protocol is used for women who are poor responders or who have evidence of reduced ovarian reserve. This protocol involves the administration of oral contraceptives for a period of 3 weeks. Theoretically, the administration of the oral contraceptives suppresses gonadotropin release and puts the ovaries to rest. After the 3-week course of the oral contraceptives has been completed, small doses of Lupron and FSH are administered twice daily. When Lupron is administered in

this fashion it acts as a stimulatory agent because it induces the release of FSH and LH, and after continued administration there is inhibition of the LH surge.

Pituitary suppression with a GnRH antagonist

GnRH antagonists result in the instant suppression of FSH and LH release from the pituitary gland, as opposed to agonists which take several days to suppress the pituitary. The use of GnRH antagonist protocols is becoming more popular. The advantages include fewer injections and elimination of the ovarian suppression that may occur after administration of Lupron. For this protocol, gonadotropins are started on cycle day 2. When a lead follicle reaches a diameter of 14 mm on transvaginal ultrasound examination, the daily administration of the GnRH antagonists is started (with the gonadotropins). The administration of the antagonist results in a decrease in the serum estradiol level, in part because the antagonist completely eliminates all LH secretion. Some have advocated the addition of LH to compensate, but published data have failed to conclude that this is necessary.

Monitoring

During the ovarian stimulation, the woman's response is monitored with serum estradiol levels and vaginal ultrasound examinations. The estradiol level is used to determine the dose of gonadotropins and whether excessive stimulation is occurring. However, some studies have concluded that serum estradiol monitoring is not always necessary and the response to treatment can be followed with ultrasound monitoring alone. The goal of the ovulation induction is to develop at least three mature follicles that are 17 mm in diameter or larger. Once this is achieved FSH and other medications are discontinued, and a single injection of hCG is given to mature the eggs to allow fertilization. The egg retrieval is scheduled 36 hours after the hCG injection, which is several hours prior to when ovulation would otherwise occur.

OOCTYE RETRIEVAL

The egg retrieval is performed under vaginal ultrasound guidance. After the vaginal ultrasound is placed in the vagina and the ovarian follicles are located, a needle is directed through the back wall of the vagina and directed into the ovarian follicles (Figure 8.2). The fluid is aspirated and then examined by an embryologist to identify the microscopic egg (Figure 8.3). All follicles within both ovaries are aspirated. Once the eggs are retrieved, they are placed in culture plates with nutrient media and then placed in the incubator. The procedure is performed under a light anesthesia and generally takes less than 10–15 minutes to complete. Prophylactic antibiotics are often administered. The overall complication rate is < 1%.

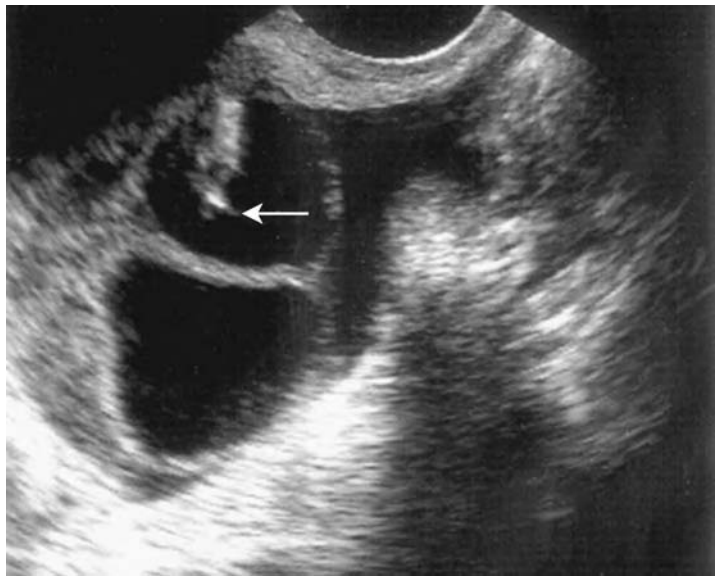

Figure 8.2 Vaginal ultrasound-guided egg retrieval. This is an ultrasound image taken at the time of an egg retrieval. During the procedure the ovary is positioned on the other side of the vaginal wall. A needle has been inserted through the vaginal wall and the tip of the needle is positioned in the center of the follicle (see arrow). After proper placement of the needle the fluid from the follicle is aspirated

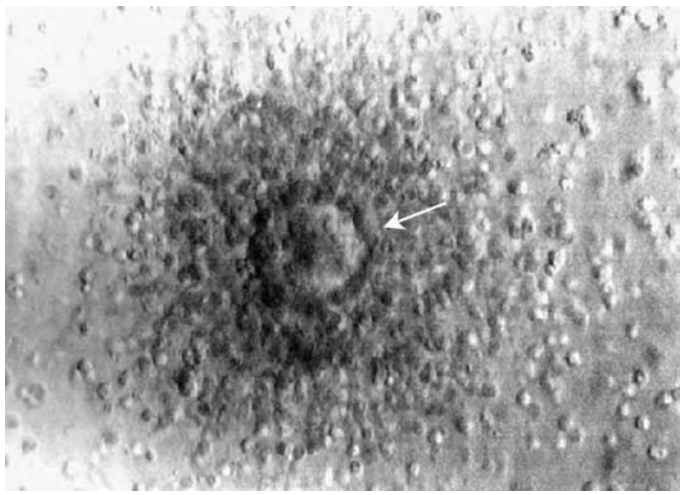

Figure 8.3 An oocyte. This picture is of an oocyte obtained at the time of an egg retrieval. The oocyte (see arrow) is surrounded by a group of granulosa cells called the cumulus. During normal fertilization the acrosome of the sperm releases enzymes which disperse the cumulus cells therefore allowing the sperm to penetrate and fertilize the oocyte

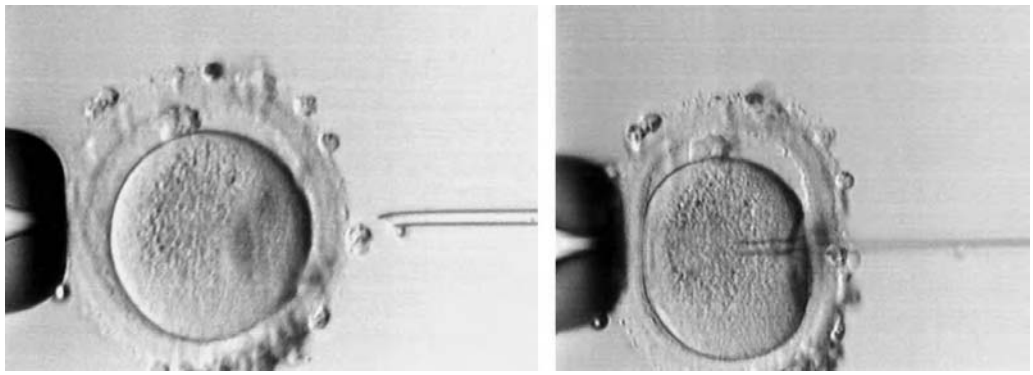

Figure 8.4 The ICSI procedure is performed with very fine instruments under a microscope. After the granulosa cells have been stripped away from the oocyte with enzymes, the oocyte is held in place by a holding pipet. The other pipet which is much smaller and sharper, is used to pick up a single sperm. The smaller pipet is then brought into proper position (left panel) and then inserted through the zona pellucida and into the cytoplasm of the oocyte where the sperm is injected (right panel)

OOCYTE INSEMINATION

Standard insemination

After the sperm sample is produced the sperm concentration and motility are assessed. If the sperm sample is adequate, then a sperm prep is done to isolate the most motile sperm. A total of 50 000 motile sperm is placed with the eggs in a culture dish, which is then placed in the incubator.

Intracytoplasmic sperm injection

Intracytoplasmic sperm injection (ICSI) is used in cases of male factor, or in cases when standard IVF results in <30% of eggs fertilized, or no fertilization at all. ICSI involves the injection of a single sperm directly into the oocyte (Figure 8.4). In the United States, ICSI is used in about 40% of IVF cycles. Fertilization rates following this procedure are between 60 and 70% (comparable to the rates achieved with a standard insemination). Males with severe oligospermia (count <5 million sperm/cc) should have a karyotype performed since they are at greater risk for having a chromosomal abnormality. Couples should be counseled that there is an increased risk of sex chromosomal anomalies in infants born following the ICSI procedure. The rate of sex chromosomal aneuploidy in infants conceived naturally is 0.2% and is 0.8% following the ICSI procedure. These chromosomal abnormalities are not the result of the ICSI procedure itself but are most likely due to a low level of mosiacism present in the spermatogonia. Couples may opt for a genetic amniocentesis after pregnancy is established. Studies have confirmed

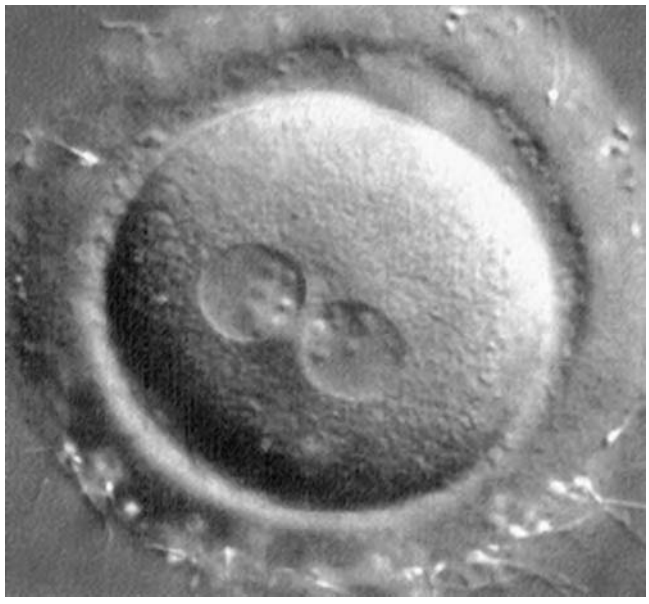

Figure 8.5 A fertilized egg. Note the two pronuclei (one from the sperm and one from the egg) present within the egg

that many cases of male factor infertility are caused by microdeletions on the Y chromosome. Couples should be counseled that this genetic testing is available and if a defect is found then it could be transmitted to an offspring.

The morning after the insemination the eggs are examined to determine whether fertilization has occurred. A fertilized egg is shown in Figure 8.5. Note the two pronucleii (one from the sperm and the other from the egg) present within the egg. Within a few hours the nuclei unite and the embryo will start to divide (Figure 8.6).

EMBRYO TRANSFER

The embryo transfer is usually performed 72 hours after the egg retrieval. Generally, two to five embryos are transferred into the uterine cavity under abdominal ultrasound guidance. At this stage, good quality embryos are between 6 and 10 cells in development. The recommended number of embryos to transfer is determined by the woman's age, cause of the infertility, previous pregnancy history, and other factors. We perform the embryo transfer under abdominal ultrasound guidance. A full bladder creates a window so the uterus can be easily visualized. An echogenic catheter can be easily seen as it courses through the cervical canal and up into the cavity (Figure 8.7). The catheter is positioned 1–2 cm from the top of the cavity where the embryos are placed. Extra embryos

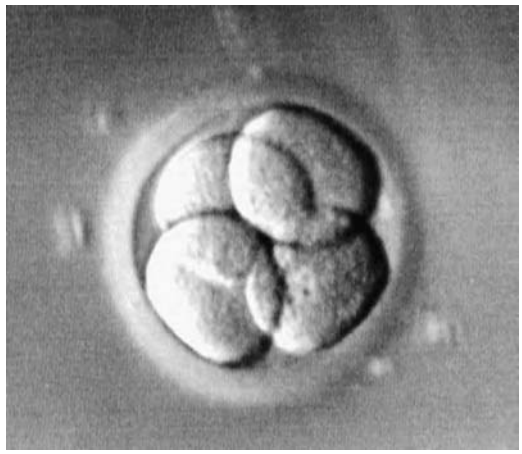

Figure 8.6 A four-cell embryo. This stage of development is achieved at 24–48 hours after fertilization. Note the outer membrane called the zona pellucida that surrounds the embryo

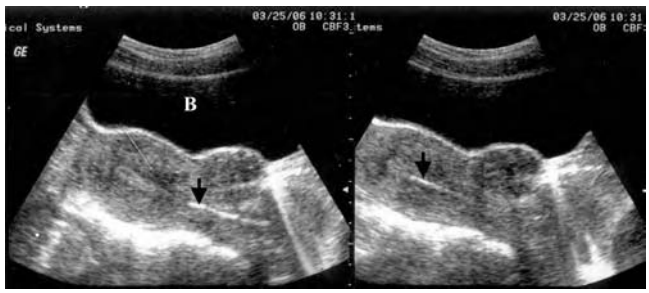

Figure 8.7 Ultrasound-guided embryo transfer. In the left panel the filled bladder (B) allows adequate visualization of the uterine cavity. The tip of the catheter (black arrow) has been advanced to the lower aspect of the uterine cavity. In the right panel the catheter has been advanced to approximately 1.5 cm from the top of the cavity where the embryos are placed. A small anterior serosal fibroid can be seen slightly impinging on the bladder

that are of sufficient quality can be frozen and stored for future use. A serum pregnancy test is performed 11 days later.

Luteal phase support

Progesterone, a hormone produced by the ovary following ovulation, matures the lining of the uterus for implantation. Studies have shown that some women who have taken ovulation induction drugs may need supplemental progesterone. For this reason, it is standard to administer progesterone the day after the egg

retrieval. Natural progesterone is available and can be administered vaginally (Crinone®, Prometrium®) or by intramuscular injection. If pregnancy occurs, the progesterone may be continued for a period of time. Studies have confirmed that there is no increased risk of birth defects or health risks to women who take natural progesterone supplements during pregnancy. In lieu of progesterone, hCG injections (1500 U every 3 days × 3 doses beginning the day after the oocyte retrieval) can be administered in the luteal phase.

IVF RELATED PROCEDURES

Frozen embryo transfer (FET)

Embryos that are cryopreserved during an IVF or GIFT procedure can be replaced after a spontaneous ovulation or the creation of an 'artificial' endometrium with estrogen and progesterone. The success rate following this procedure is between 20–30% and is dependent on the number and quality of embryos that are transferred. The main advantage of a frozen embryo transfer as compared to a medicated IVF cycle is that ovulation induction drugs are not taken and, obviously, the oocyte retrieval is not performed. It is reassuring that there is no increased risk of congenital anomalies in infants born following the transfer of cryopreserved embryos.

Natural cycle IVF

For couples who want to minimize the risk of a multiple pregnancy or would like to avoid the risks of the ovulation induction drugs, a natural cycle IVF approach can be considered. The woman undergoes monitoring with blood work and ultrasound examinations beginning on cycle day 10. hCG is administered when a mature follicle is identified. If a LH surge occurs then the cycle is cancelled. The goal of the natural cycle approach is the retrieval of one egg and the replacement of one embryo. The success rate is less than 5%, which is a major disadvantage of this approach.

Gamete intrafallopian transfer (GIFT)

This treatment involves the first two steps of IVF treatment: ovulation induction and egg retrieval. In contrast to IVF, the GIFT procedure places the eggs and sperm in the Fallopian tube, allowing the tube to be the natural incubator. Usually, four to six eggs are replaced. The disadvantage of the GIFT procedure is that a laparoscopy has to be performed under general anesthesia. A prerequisite to performing the GIFT procedure is that the woman must have at least one normal Fallopian tube. This procedure was quite popular in the 1980s but is rarely performed now that success rates with IVF have improved. Actually less than 1% of assisted reproductive technology (ART) procedures performed are GIFT.

Indications for resorting to GIFT include altered cervical anatomy that prevents a successful uterine transfer and if religious reasons preclude IVF.

Tubal embryo transfer (TET)

This treatment involves the first three steps of IVF: ovulation induction, egg retrieval, and fertilization of the eggs in the laboratory. In contrast to IVF, the TET procedure involves the laparoscopic placement of the embryos in the fallopian tube(s). Usually, two to four embryos are replaced. The disadvantage of the TET procedure is that two separate procedures are performed requiring anesthesia including the egg retrieval and a laparoscopy. This procedure is rarely performed but should be considered when there is altered cervical anatomy precluding an intrauterine transfer of the embryos and the GIFT procedure is not an option (i.e. when the ICSI procedure is required).

Egg donation

Egg donation can be considered for a woman who is a poor responder to the ovulation induction medications, has evidence of reduced ovarian reserve, or is a carrier of a genetic condition. All of the steps of IVF are performed except the egg donor undergoes the ovulation induction and egg retrieval. Once the eggs are retrieved, they are then fertilized with the partner's sperm. The recipient is treated with hormones including estrogen and progesterone, which create an endometrium that will allow implantation of the embryos. The donor can be anonymous or known (i.e. a relative, friend). Before this treatment is begun all parties involved should undergo medical, psychologic, and legal counseling. This topic is further discussed in Chapter 10.

Gestational surrogacy

Some women cannot carry a pregnancy but can produce eggs and embryos from IVF. Indications for gestational surrogacy are when the woman has no uterus, a congenitally deformed uterus, a uterus which is unable to support a pregnancy, or has a medical condition which precludes her from successfully carrying a pregnancy. All the steps of IVF treatment are performed except the embryos are transferred into a gestational carrier. Before this treatment is begun, all parties involved must undergo medical, psychologic, and legal counseling.

Embryo donation

When a couple decides that they do not want any more children or to stop treatment they must decide what to do with their frozen embryos. Because of religious or moral beliefs, some couples find it unacceptable to discard the embryos. One option is to donate the embryos to another couple. Embryo donation is just

emerging as a treatment option for infertile couples and will be used more and more in the future. Embryo donation is very similar to an adoption. Medical, psychologic, and legal counseling are important components of the treatment.

Epididymal sperm aspiration

In some cases of azoospermia, sperm are being produced but do not find their way to the ejaculate. This may be the result of an obstruction (e.g. previous vasectomy, infection), congenital absence of the vas deferens, or in cases of severely impaired sperm production. In these cases, aspiration of epididymal sperm or testicular sperm by a urologist may be considered. In years past, the only way to aspirate epididymal sperm was via the microscopic epididymal sperm aspiration (MESA) procedure. This procedure is performed in the operating room under general anesthesia. The percutaneous epididymal sperm aspiration (PESA) procedure is another approach. It can be accomplished under local anesthesia and a much shorter recuperation than the MESA procedure. If epididymal sperm aspiration does not produce viable sperm, then the urologist can resort to testicular sperm extraction (TESE). In all cases of sperm aspiration, the motility of the sample is quite poor so the ICSI procedure must be performed. To accomplish this procedure there must be coordination with the urologist and the IVF team. The sperm aspiration can be performed on the day of the oocyte recovery or prior to the IVF cycle and the samples frozen.

LABORATORY PROCEDURES

Assisted hatching

Assisted hatching is a procedure in which the zona pellucida, the outer membrane surrounding the embryo, is thinned by the application of a dilute acidic solution and mechanically disrupted. It has been theorized that some implantation failures may be the result from failure of the embryo to hatch out from the confines of the zona pellucida. However, the published studies are inconclusive about the benefit of this procedure. Therefore it should not be used universally but might be considered in patients who have undergone several IVF cycles that have been unsuccessful, or in older women.

Blastocyst culture

The blastocyst stage of embryonic development occurs just prior to implantation. The blastocyst is an embryo made up of 50–100 cells and reaches this stage of development 5–6 days after the egg retrieval (Figure 8.8). During IVF treatment, the standard timing of the embryo transfer has been 3 days after the egg retrieval. At this stage, the embryos are between 5 and 10 cells in development. From this stage to the blastocyst stage the embryo requires a different culture medium environment. Commercially available culture media systems have

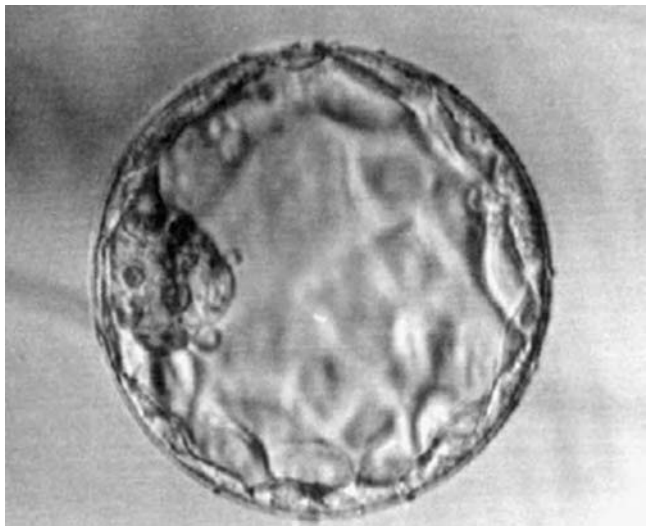

Figure 8.8 A blastocyst. Approximately 30–50% of embryos will develop to the blastocyst state 5–6 days after the egg retrieval. The blastocyst is made up of 50–100 cells

become available which will support more advanced embryonic growth to the blastocyst stage. Generally, 30–50% of embryos develop to the blastocyst stage. Therefore, the benefit from blastocyst culture is that it allows the selection of the better quality embryos. Furthermore, by reducing the number of transferred blastocysts to two, the chance of a high-order multiple pregnancy is significantly reduced and the patient has an excellent chance of pregnancy. A disadvantage of blastocyst transfer is an increased risk of monozygotic twinning, which has been reported to be as high as 5%.

Preimplantation genetic diagnosis (PGD)

In the past when a couple was at risk of having a child with a genetic condition, the only options for genetic diagnosis were a chorionic villous sampling or a genetic amniocentesis. These choices are not optimal since terminating a pregnancy can be quite stressful and for many couples is not considered an option. PGD provides couples with another option. The refinement of micromanipulation techniques has provided the ability to perform genetic diagnosis on a single blastomere that is removed from the embryo prior to transfer. The first successful case of PGD was performed in 1990 for a couple who were at risk of having a child with cystic fibrosis. Since that time centers worldwide have developed the expertise to perform PGD. It can be performed for autosomal recessive and dominant conditions, to assess aneuploidy, and for translocations. PGD is an emerging technology and as more and more genetic probes become available there will be an increased demand for this procedure. The topic is discussed in greater detain in Chapter 9.

Oocyte freezing

Oocyte freezing is another emerging technology. The oocyte, in contrast to the embryo, is more sensitive to the cryopreservation process. This is related to the high water content in the egg which predisposes it to ice crystal damage. Recently, breakthroughs have been made in the technique resulting in improved survival at the time of thawing. Techniques involving vitrification (fast freezing), slow freezing, and injection of sugars are promising. It is anticipated that within the next few years egg freezing will become available for routine clinical use. The indications for oocyte freezing are many fold. It gives an opportunity to women undergoing cancer treatment to preserve fertility. It also would benefit the younger woman who doesn't anticipate motherhood in the near future and wants to preserve her fertility. Finally, couples undergoing IVF could freeze extra eggs instead of embryos. Once the couple decides that their family is complete it would be much easier emotionally to discard frozen eggs instead of frozen embryos.

SUCCESS RATES

The explanations for the increased IVF success rates are many fold, including improved ovulation induction medications, refined laboratory techniques, less traumatic embryo transfer catheters, and the introduction of the intracytoplasmic sperm injection (ICSI) procedure. The success rate for any individual patient following IVF is influenced by countless factors including the number of embryos transferred, cycle number, ovarian reserve, age, and diagnosis.

Maternal age

One of the most important factors that influence a couple's fertility is the woman's age. Generally, younger women have a greater quantity and quality of eggs that, once fertilized, are more likely to implant in the uterus and result in a pregnancy. Further, the chance of a miscarriage is lower in younger women. The decreased fertility associated with advancing age is a gradual process that seems to begin around age 25 and then accelerates after the age of 40. One reason for the decreased fertility associated with aging is that there is a higher rate of aneuploidy. Women over the age of 40 should be counseled about the decreased chances of pregnancy even with aggressive treatment, such as *in vitro* fertilization (Figure 8.9). Treatment is inadvisable in women who are 44 years and older because of the dismal chance of a successful outcome. These women should be counseled and encouraged to pursue other more fruitful options such as egg donation and adoption.

Diagnosis

Women with ovulatory problems, except those with reduced ovarian reserve, tend to have higher pregnancy rates with the various treatments. Women with

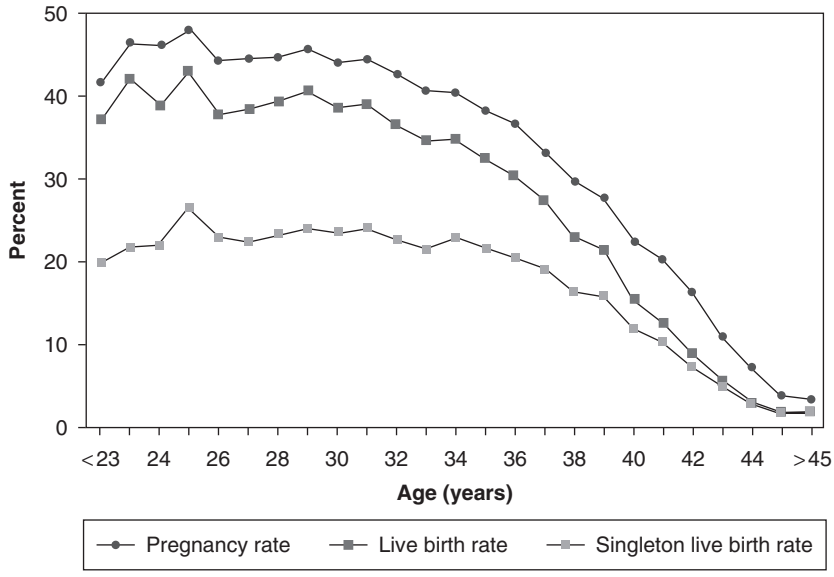

Figure 8.9 Pregnancy and live birth rates for ART cycles using fresh (non-donor) embryos by age of the woman. Obtained from published data from the Centers for Disease Control and Prevention (CDC) 2003 Assisted Reproductive Technology Success Rates. www.cdc.gov/ART/ART2003/index.htm

tubal factor infertility or severe male factor infertility seem to fair poorly with conservative interventions (i.e. ovulation induction with or without intrauterine inseminations). While the cause of the infertility may impact on success rates of the conservative treatments, there is virtually little difference between the success rates for the different diagnostic categories with IVF treatment (Figure 8.10).

Fertility Clinic Success Rate and Certification Act of 1992

Since passage of the Fertility Clinic Success Rate and Certification Act of 1992 it is mandatory that all IVF centers in the United States submit their annual success rates to a federal registry. In the past this was a joint venture of the United States Centers for Disease Control (CDC) and the Society of the Assisted Reproductive Technologies (SART), a subsidiary of the American Society for Reproductive Medicine (ASRM). After the annual data have been compiled, a finalized report is published and made available to the public for review. The published document includes a summary of national and clinic-specific success rates. The main impetus behind this law is that the reporting of clinic success rates would help the infertile couple select the 'best' IVF clinic for their treatment. Unfortunately, there are several shortcomings to this process. Because the published data are

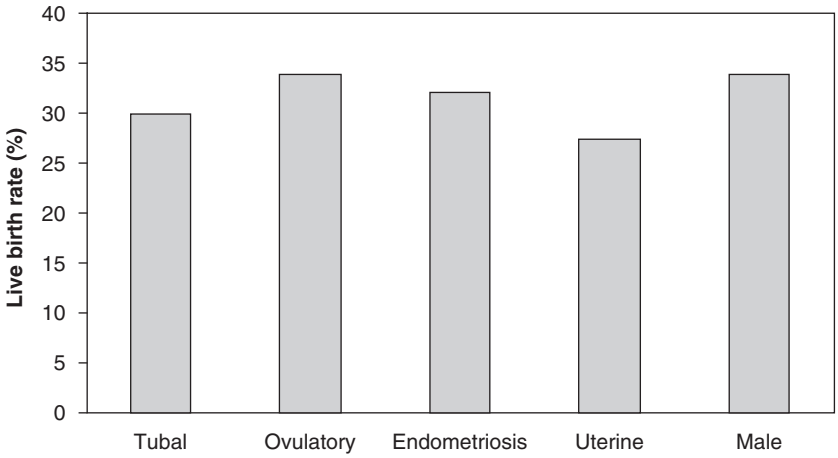

Figure 8.10 Live birth rates following IVF by primary diagnosis. Obtained from published data from the Centers for Disease Control and Prevention (CDC) 2003 Assisted Reproductive Technology Success Rates. www.cdc.gov/ART/ART2003/index.htm

based on live birth rates, the most recent data that have been published are 2–3 years old and may not reflect a clinic's current success rate. Another pitfall to the interpretation of the data is that there is no way to decipher the inclusion and exclusion criteria that any individual center used in selecting patients for treatment. Therefore, as these criteria are highly variable for each program, center-by-center comparison of success rates is not valid. Some highly experienced IVF programs attract more difficult cases which causes their statistics to be lower. Therefore, it is important for patients to not use the CDC statistics to choose an IVF program. What is more important is to determine an individual's chance of success within a particular program. An unfortunate outcome to the process is that some IVF centers have used the published data for marketing purposes. Despite these shortcomings, a major benefit of the data collection is to follow national trends and success rates of the various ART procedures. The CDC stats can be viewed online at http://www.cdc.gov/ART.

COMPLICATIONS OF TREATMENT

Multiple pregnancy

Most multiple pregnancies following IVF treatment result from the implantation of more than one embryo. Therefore, the chance of a multiple pregnancy increases with the number of embryos that are transferred. In the most recently published CDC/SART report, the percentage of pregnancies delivered that were twins was 31% and triplets or more was 3.2%. Multiple pregnancies are associated with an increased risk of most complications of pregnancy including

miscarriage, toxemia, congenital anomalies, gestational diabetes, and premature birth. The most concerning risk of a multiple pregnancy is prematurity. Babies born from a triplet pregnancy have a 20% chance of a major handicap, 17-fold increase in cerebral palsy, and 20-fold increase in death during the first year after birth (as compared to a singleton pregnancy).[1] Monozygotic twinning (MZT) is a multiple pregnancy that results from the splitting of a single embryo, which will lead to a set of identical twins. The incidence of MZT is increased in pregnancies conceived following IVF and may occur in up to 5% of pregnancies achieved after the transfer of embryos at the blastocyst stage. In addition to the above stated complications associated with a multiple pregnancy with MZT there is a greater chance of twin-to-twin transfusion, which can affect the growth of the fetuses and increase the chance of other complications. A multiple pregnancy may also pose increased emotional and financial hardship for a couple. If a multiple pregnancy develops, the couple may consider a multifetal reduction procedure. This procedure, which is performed in the first trimester of pregnancy, reduces the number of fetuses to a lower and safer number. Although the success rate is 90–95% a miscarriage may result from the procedure.

During the early 1990s there was a progressive increase in the number of triplet pregnancies. Since 1997 there has been a plateau in the number of high order multiple pregnancies. In the 1990s there was a concerted effort from the American College of Obstetricians and Gynecologists and the American Society for Reproductive Medicine to develop guidelines to help reduce the number of embryos transferred.[2,3] In addition, the progress in the field has produced higher implantation rates, which also has provided a further impetus to reduce the number of embryos transferred without impacting on pregnancy rates.[4] With the continued improvement in outcomes there is now consideration to transferring a single embryo in selected cases.

Birth defects

The possibility that IVF could increase the risk of birth defects has been a great concern for patients and clinicians. This is of particular interest since 1% of all children are now conceived following IVF. Although many studies have looked at malformations in IVF children, most have had limitations in sample size and there has been a lack of a standard definition of a minor versus a major congenital malformation. However, the majority of studies point to a slightly increased risk of malformations. A previous meta-analysis including seven studies compared the rate of birth defects between those conceived following ART (IVF and ICSI) with those naturally conceived.[5] The pooled odds ratio was 1.40 (95% CI 1.28–1.53) and confirmed an increased risk of major birth defects in the babies conceived by ART. The explanation for the increased risk of malformations is questionable but, if present, may result from some aspect of the treatment itself or genetic factors in the patients who undergo the treatment. Most studies do not use infertile women who were not treated by IVF – this is unfortunate since it is well known

that congenital malformations are more common in the infertile population. ICSI does not appear to increase the rate of malformations in comparison to the standard insemination technique.[6,7] The transfer of previously cryopreserved embryos does not convey a higher rate of malformations in comparison to the transfer of fresh embryos.[8,9] In conclusion, infertile women who conceive naturally or following treatment are at risk of having a child with congenital malformations. It is unclear whether there is an increased risk following IVF itself but, if so, the overall risk is still low when one considers the baseline major malformation rate which is 3% in the United States. This information needs to be conveyed to our patients and should be part of the informed consent process.

Ovarian hyperstimulation syndrome (OHSS)

OHSS can be a complication following the use of any ovulation induction agent but is more common following the use of injectable medications. It is a clinical situation whereby cysts develop in the ovaries following hCG administration. The symptoms that occur depend on the number and sizes of the cysts that are present. Patients at risk for OHSS are those with PCOS, high estradiol levels, and those with many smaller follicles (< 12 mm) at the time of the hCG administration. However, many patients who develop OHSS do not have any risk factors. The timing of the development of symptoms is generally 7–10 days after the hCG administration. Over half of the cases of OHSS are brought on by the rising β-hCG levels during the early stages of pregnancy. Approximately 20–30% of IVF patients develop mild OHSS and their symptoms include mild lower abdominal discomfort and distention. The symptoms are self-limited and resolve in a week. Approximately 1% of women who undergo IVF develop symptoms compatible with severe OHSS. The abdominal pain and distention are more significant and can be accompanied by the development of shortness of breath (SOB), nausea, vomiting, and decreased urine output. With severe OHSS there is the accumulation of ascitic fluid which, via the lymphatics, can traverse into the pleural spaces. With the accumulation of ascites there can be contraction of intravascular volume with resultant hemoconcentration that can lead to thrombotic events resulting in stroke, kidney damage, and possibly death.

Management

All patients should be educated on the symptoms of OHSS. Any patient who develops symptoms of OHSS must be evaluated. If the symptoms are mild then the patient is instructed to take daily weights and maintain oral fluids. The patient is called on a daily basis to be assessed. If she increases her weight by 2 or more pounds, has worsening pain, or develops SOB she is brought in for an evaluation. A physical exam is performed along with vital signs. The presence of tachycardia can be a sign of contraction of the intravascular volume, which can occur with acute ascites. On the lung exam reduced breath sounds at the bases can be a sign

of a pleural effusion. A gentle abdominal exam will provide an idea as to the severity of the ascites. A pelvic exam is not performed since the ovarian cysts are prone to rupture. A vaginal and abdominal ultrasound exam will delineate the extent of the ascites. Laboratory studies are obtained including a complete blood count (CBC), prothrombin time (PT), partial thromboplastin time (PTT), and electrolytes. The result of the CBC is most important and will give an idea of the degree of the hemoconcentration. If the hematocrit is >48% then prophylactic heparin is administered until the hematocrit returns to normal. Indications to perform a vaginal paracentesis include severe pain, SOB, or evidence of hemoconcentration.

Traditionally, the treatment for severe OHSS was hospitalization with fluid restriction and careful fluid management. Intravenous albumin was administered to mobilize the fluids. Our present management is to perform a vaginal ultrasound-guided paracentesis to remove the ascites. We have found that this approach speeds up the recovery and resolution of the process. We have removed up to 3 liters of fluid without any problem. This has essentially eliminated the need for hospitalization.

Ovarian cancer

In the general population, every woman has a 1 in 70 chance of developing ovarian cancer during her lifetime. Known risk factors for ovarian cancer include infertility and nulliparity. Alternatively, birth control pill use and pregnancy reduce a woman's lifetime risk of developing ovarian cancer. It has been theorized that the number of ovulations that occur during a woman's lifetime increases the chance of cancer formation. Hence there is concern that the use of fertility medications could heighten the risk. This was the subject of a recent review by Brinton et al.[10] After reviewing current studies the authors concluded that there is no conclusive link between fertility drug use and ovarian cancer. However, there is a need for continued surveillance and long term studies.

Table 8.2 Live birth rates (per cycle initiated) by age group for various IVF procedures.

	Live birth rates by age group (%)				
Treatment	*<35*	*35–37*	*38–40*	*41–42*	*Multiple pregnancy rate*
IVF (±ICSI)*	37.3	30.2	20.2	11.0	34.2%[†]
Frozen embryo transfer[‡]	29.4	28.4	22.6	16.5	
Egg donation[‡]		50.8			

*Live-birth rates per cycle initiated

[†]Multiple pregnancy rate includes: twins – 31.0% and triplets and more – 3.2%

[‡]Live birth rates per embryo transfer

CONCLUSION

IVF is one of the most significant developments in the field of reproductive medicine in the past century. As the technique has been improved success rates have continued to go up and now IVF is the most successful and safest treatment that we can offer our patients. IVF also has dramatically changed our approach to the treatment of the infertile couple allowing us to bypass unnecessary surgeries and months upon months of less successful treatments. Continued improvements will no doubt continue to improve IVF outcomes. When a single embryo transfer becomes the standard of care all other treatments will fall by the wayside.

REFERENCES

1. American College of Obstetricians and Gynecologists. Clinical Management Guideline for Obstetricians and Gynecologists. Multiple gestation: complicated twin, triplet and high order multifetal pregnancy. Number 56, October 2004.
2. American Society for Reproductive Medicine. Guidelines on number of embryos transferred. A Practice Committee Report – A Committee Opinion (Revised). American Society for Reproductive Medicine, 1999.
3. American College of Obstetricians and Gynecologists. Nonselective embryo reduction: Ethical Guidance for the Obstetrician-Gynecologist ACOG Committee Opinion 215. Washington: American College of Obstetricians and Gynecologists, 1999.
4. Tepleton A, Morris JK. Reducing the risk of multiple births by transfer of two embryos after in vitro fertilization. N Engl J Med 1998; 339(9): 573–7.
5. Hansen M, Bower C, Milne E et al. Assisted reproductive technologies and the risk of birth defects – a systematic review. Hum Reprod 2005; 20: 328–38.
6. Bonduelle M, Liebaers I, Deketalaere V et al. Neonatal data on a cohort of 2889 infants born after ICSI (1991–1999) and of 2995 infants born after IVF (1983–1999). Hum Reprod 2002; 17: 671–94.
7. Palermo GD, Colombero LT, Schattman GI et al. Evolution of pregnancies and initial follow-up of newborns delivered after intracytoplasmic sperm injection. JAMA 1996; 276: 1893–7.
8. Wennerholm UB, Albertsson-Wikland K, Bergh C et al. Postnatal growth and health in children born after cryopreservation as embryos. Lancet 1998; 351: 1085–90.
9. Wada I, Macnamee MC, Wick K et al. Birth characteristics and perinatal outcome of babies conceived from cryopreserved embryos. Hum Reprod 1994; 9: 543–6.
10. Brinton LA, Moghissi KS, Scoccia B et al. Ovulation induction and cancer risk. Fertil Steril 2005; 83: 261–74.

9.

Preimplantation genetic screening and diagnosis

Alison E Zimon and Kim L Thornton

Preimplanation genetic screening (PGS) and diagnosis (PGD) are techniques that provide genetic and chromosomal information about developing embryos through biopsy and analysis of embryonic cellular material. This technology is applicable and helpful to many couples seeking conception through IVF, particularly those with a known risk of transmitting single gene disorders to their offspring or those at risk of generating embryos with structural or numeric chromosomal abnormalities. In couples using PGD, accurate and reliable determination of single gene defects, chromosome structure, and chromosome number in blastomere or polar body biopsies is used to guide embryo selection prior to transfer. For many, this is a far more desirable option than awaiting fetal diagnosis in the first or second trimester of pregnancy via chorionic villus sampling or amniocentesis. While continuing to rapidly expand, PGD has become a routine option for patients to prevent the transmission of known single gene diseases and to enhance the chance of pregnancy and live birth for couples with repeated IVF failure, recurrent pregnancy loss, or advanced maternal age.

TECHNIQUES

Embryo biopsy

To perform PGD, cellular material for analysis can be obtained using one of three techniques: polar body biopsy of the oocyte prior to the completion of fertilization, blastomere biopsy of 3-day old embryos at the 6–10 cell stage, or trophoectoderm biopsy of day 5 blastocysts.

Polar body biopsy

Polar body biopsy involves the removal of one or both of the polar bodies that are generated and extruded during the oocyte divisions that complete meiosis at

ovulation and fertilization. Polar bodies may be safely removed following mechanical or chemical penetration of the zona pellucida surrounding the oocyte without disrupting the oocyte or future embryo. Analysis of oocyte polar bodies strictly involves maternally derived genetic material and therefore paternally derived genetic or chromosomal abnormalities are not evaluated. In cases of maternally transmitted genetic disease or aneuploidy related to oocyte age, polar body PGD is 95–98% accurate.

Blastomere biopsy

Blastomere biopsy of cleavage stage embryos is the most commonly employed method to obtain genetic material for PGD. This is performed on day 3 of embryo development at the 6–10 cell stage when embryonic cells are totipotent and have not begun the process of compaction. One or two blastomeres, if less than 25% of total embryo cellular material, can be reliably removed from the embryo without compromising further development (Figure 9.1). Removed blastomeres are subsequently analyzed for gene mutations or chromosomal abnormalities while the biopsied embryos continue to be observed in the laboratory. Once PGD results are available, normal embryos that have become blastocysts are selected for transfer on day 5. Interestingly, not all blastomeres of a single embryo share identical chromosomal constitution, and this variance, termed mosaicism, poses an unavoidable limitation of blastomere analysis. Studies which have analyzed blastomeres from embryos at the cleavage stage with follow-up blastomere analysis at the blastocyst stage have confirmed that mosaicism may be present in upwards of 50% of embryos. However, overall, it has been estimated that blastomere mosaicism contributes at most an error rate of 5%.

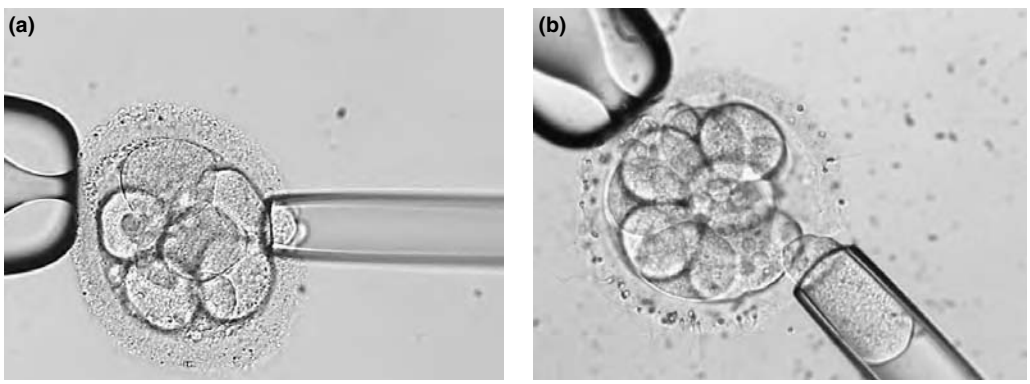

Figure 9.1 Performance of an embryo biopsy. (a) A small opening is created in the zona pellucida of a day 3 embryo. The biopsy pipette is positioned and then inserted through the opening. (b) A blastomere has been removed and is seen in the lumen of the pipette. These pictures were provided by Mark Hughes, MD, PhD, Genesis Genetics Institute and the Applied Genomic Technology Center, Detroit, MI.

Thus, PGD through blastomere biopsy is reliable and remains the current standard for preimplantation genetic analysis with a diagnostic efficiency of 95–98%

Trophoectoderm biopsy

The final available method for embryo cellular analysis is trophoectoderm biopsy of blastocyst embryos at day 5 of development. Here, the zona is penetrated chemically or mechanically generating a fenestration through which several herniated trophoectoderm cells are removed. However, this technique is limited and has not been applied extensively since a biopsy performed at this stage of development does not provide sufficient time for genetic analysis before transfer.

Genetic analysis

Embryonic cellular material obtained via biopsy can be analyzed for specific gene sequences to diagnosis single gene defects through using polymerase chain reaction (PCR) or for chromosomal enumeration to screen for aneuploidy or chromosomal structural abnormalities using fluorescent *in situ* hybridization (FISH) or comparative genomic hybridization (CGH).

Polymerase chain reaction

The PCR technique provides the ability to screen preimplantation embryos for single gene defects with known mutation sequences. Following extraction of DNA from biopsied cells, oligonucleotide primers specific for the gene region of interest are used as the starting point for DNA replication by a temperature specific polymerase. Through repeated specific temperature cycles, selected gene regions are amplified thereby providing sufficient DNA to determine whether the normal or mutated gene sequence is present. Challenges to optimizing this technique include the small initial amount of DNA available from embryo biopsy and the risk of amplifying contaminating DNA. The nested PCR technique or simultaneous PCR amplification of different gene fragments by multiplex PCR are routinely used to enhance the reliability in this setting.

Fluorescent in situ hybridization

The most commonly used method to analyze chromosomal integrity and number is fluorescent *in situ* hybridization (FISH). Interphase chromosomes of biopsied cells can be detected, visualized, and counted by using fluorescent-tagged probes that interact and hybridize with the DNA of the selected chromosomes of interest. Multiple chromosomes can be tested by using differently colored tags and performing repeated hybridization steps. Once hybridization is performed, the signals for each chromosome are counted and cellular euploidy or aneuploidy is determined. This technique can also be used to identify translocations or other

chromosomal structural defects. The inherent error rate for FISH can be reduced by repeating selective analysis with alternative probes in cases where an appropriate signal is lost or an artifact signal is detected. As there is a threshold number of chromosomes that can be tested in one cell due to interference of probe signals, the results of FISH are limited. Presently it is standard to test only 9–12 of all 23 chromosome pairs. The chromosomes most often selected for testing by FISH are those with the highest observed incidence of aneuploidy in early embryos and pregnancy losses and include chromosomes X, Y, 8, 13, 14, 15, 16, 17, 18, 20, 21, and 22.

Comparative genomic hybridization

Comparative genomic hybridization (CGH) is a recent technique that allows simultaneous and complete enumeration of chromosomes from a single biopsied cell without cellular fixation. In contrast to FISH, chromosomes are not directly visualized but the relative copy number of chromosome specific probes between the test DNA and a control DNA is assessed after concurrent PCR amplification. The technique is not only capable of screening biopsied cells for aneuploidy, but may detect subtle differences in DNA copy numbers that reflect translocations or other chromosomal structural defects. Presently, use of CGH is limited because the technique requires several days to perform. Since CGH cannot be completed during the window between biopsy and fresh transfer, embryos screened in this manner must be frozen during the diagnostic period and subsequently thawed and transferred in a later cycle once CGH results are available. Optimizing the technique and developing alternative methodologies, such as whole genome amplification with an isothermal polymerase and strand replacement, may ultimately shorten the procedural time required for CGH and render it more widely applicable clinically.

INDICATIONS FOR PGD

As the technology for PGD advances, the indications for genetic evaluation of embryos prior to transfer are expanding. At present, PGD is routinely used for couples with or carrying known sex-linked diseases or autosomal single gene defects. PGD is also commonly employed for patients at increased risk of chromosomal aneuploidy due to advanced ovarian age, translocation carrier status, repeated implantation failure with IVF, and recurrent pregnancy loss.

Sex-linked diseases

Since original reports of successful PGD pregnancies in 1990, the technology has been widely used to screen embryos at risk for sex-linked disorders. For patients with or carrying sex-linked disorders, knowledge of the specific genetic

mutation is not required as carrier or disease status can be deduced based on sex determination. X-linked recessive disorders are the most common of the sex-linked disorders and include hemophilia A, Duchenne muscular dystrophy, adrenal leukodystrophy, Lesch-Nyhan syndrome, and fragile X syndrome. Fathers affected by a sex-linked disorder have a 50% chance of passing on carrier status to daughters, but cannot pass the disorder on to male offspring. Mothers carrying an X-linked disorder have a 50% chance of transmitting the disease state to male offspring and a 50% chance of transmitting the carrier state to female offspring. X-linked dominant disorders, such as incontintentia pigmenti, are less common. Here, affected mothers have a 50% chance of passing the disease onto their offspring, whereas affected fathers can only pass the disease state to female offspring. Preimplantation genetic diagnosis offers an option for these couples to determine the embryo sex and transfer sex-selected embryos to avoid disease and/or carrier status in their children. Sex determination of biopsied embryos can be performed with PCR or FISH with excellent accuracy estimated at approximately 99%.

Single gene defects

With the completion of the Human Genome Project, the sequence information for single gene disorders has rapidly expanded allowing the application of PGD to detect disease or carrier status in embryos. Autosomal recessive disorders are more common and many have been successfully screened by PGD including cystic fibrosis, Tay-Sachs disease, sickle cell anemia, ß-thalassemia, spinal muscular atrophy, and familial dysautonomia. Autosomal dominant disorders for which PGD has been applied include Huntington's disease, neurofibromatosis, retinitis pigmentosa, Marfan's syndrome, and familial adenomatous polyposis coli. Among the challenges of preimplantation diagnosis of monogenic diseases is the ability to screen for the various mutations leading to disease. For example, cystic fibrosis can be caused by over 1000 known mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, of which 25 are routinely tested. With known sequence and mutation data, fluorescent and multiplex PCR can provide accurate diagnostic screening of biopsied embryo cells with an error rate of less than 5% (Table 9.1).

Aneuploidy

Even in the best prognosis patients, pregnancy success per cycle of IVF is at best 40–50% and the chance of miscarriage is 15–20%. The overwhelming majority of failed implantations and pregnancy loss is due to chromosomal non-disjunction resulting in non-viable aneuploid embryos. In part because human oocytes are arrested in meiosis for the duration of a woman's life until the time of conception, it is believed that the chromosomal spindle apparatus and the chiasmata adhering

Table 9.1 Most common genetic disorders evaluated by PGD

Achondroplasia (FGFR3)
Adrenoleukodystrophy (ABCD1)
Agammaglobulinemia-Bruton (TyrsKnse)
Alpha Thalassemia (HBA1)
Alpha-Antitrypsin (AAT)
Alport syndrome (COL4A5)
Alzheimer (very early onset-PSEN1)
Beta Thalassemia (HBB)
Bloom syndrome (Blm)
Canavan disease (ASPA)
Charcot Marie Tooth neuropathy–2E
Charcot-Marie-Tooth neuropathy–1B
Choroideremia (CHM)
Chronic Granulomatous Dz (CYBB)
Citrullinemia (ASS)
Cleidocranial dysplasia (RUNX2)
Congenital adrenal hyperplasia (CYP31A2)
Congenital erythropoietic porphyria (UROS)
Crigler Najjar (UGT1A1)
Cystic fibrosis (CFTR)
Darier disease (ATP2A2)
Diamond Blackfan (DBA-RSP19)
Diamond Blackfan (DBA2)
Duchenne muscular dystrophy (DMD)
Dystrophy myotonica (DMPK)
Emery-Dreifuss muscular dystrophy
Epidermolytic hyperkeratosis (KRT10)
factor 13 deficiency (F13A1)
Familial adenomatous polyposis (APC)
Familial dysautonomia (IKBKAP)
Fanconi anemia A (FANCA)
Fanconi anemia C (FANCC)
Fanconi anemia F (FANC F)
Fanconia anemia G (FANCG)
Fragile X (FMR1)
Friedreich ataxia I (FRDA)
Gaucher disease (GBA)
Glutaric acidemia–2A
Hemophilia A (F8)
Hemophilia B (F9)
HLA DRBeta1 Class II MHC (HLA DRB1*)
HLA-A Class I MHC (HGNC HLA-A)
Hunter syndrome (IDS)
Huntington disease (HD)
Hurler syndrome (MPSI-IDUA)
Hyper IgM (CD40-ligand; TNFSF5)
Hypophosphatasia (ALPL)
Incontinentia pigmenti (KBKG-NEMO)
Kennedy disease (AR)
Krabbe (GALC)
Lesch-Nyhan (HPRT1)
Leukemia, acute lymphocytic (for HLA)
Leukemia, acute myelogenous (for HLA)
Leukemia, chronic myelogenous (for HLA)
Leukocyte adhesion deficiency (ITGB2)
Li-Fraumeni syndrome (TP53)
Lymphoproliferative disorder (X-linked)
Marfan syndrome (FBN1)
Menkes (ATP7A)
Metachromatic leukodystrophy (ARSA)
Mucolipidosis 2 (I-Cell)
Neurofibromatosis (NF1 & NF2)
Niemann-Pick type C (NPC1)
Ornithine transcarbamylase deficiency (OTC)
Osteogenis imperfecta (COL1A1)
Pachyonychia congenita (KRT16 & KRT6A)
Periventricular heteropia (PH)
Polycystic kidney disease (AR-PKD1)
Polycystic kidney disease (PKD1)
Retinoblastoma 1 (RB1)
Rhesus blood group D (RHD)
Rhizomelic chondrodysplasia puncta (RCDP1)
Sacral agenesis (HLXB9)
Sanfilippo A (MPSIIIA)
SCID-X1 (Severe combined immunodeficiency) (IL2RG)
Sexing for X-linked Dz (AMELX/Y; ZFX/Y)
Shwachman–Diamond syndrome (SBDS)
Sickle cell (HBB)
Smith–Lemli–Opitz (SLOS)
Spinal muscular atrophy (SMN1)
Spinocerebellar ataxia-3 (SCA3)
Spinocerebellar ataxia-2 (SCA2)
Tay-Sachs (HEXA)
Treacher Collins (TOCF1)
Tuberous sclerosis 1 (TSC1)
Wiskott-Aldrich syndrome (WAS)

paired chromosomes are particularly vulnerable to damage accumulating with oocyte age. Aneuploidy is therefore perhaps the greatest limitation of human reproduction and at present there are no potential methods to prevent or reverse this phenomenon. Unfortunately, the current grading of embryos by morphologic analysis does not correlate with chromosomal status and neither this nor any other non-invasive method can accurately predict euploid or aneuploid status in early embryos. PGD for chromosomal enumeration using FISH is therefore a valuable technology to select chromosomally normal embryos prior to transfer. While polar body biopsy evaluates only the maternal chromosomal contribution to the embryo, it is estimated that 90% of aneuploidy in embryos is maternal in origin and therefore polar body analysis can be used as a reliable approach. However, PGD of blastomere biopsies is favored by most fertility centers as both the paternal and maternal contribution is assessed and the analysis can be completed by day 5 of development to allow for blastocyst transfer. The current common indications for aneuploidy PGD (also called preimplantation genetic screening or PGS) include advanced maternal age, repeated IVF failure, and recurrent pregnancy loss; however, a consensus regarding the attributable benefit of this screening in each of these conditions has not yet been established.

Advanced maternal age

As aneuploidy increases with maternal age, aneuploidy screening by PGD is an option for women of advanced reproductive age, generally considered to be 35 years and older. The original retrospective studies examining the effect of PGD on aneuploidy screening demonstrated a significant increase in implantation rate and decreased miscarriage rate. The largest and most strictly designed study examining the impact of PGD aneuploidy screening is a randomized control trial based in Belgium which failed to demonstrate a statistically significant difference in implantation, ongoing pregnancies, or pregnancy losses in 148 PGD subjects and 141 control subjects undergoing blastocyst transfer without PGD. Significantly fewer embryos were transferred in the PGD group and, though not statistically significant, the twin gestation rate was lower in the PGD group. While further data examining the clinical impact of PGD aneuploidy screening are forthcoming, couples may find the added assurance of embryo chromosomal status invaluable for decisions regarding selection of embryos for transfer and cryopreservation.

Recurrent pregnancy loss

For couples with two or more previous spontaneous abortions, screening for aneuploidy, together with chromosomal translocations, may provide valuable information, enhance pregnancy success, and decrease pregnancy loss. Based on PGD studies in patients with a prior history of an aneuploidy loss, the risk of subsequent aneuploidy is increased, particularly in women aged less than 35 years.

In women with recurrent loss and advanced maternal age greater than 40 years, the potential benefits are less clear due to the decreased yield of embryos developing beyond day 3 and also because of the known extremely high rate of aneuploidy in surviving embryos.

Repeated IVF failure

Similar to recurrent pregnancy loss, it is presumed that a significant contributing etiology to failed IVF in poor prognosis patients is chromosomal aberrations. Mean aneuploidy rates may be as high as 70% in embryos of these couples. Though opinions differ as to the true benefit of PGD in repeated IVF failure, PGD can certainly be offered to these patients.

Chromosomal translocations

PGD is also beneficial in couples where a parental chromosomal translocation is discovered during the evaluation for recurrent pregnancy loss or infertility. Chromosomal structural aberrations can be evaluated with PGD and FISH. Though data are not extensive, in one report of nearly 500 patients undergoing PGD for parental Robertsonian and reciprocal translocations the loss rate was significantly reduced to 2% with an overall probability of pregnancy of 20–36%.

Future PGD indications

Recent data from PGD performed in healthy and young egg donors indicate that the ratio of aneuploid to normal embryos is high, approximating more than 30%. These data have led some clinicians to consider whether couples using oocyte donation may benefit from PGD analysis. As more outcome data become available, it is possible that PGD may be more widely applied to assess chromosomal status in donor cycles and perhaps all cycles in the future.

SELECTION AND COUNSELING OF PATIENTS WHO MAY BENEFIT FROM PGD

Clinicians can best identify those patients who are likely to benefit from PGD by obtaining a thorough genetic and obstetric history. Patients who may have or carry single gene defects may have a history of genetic disease in family members or a family history of unexplained pregnancy losses or neonatal deaths. A couple's family history may also reveal specific ethnicities that are associated with increased rates of genetic disease such as the association between sickle cell anemia and African American heritage or the association between cystic fibrosis and Northern European or Ashkenazi Jewish heritage. Couples with recurrent pregnancy loss or recurrent implantation failure are at increased risk of carrying a

chromosomal translocation which can be tested for by PGD. Women with poor pregnancy or IVF outcomes or those of advanced maternal age are more likely to produce aneuploid embryos and therefore should also be offered PGD.

It is our policy that all couples undergoing PGD meet with a genetic counselor so they have a complete understanding of the genetic disorder of concern, as well as the limitations of PGD. When counseling couples it is also important that they be made aware of alternative options including the use of donor gametes. For those couples at risk of chromosomal or genetic abnormalities who do not undergo PGD and do become pregnant, prenatal diagnosis can be performed later in pregnancy by chorionic villus sampling (CVS) at 12–14 weeks or amniocentesis at 16–20 weeks. Those couples who desire PGD should also be made aware of the inherent limitations of the testing due to a baseline error rate, the contribution of embryonic mosaicism, and the possibility of a reduced overall embryo yield per cycle. Further, if pregnancy is achieved following PGD we strongly recommend a CVS or amniocentesis to confirm the diagnosis.

CONCLUSIONS

In summary, PGD is a rapidly expanding technologic advance and may greatly benefit couples at risk for transmitting genetic or chromosomal abnormalities to their offspring. As more published data become available, it is likely that the use of PGD will become more widespread and may prove to be beneficial to more if not all couples using assisted reproductive technologies.

RECOMMENDED READING

Baart EB, Martini E, van den Berg I et al. Preimplantation genetic diagnosis reveals a high incidence of aneuploidy and mosaicism in embryos from young women undergoing IVF. Hum Reprod 2006; 21: 223–33.

Braude P, Pickering S, Flinter F, Ogilivie CM. Preimplantation genetic diagnosis. Nature Rev 2002; 3: 941–53.

Carp HA, Dirnfeld M, Dor J, Grudzinksas JG. ART in recurrent miscarriage: preimplantation genetic diagnosis/screening or surrogacy? Hum Reprod 2004; 19: 1502–5.

Kuliev A, Verlinsky Y. Place of preimplantation diagnosis in genetic practice. Am J Med Genet 2005; 134A: 105–10.

Munne S, Chen S, Fischer J et al. Preimplantation genetic diagnosis reduces pregnancy loss in women aged 35 years and older with a history of recurrent miscarriage. Fertil Steril 2005; 84: 331–5.

Sermon K, Van Steirteghem A, Liebaers I. Preimplantation genetic diagnosis. Lancet 2004; 363: 1633–41.

Staessen C, Platteau P, Van Assche E et al. Comparison of blastocyst transfer with or without preimplantation genetic diagnosis for aneuploidy screening in couples with advanced maternal age: a prospective randomized controlled trial. Hum Reprod 2004; 19: 2849–58.

10.

Third party reproduction: egg donation and gestational surrogacy

Brian M Berger

Over the past 20 years, the use of assisted reproductive technologies has changed the choices available for older women. These choices include donor egg *in vitro* fertilization (DE IVF), which is now a standard treatment in most IVF centers. Patients who might benefit from DE IVF include women with premature ovarian failure, ovarian failure due to either chemotherapy or radiation, and women with gonadal dysgenesis. A second and much larger group includes women with diminished ovarian function, and today, the predominant indication for egg donation at most IVF centers is diminished ovarian reserve in women with functioning ovaries. Other candidates include women who have previously failed multiple IVF attempts and women carrying transmittable genetic abnormalities that could affect their offspring.

INCREASING NUMBER OF DE IVF CYCLES

There are many reasons for the recent increase in the number of women who are candidates for egg donation patients with diminished ovarian function. Surveys have shown that many couples prefer to delay childbearing and rear their children only after establishing a stable relationship and financial security. There are also increasing numbers of late and second marriages and more women now wish to finish their education and establish a career before trying to start a family.[1] In 2003, 399 programs reported use of donor oocytes to the American Society for Reproductive Medicine/Society for Assisted Reproductive Technology Registry. A total of 8970 fresh donor oocyte cycle transfers were performed with a delivery rate per transfer of 50.8%.[2,3]

Table 10.1 Five steps to completing a donor egg cycle

Responsible party	*Steps*
IVF center	Completion of the recipient eligibility screening process
Recipient/IVF center	Determination of insurance eligibility/financial clearance
Recipient	Selection or identification of a potential donor
IVF center	Screening of the potential donor
IVF center	Cycle co-ordination

ETHICS OF DE IVF

Several papers have addressed the important ethical considerations and social issues related to egg donation in postmenopausal women. Generally, there are three main objections related to this treatment: (1) the physical risk to the older woman during pregnancy,[4] (2) the rights of the children born to older women,[5] and (3) the use of scarce health-care resources that might deprive younger patients of treatment. Other issues which have been raised against treating older patients include the views of donors about using their oocytes for treating older women, and the psychologic effect of giving birth beyond the age of 50, which is unknown at present.[4] Those who are in favor of treating older patients argue that, by careful selection of patients, the risk of complications is reduced to a minimum and most older women wanting children are quite willing to accept the small risk of complications. There is also argument about the definition of what constitutes advanced maternal age, especially given the fact that the life expectancy of both men and women has increased very considerably.[6]

STEPS TO COMPLETING A CYCLE OF DE IVF

The process of completing a DE IVF cycle has five distinct steps (see Table 10.1). The patients are instructed to first set up an appointment with their physician to discuss the medical aspects of DE IVF. Spouses or partners must accompany the recipient to this appointment.

THE DONOR EGG TEAM

At Boston IVF we have a designated DE team which is responsible for working with all recipients to ensure that the recipient and her partner (if applicable) and later the egg donor have been properly screened, and for synchronizing and co-ordinating the recipient's and donor's menstrual cycle. The recipients are instructed to attend an egg recipient seminar with the egg donation program co-ordinator. At this seminar, comprehensive information about egg donation is

Table 10.2 FDA required testing for communicable disease agents or diseases in oocyte donors[7]

- Human immunodeficiency virus (HIV), types 1 and 2
- Hepatitis B virus (HBV)
- Hepatitis C virus (HCV)
- *Treponema pallidum* (syphilis)
- *Chlamydia trachomatis*
- *Neisseria gonorrhea*

given and all questions regarding the process are answered. We also have the patients meet with the financial coordinator. Depending on the patient's circumstances, they may learn about what their insurance policy may cover, discover what testing may be required by the insurance company, and lastly, discover what their out of pocket costs will be.

FDA REGULATIONS AND EGG DONATION

The FDA has recently published the final rules to strengthen regulation of human tissue, and expanded the regulations to include human cells, tissues, and cellular and tissue-based products.[7] The new regulations apply to reproductive tissues such as eggs, embryos, and semen. The FDA began requiring various establishments to register with the agency and list the products manufactured, starting on 29 March 2004. These establishments include those that recover, process, store, label, package, or distribute the products, or that screen or test donors of them. More than 350 reproductive establishments, including semen banks and fertility clinics, have registered with the FDA.

Reproductive establishments including IVF centers were required to comply with donor eligibility requirements, which became effective on 25 May 2005. These requirements establish screening and testing criteria for donors of human cells, tissues, and cellular and tissue-based products to help prevent the transmission of communicable diseases. People who are donating to their own sexual partners are not required to be screened or tested.

For egg donors, the collection of a donor specimen for testing must occur up to 30 days before recovery of the oocytes or egg retrieval[8] (see Table 10.2). For sperm donors (fresh specimen), the center may collect the donor specimen up to 7 days before or after the sperm is donated[8] (see Table 10.3).

Required testing must be performed by an FDA certified laboratory. Centers must also use an appropriate FDA licensed, approved, or cleared donor screening test if available. A donor whose specimen tests reactive on a non-Treponemal screening test for syphilis and negative on a specific Treponemal confirmatory test may nevertheless be considered eligible, as long as all other required testing and screening are negative. A donor whose specimen tests reactive on a Treponemal confirmatory test is not eligible.

Table 10.3 Additional tests required for sperm donors[7]

- Human T-lymphotropic virus, types I and II
- Cytomegalovirus

THE EGG RECIPIENT EVALUATION

All recipients are tested according to FDA regulations as described above. In addition, if recipients have not already done so, we require a recent (within 6 months) uterine cavity evaluation; this can be accomplished with a hysterosalpingogram, sono-hysterogram, or hysteroscopic examination of the uterine cavity. Recipients are instructed to once again schedule an appointment with their physician. The physician will review the results of the recipient evaluation and then finalize the orders for the treatment cycle.

All recipients are required to schedule an appointment with a social worker. Once again, the spouse/partner must attend this appointment. This consultation allows them to explore the psychologic issues involved in egg donation. If recipients are working with an egg donor who is known by or related to them (known donor or KD), we require that they meet once with a social worker as a couple, the donor and her spouse (if applicable) meet with the social worker once as a couple, and then all four meet again for a joint consultation.

To prevent miscommunication and confusion, we only allow the screening of one potential egg donor at a time. Recipients are also told that they are financially responsible for services rendered to the donor, even if she is not accepted as a donor following her medical screening.

DONOR EGG AGENCIES AND ANONYMOUS DONORS

Boston IVF allows anonymous donors to be recruited by approved egg donor agencies *only*. We will not permit recipients to recruit their own donors through the Internet or through any other means. This policy is necessary to ensure that anonymity is preserved and that the necessary legal contracts are properly in place. Recipients are given tremendous guidance in selecting an appropriate egg donor (see Table 10.4).

Egg donors should be healthy, between the ages of 21 and 35,[9,10] and free of infectious diseases. All egg donors, whether anonymous or known, must be screened to ensure that their motivation appears reasonable and voluntary. Egg donation presents a number of unique medical, legal, and emotional issues, which need to be carefully considered.

Table 10.4 Features to seek in a donor egg agency

Qualities	*Importance*
Medical expertise	An agency that offers a staff member with medical training is invaluable. Medical expertise is important to make decisions about which donors the agency will accept and make available to recipients
One rate of compensation for every donor	The compensation provided to an egg donor is not a payment for her eggs. It is compensation for her inconvenience, time, effort, discomfort, and the medical risk that she assumes. Agencies that offer an elite class of egg donor, or who allow donors to choose their own fees, are taking advantage of recipients who are willing to pay for certain personal characteristics like a commodity. This practice is considered unethical and is discouraged by the American Society for Reproductive Medicine
Legal counsel for both the donor and recipient	Legal consultation for both the donor and the recipient protects the interests of both parties by establishing a mutually acceptable legal contract. An agency should facilitate this process and should provide this service as a part of the agency package
Short term medical insurance policy for the egg donor	Should an egg donor experience any adverse medical event related to the egg retrieval or the medications, the recipient is financially responsible for her medical care and treatment. A good agency should offer a short-term insurance policy for purchase that covers any potential problems related to the procedure and the medications
Professional, courteous staff	A staff that is professional and courteous will treat egg donors and recipients with respect and ensure that the needs of each are met in an efficient manner. Professional demeanor usually reflects a company that is organized and efficient

APPROVED AGENCIES

According to guidelines published by the American Society for Reproductive Medicine (ASRM), programs recruiting oocyte donors and those assisting couples that have recruited their own donors should establish a level of compensation that minimizes the possibility of undue inducement of donors and the suggestion that payment is for the oocytes themselves: 'To avoid putting a price on human gametes or selectively valuing particular human traits, compensation should not vary according to the number or quality of oocytes retrieved or the donor's ethnic or other personal characteristics'.[11] Boston IVF adheres to these guidelines and will not work with agencies that are in direct violation of the ASRM guidelines.

KNOWN EGG DONORS

Known egg donors include sisters, relatives, friends, or colleagues. Known egg donors must be medically and psychologically screened as rigorously as anonymous donors. Cross-generation egg donation in which a daughter

Table 10.5 Genetic testing on all donors

- Karyotype
- Cystic fibrosis
- Fragile X
- Hemoglobin electrophoresis

donates to her mother or a mother donates to her daughter is not permitted at Boston IVF.

LEGAL CONTRACTS

We require legal consultation and establishment of a legal contract with the donor, anonymous or known. The recipient couple is generally responsible for legal fees incurred by the donor although many donor egg agencies include this fee in their administrative fees.

INITIATING THE TREATMENT CYCLE

When recipients have selected a potential donor, the agency (or recipient if using a known donor) calls the egg donation program co-ordinator who will mail them application and history forms, register the donor at Boston IVF, and schedule the donor's appointments. The donor should bring her completed forms and any previous medical records with her to her appointments. If using an agency, it is important for recipients to find out all of the costs of the agency before selecting an agency or paying a fee. Agency fees typically include the egg donor's compensation, a short-term medical insurance policy for the egg donor, and legal fees. In addition, if they select a donor who lives out of state, we require that she travels to Boston IVF twice: once for her screening appointments, and once again for the monitoring and egg retrieval. At the time of the egg retrieval she usually stays locally for one week.

SCREENING DONORS

Boston IVF screens potential egg donors thoroughly according to FDA regulations. An eight-page phone screen is first performed and a decision is made on whether or not to schedule a screening appointment. The Boston IVF physician, social worker, and the DE program co-ordinator work as a team to determine whether a donor candidate is appropriate. We perform a karyotype and genetic testing on all donors (Table 10.5). If donors belong to certain ethnic groups, i.e. African American, Ashkenazi Jewish, Mediterranean, etc., they are screened for additional genetic tests that apply. If a donor completes her screening and is approved by the medical director, the DE program co-ordinator is responsible for synchronizing the recipient's cycle with the egg donor's cycle.

Table 10.6 Donor ovulation induction protocol

Medication regimen
- OCP start date:_____
- OCP stop date **Monday*:**_____
- Start FSH/Luveris on **Saturday**:**_____
- FSH dose 225 units LH dose 75 units daily × 2 days or
- FSH dose _____units/LH daily × 2 days

Antagonist
With lead follicle ≥ 14 mm:
- Cetrotide® 0.25 mg s.c. q.d._____
- Ganirelix 0.25 mg s.c. q.d._____

*Stop OCPs on Monday, start FSH/LH on Saturday
**If menses on Tues/Wed, begin FSH/LH on Friday

CYCLE COORDINATION

Donors

Implantation and success in DE IVF

The process of implantation remains poorly understood, but two factors are clearly required: endometrial receptivity and synchronization of embryo and endometrial development. In the natural cycle, these factors are induced by the simultaneous development of the follicle and the hormonal events surrounding ovulation. In the DE IVF treatment, these events are by definition separated and need to be controlled and synchronized by a sequence of ovarian downregulation and endometrial preparation. Because of these factors, controlled timing of follicle growth and egg maturation and ovulation in the donor, and adequate stimulation of the endometrium with an estrogen–progesterone sequence in the recipient, need to be performed.

Donor ovulation induction protocol

All donors are initially started on oral contraceptives (OCPs). The OCP is started with the donor's menses and continues for 16 to 35 days. OCP pretreatment in high responders has been shown to improve the success of the treatment and also reduce the risk of ovarian hyperstimulation syndrome.[12] The OCP is stopped on a Monday and the donor is instructed to call with the first day of her withdraw bleed. Gonadotropin stimulation is then started the following Saturday. This regimen assures that the egg retrieval will most often occur in the middle of the week.[13]

For several years, we have used a regimen consisting of FSH/LH and a GnRH antagonist (see Table 10.6). This protocol allows us maximum flexibility in treatment and also has allowed us to almost eliminate the incidence of ovarian

Table 10.7 Monitoring protocol for donors

- E2 only on stimulation day 3 and day 5
- Ultrasound only after stimulation day 5
- On stimulation day 3 if E2 > 150, decrease by 75 IU
- On stimulation day 3 if E2 < 75, increase by 75 IU
- On stimulation day 5 if E2 > 500, decrease by 75 IU
- On stimulation day 5 if E2 < 150, increase by 75 IU

hyperstimulation (< 0.2%).[14] We perform frequent estradiol measurements in the beginning of the cycle in order to adjust the stimulation and also to ensure that the donor is responding adequately (see Table 10.7). We have also successfully utilized a protocol in which early adjustments in FSH dose are implemented based on the estradiol measurements on days 3 and 5.[15] Following day 5, all monitoring is done with ultrasound only unless the cycle does not appear to be progressing normally, i.e. poor follicle number or growth pattern.

Recipients

Downregulation of recipient

Prior to the uterine preparation treatment, downregulation of the cycle is usually performed due to studies that have clearly indicated that adequate downregulation of the menstrual cycle beforehand is beneficial. Borini et al[16] studied the effect of long-term downregulation on pregnancy and implantation rates in 122 cyclic patients who received donor oocytes. Recipients who were either menopausal or cyclic but had long-term downregulation had significantly higher pregnancy and implantation rates. Apart from the improved pregnancy and implantation rates after long-term downregulation, these data not only demonstrate an important role of the endometrium in implantation, but also suggest that a period of amenorrhea improves the pregnancy rate.

In cyclic patients (patients with natural menstrual cycles), suppression of the cycle is accomplished with a GnRH agonist analog (Lupron®). Lupron® has the added advantage that it can be used for several months at a time without causing any permanent changes to the reproductive system or detrimental effect on the success of the cycle. This ensures a degree of flexibility that allows egg donation to function successfully.

Estrogen replacement for recipients

Lutjen et al[17] first reported egg donation to a recipient with premature ovarian failure in 1984. They used a steroid replacement regimen for the recipient

consisting of estrogen valerate (Progynova®; Schering, Sydney, Australia) and progesterone suppositories (Utrogestan®; Piette, Brussels, Belgium). Since then, many different regimens of estrogen and progesterone replacement have been tried successfully, differing in both the method of administration and timing.

There are many reports dealing with the recommended type and dosage of estrogen and progesterone supplementation in artificial endometrial preparation before the transfer of embryos. We know from oocyte donation programs that a maximum flexibility is necessary to synchronize the recipient until oocytes are available. The aim is an open so-called 'window of implantation' with a highly receptive appearing endometrium at the time of embryo transfer. This period lasts a maximum of 48 hours. At the end of endometrial preparation should be an overlapping between the 'window of transfer', during which a transfer is planned, and this 'window of implantation'.

Many studies have examined the effects of different estrogen replacement regimens. Most have shown that the length of estrogen administration could be varied and delayed. In fact, successful implantation was observed in an extreme situation even after 100 days of unopposed estradiol valerate administration.[18] Ovulatory patients in this study received a GnRH analog simultaneously. 'Break-through bleeding' increasingly appeared according to the duration of estrogen replacement. These clinical observations provide evidence that the concept of 'prolonged follicular phase' estrogen replacement for ovum donation can be maintained, at least as long as 15 weeks. Because of the high incidence of break-through bleeding after 9 weeks (>44%), the authors recommended stopping estrogen replacement after this time. Yaron et al[19] extended uterine preparation with estradiol as long as 5 weeks without significantly decreased pregnancy rates.

It was suggested that shorter and lower dosage protocols of estradiol priming of the endometrium could result in higher abortion rates. This indicates an optimal endometrial proliferation which is necessary to enable optimal development of progesterone receptors and subsequent transformation into an endometrium receptive to the transferred embryo.[20] Neither endometrial thickness nor serum estradiol was able to predict optimal receptivity and therefore outcome in oocyte donation.

At Boston IVF, we continue estrogen replacement (both oral and transdermal) until 10 weeks estimated gestational age.

Progesterone replacement for recipients

Much controversy surrounds the issue of progesterone replacement in DE IVF cycles. Unfortunately, prospective studies comparing different types and durations of progesterone supplementation before transfer of DE IVF embryos with regard to treatment outcome have not yet been performed. With regard to timing of progesterone, several retrospective studies have shed light on the implantation

Table 10.8 Administration of medications

Class of medication	*Typical form*
Oral contraceptives	Oral tablet
Luveris®	Subcutaneous injection
Cetrotide®/Ganirelix	Subcutaneous injection
Lupron®	Subcutaneous injection
Estrogen	Oral tablet; skin patch
Progesterone	Vaginal gel, vaginal suppository, or intramuscular injection

window. In one study, 4–5 days of progesterone administration were optimal for embryo transfer comparing results after transfers between day 2 and day 7 of progesterone administration. Rosenwaks[21] reported best results after transfers on days 3–5 of progesterone supplementation.

Prapas et al[22] performed an interesting retrospective study on the association between the 'window of embryo transfer' and the duration of progesterone therapy. They transferred day 2 embryos (4–6 cell) after 2, 3, 4, 5, and 6 days following initiation of endometrial exposure to progesterone. Their results indicate that the window of implantation depends on the duration of progesterone treatment. It begins ~48 hours after starting progesterone administration and lasts for ~4 days. Highest pregnancy rates were achieved after 5 days (48.3%), with lower rates after 4 days (40%), 6 days (20.4%), and 3 days (12%). No pregnancies were observed after 2 days of progesterone administration.

Progesterone is also a critical factor in the late follicular phase of fresh IVF cycles. There is much debate on the question of whether a subtle, late follicular phase, prehCG rise of progesterone above a certain threshold (1.0 ng/ml) has an impact on the outcome of treatment in IVF cycles. Taking all information together, there seems to be no effect on oocyte and embryo quality and therefore no reason to cancel DE IVF cycles when progesterone measurements are over that threshold.

We use both vaginal and intramuscular progesterone replacement regimens and have not seen a difference in success rates. The medications and forms of administration are listed in Table 10.8. As with the estrogen replacement, we continue progesterone replacement until 10 weeks estimated gestational age.

Recipient monitoring

In most cases, recipients are monitored only once with an ultrasound to measure the endometrial thickness. This typically occurs on day 5–7 of the donor's stimulation cycle. This allows us to adjust the medications in the event that the lining is not adequate (≥ 7 mm).[23]

GESTATIONAL CARRIER IVF

In 1985, Utian et al[24] described the first successful pregnancy using a gestational carrier. The patient had undergone a hysterectomy. She had her eggs removed and then fertilized with her husband's sperm. The embryos were then transferred into the gestational carrier. There are two groups of patients that are candidates for gestational carrier IVF (GC-IVF): women without a functioning uterus or those whose pregnancy would severely exacerbate a medical condition. It is important to note that IVF with a gestational carrier differs from traditional surrogacy. In a traditional surrogacy arrangement, the surrogate mother provides the oocyte *and* the uterus to foster a pregnancy. With a gestational carrier IVF cycle, the gestational carrier is not the genetic mother because she does not provide the oocyte. At Boston IVF, we do not participate in traditional surrogacy treatment.

Prescreening and counseling

At our center, the minimum age of gestational carriers is 21 years, with an upper limit of 40 at the initiation of the IVF cycle. All gestational carriers must have carried at least one child and preferably have completed their families. Couples undergoing gestational carrier IVF (the intended patents or IPs) and their gestational carrier undergo screening as recommended by the guidelines of the American Society for Reproductive Medicine. Before ovarian stimulation, issues discussed with the IPs, the gestational carrier, and her partner, include selective reduction for multiple gestations in excess of twins, chorionic villus sampling, amniocentesis, risks of the procedure, and mode of delivery. All of the IPs, the gestational carriers, and their partners undergo psychologic and legal counseling, including appropriate legal contracts. Unlike DE IVF, there are no agencies and therefore legal contracts must be done with an attorney specializing in reproductive law. It is important that the IPs and the gestational carrier have separate representation.

Cycle synchronization and ovulation induction

Cycle synchronization between the IPs and the gestational carrier is achieved after downregulation with leuprolide acetate. The stimulation protocols and ovulation induction protocols are identical to those previously described for DE IVF. Estrogen replacement for the carrier (both oral and transdermal) and progesterone replacement are continued until 10 weeks EGA.

FDA regulations

Both of the intended parents are regarded as 'gamete donors' according to FDA regulations.[7] The intended mother must therefore be screened for the same tests

as an oocyte donor up to 30 days prior to the egg retrieval (Table 10.2), and the intended father must be screened for the required tests (Table 10.3) within 7 days before or after the egg retrieval.

REFERENCES

1. Bloom DE, Trussell J. What are the determinants of delayed childbearing and permanent childlessness in the United States? Demography 1984; 21(4): 591–611.
2. Centers for Disease Control and Prevention. CDC 2003 Assisted Reproductive Technology (ART) Report 2003. www.cdc.gov/ART/ART2003/index.htm.
3. Wright VC, Schieve LA, Reynolds MA, Jeng G. Assisted reproductive technology surveillance – United States, 2002. MMWR Surveill Summ 2005; 54(2): 1–24.
4. Joseph KS, Allen AC, Dodds L et al. The perinatal effects of delayed childbearing. Obstet Gynecol 2005; 105(6): 1410–18.
5. Benagiano G. Pregnancy after the menopause: a challenge to nature? Hum Reprod 1993; 8(9): 1344–5.
6. Olshansky SJ, Passaro DJ, Hershow RC et al. A potential decline in life expectancy in the United States in the 21st century. N Engl J Med 2005; 352(11): 1138–45.
7. Eligibility determination for donors of human cells, tissues, and cellular and tissue-based products. Final Rule. Fed Regist 2004; 69(101): 29785–834.
8. Human cells, tissues, and cellular and tissue-based products; donor screening and testing, and related labeling. Interim final rule; opportunity for public comment. Fed Regist 2005; 70(100): 29949–52.
9. Shulman A, Frenkel Y, Dor J et al. The best donor. Hum Reprod 1999; 14(10): 2493–6.
10. Cohen MA, Lindheim SR, Sauer MV. Donor age is paramount to success in oocyte donation. Hum Reprod 1999; 14(11): 2755–8.
11. Financial incentives in recruitment of oocyte donors. Fertil Steril 2004; 82(Suppl 1): S240–4.
12. Damario MA, Barmat L, Liu HC et al. Dual suppression with oral contraceptives and gonadotrophin releasing-hormone agonists improves in-vitro fertilization outcome in high responder patients. Hum Reprod 1997; 12(11): 2359–65.
13. Barmat LI, Chantilis SJ, Hurst BS, Dickey RP. A randomized prospective trial comparing gonadotropin-releasing hormone (GnRH) antagonist/recombinant follicle-stimulating hormone (rFSH) versus GnRH-agonist/rFSH in women pretreated with oral contraceptives before in vitro fertilization. Fertil Steril 2005; 83(2): 321–30.
14. Morris RS, Paulson RJ, Sauer MV, Lobo RA. Predictive value of serum oestradiol concentrations and oocyte number in severe ovarian hyperstimulation syndrome. Hum Reprod 1995; 10(4): 811–14.
15. Berger BM, Ezcurra D, Alper MM. A standardized protocol with minimal monitoring for controlled ovarian stimulation of egg donors results in improved pregnancy rates. Fertil Steril 2004; 82: S121.
16. Borini A, Violini F, Bianchi L et al. Improvement of pregnancy and implantation rates in cyclic women undergoing oocyte donation after long-term down-regulation. Hum Reprod 1995; 10(11): 3018–21.
17. Lutjen P, Trounson A, Leeton J et al. The establishment and maintenance of pregnancy using in vitro fertilization and embryo donation in a patient with primary ovarian failure. Nature 1984; 307(5947): 174–5.
18. Remohi J, Gutierrez A, Cano F et al. Long oestradiol replacement in an oocyte donation programme. Hum Reprod 1995; 10(6): 1387–91.
19. Yaron Y, Amit A, Mani A et al. Uterine preparation with estrogen for oocyte donation: assessing the effect of treatment duration on pregnancy rates. Fertil Steril 1995; 63(6): 1284–6.

20. Navot D, Scott RT, Droesch K et al. The window of embryo transfer and the efficiency of human conception in vitro. Fertil Steril 1991; 55(1): 114–18.
21. Rosenwaks Z. Donor eggs: their application in modern reproductive technologies. Fertil Steril 1987; 47(6): 895–909.
22. Prapas Y, Prapas N, Jones EE et al. The window for embryo transfer in oocyte donation cycles depends on the duration of progesterone therapy. Hum Reprod 1998; 13(3): 720–3.
23. Zenke U, Chetkowski RJ. Transfer and uterine factors are the major recipient-related determinants of success with donor eggs. Fertil Steril 2004; 82(4): 850–6.
24. Utian WH, Sheean L, Goldfarb JM, Kiwi R. Successful pregnancy after in vitro fertilization and embryo transfer from an infertile woman to a surrogate. N Engl J Med 1985; 313(21): 1351–2.

11.

Modern management of ectopic pregnancy

David A Ryley

The diagnosis and management of ectopic pregnancy continues to be a challenge for the gynecologist. Infertility is a risk factor for the development of an ectopic pregnancy. Underlying tubal disease is the mitigating cause in most cases. The management of this clinical entity has changed dramatically over the years because of earlier diagnosis and the addition of medical treatment with methotrexate. This chapter will provide an overview of the clinical problem and current management recommendations.

EPIDEMIOLOGY

Approximately 1–2% of all pregnancies do not implant in the uterine cavity and are ectopic in location. The majority (95%) of ectopic pregnancies are located in the fallopian tube and the remainder (5%) are located in the ovary, cervical canal, or the abdominal cavity. Risk factors for an ectopic pregnancy include a previous pelvic infection, current or previous use of an intrauterine device (IUD), history of pelvic inflammatory disease, tubal reconstructive surgery, infertility, increased maternal age, *in utero* exposure to DES, and smoking. Women who have had a previous ectopic pregnancy have a 10% chance of a recurrent ectopic pregnancy with a future pregnancy. These women should be counseled that they should have a pregnancy test if they have an abnormal menstrual period, intermenstrual bleeding, or worsening lower abdominal pain.

CLINICAL PRESENTATION OF AN ECTOPIC PREGNANCY

The classic symptoms of an ectopic pregnancy are amenorrhea, unilateral abdominal pain, and abnormal vaginal bleeding. However, these symptoms only result when the ectopic pregnancy is at an advanced stage. Monitoring with vaginal ultrasonography and serial β-hCG titers during the early part of pregnancy has helped us to diagnose an ectopic pregnancy at an early stage before symptoms

Table 11.1 The 50th percentile is the expected median increase for a viable intrauterine pregnancy. The one percentile is the slowest expected increase for a normal pregnancy (99% of pregnancies will have a more rapid increase). This table was modified from Barnhart et al[3]

	Relative increase in β-hCG titers from baseline			
Percentile	*1 day later*	*2 days later*	*3 days later*	*4 days later*
1	1.24	1.53	1.88	2.33
5	1.31	1.71	2.23	2.91
10	1.35	1.81	2.44	3.28
15	1.37	1.89	2.59	3.56
50	1.50	2.24	3.35	5.00
85	1.63	2.65	4.32	7.04
90	1.66	2.76	4.59	7.63
95	1.71	2.93	5.02	8.60
99	1.81	3.28	5.94	10.76

develop. An ectopic pregnancy can be diagnosed when the vaginal ultrasound demonstrates the presence of a gestational sac outside the uterine cavity. A presumed ectopic can be considered when there is lack of visualization of a gestational sac in the uterine cavity by vaginal ultrasound at 6 weeks of gestation or when the β-hCG titer is >2000 mIU/ml. An ectopic pregnancy should also be suspected when the β-hCG titers are not rising normally.

As a general rule, the mean doubling time for the β-hCG titer in a normal pregnancy is 48 hours, but there is variability in the rise of β-hCG titer.[1,2] In a recent publication, Barnhart et al followed the β-hCG titers in 287 women who were confirmed to have a viable intrauterine pregnancy.[3] Using a 99% CI they concluded that viable pregnancies have at least a 53% increase in β-hCG titer in 2 days and an 88% increase in 3 days (Table 11.1). If the rate of rise of β-hCG is below the 99th percentile then one can safely conclude that the pregnancy is not viable. Studies have confirmed that abnormal pregnancies generally are associated with abnormal rising titers. However, approximately 20% of ectopic pregnancies are associated with normal rising β-hCG levels.[4]

MANAGEMENT OPTIONS

The clinician now has several treatment options to choose from for the management of an ectopic pregnancy. The appropriate treatment will depend on the presentation and other considerations.

The Role of a D&C

When an abnormal pregnancy is diagnosed and the ultrasound fails to confirm either an intrauterine pregnancy or an ectopic pregnancy, should a D&C be

performed first prior to administration of the methotrexate? The advantage of going directly to methotrexate is it can be done more quickly and the patient avoids a surgical procedure. The advantages of performing a D&C first are that the clinician can more confidently make the diagnosis of an ectopic pregnancy and the D&C may resolve an unsuspected missed abortion. A publication by Barnhart et al[5] sheds further light on the issue. In this retrospective study they reported on 112 patients who had abnormally rising β-hCG titers and an inconclusive ultrasound. All of these patients underwent a D&C. The investigators reported that 46% of women with titers >2000 mIU/ml and 31.2% with titers <2000 mIU/ml were confirmed to have a non-viable intrauterine pregnancy. This study supports a good argument that a D&C should be performed initially before medical treatment is started. However, one problem is that it may take several days before the final pathology report is made available. A solution is that a β-hCG titer can be checked the day following the D&C. If the titer rises or fails to decrease by 15% then an ectopic pregnancy is strongly suggested.[6]

Observation

Patients who are suspected of having an ectopic pregnancy and are clinically stable should have the β-hCG titer repeated in 2–3 days. If the titer decreases, then the ectopic pregnancy could be undergoing spontaneous resolution and observation is the indicated treatment, as long as the titers continue to decrease and the patient remains clinically stable. Spontaneous resolution is more likely to occur when the β-hCG titers are lower.[7] A previous study confirmed that 90% of abnormal pregnancies with β-hCG titers less than 200 mIU/ml resolved without intervention.[8] It is important to realize that even if the titers are decreasing, tubal rupture can still occur. For this reason, any complaints of abdominal pain experienced by the patient should be investigated.

Medical treatment with methotrexate

In the past, the treatment for an ectopic pregnancy was almost exclusively a surgical approach. Over 15 years ago, methotrexate was introduced as a medical treatment for this condition. Initially, methotrexate was administered to women who had persistent trophoblastic tissue that remained in the fallopian tube following a salpingostomy. There have been several published studies demonstrating the effectiveness and safety of methotrexate when used as primary treatment for an ectopic pregnancy.[9] In today's medical practice, medical treatment for an ectopic pregnancy offers an alternative to surgery.[10–13]

Methotrexate can be administered by single injection (with repeat weekly injections if needed) or the multidose protocol. In the multidose protocol on alternative days methotrexate and citrovorum rescue factor are given. The single dose protocol has obvious advantages, but there has been some debate as to whether it is as efficacious as the multidose protocol. In a previous meta-analysis

the multidose regimen was concluded to be more effective.[14] In a recent study Lipscomb et al[15] reported on 643 patients who were treated with methotrexate for ectopic pregnancy. They reported that there was no statistical difference in the success rates following the single dose protocol vs the multidose protocol (90% vs 95%, $p=0.18$).

Action

Methotrexate is a folic acid antagonist that binds to the catalytic site of dihydrofolate reductase, which interrupts the synthesis of the purine nucleotide thymidilate and amino acids, serine and methionine. Thus, methotrexate interferes with deoxyribonucleic acid (DNA) synthesis and cell multiplication. Actively proliferating trophoblastic tissue is sensitive to this effect of methotrexate, which forms the rationale for its use in the treatment of ectopic pregnancy as well as gestational trophoblastic disease.

Indications for methotrexate administration

A woman who may be considered a candidate for methotrexate administration is one who has any of the following indications:

1. Is interested in future fertility;
2. Has a documented gestational sac outside of the uterine cavity;
3. Has an ectopic pregnancy in a location (i.e. the cervix, cornua, or ovary) that is not amenable to surgical treatment;
4. Is a poor operative risk;
5. Has a suspected ectopic pregnancy:
   (a) abnormally rising β-hCG titers
   (b) no evidence of an intrauterine pregnancy by vaginal ultrasound when the β-hCG titer has reached 2000 mIU/ml and/or at 6 weeks of gestation
   (c) no villae identified in the tissue removed with a D&C and rising or plateauing β-hCG titers during the postoperative period;
6. Has rising or plateauing β-hCG titers following a linear salpingostomy.

Contraindications for methotrexate administration

A woman who is not considered a candidate for methotrexate administration is one who has any of the following:

1. Is clinically unstable (decreased hematocrit, evidence of hemorrhage, or worsening abdominal pain);
2. Has impaired renal and liver function, thrombocytopenia or leukopenia;
3. Has a co-existing viable intrauterine pregnancy;
4. Is non-compliant;

5. Is breastfeeding;
6. Has any of the following:
   (a) history of alcohol abuse
   (b) active pulmonary disease
   (c) peptic ulcer disease
   (d) liver disease;
7. Has gestational sac (>3.5 cm), β-hCG titer >5000 mIU/ml, or fetal heart activity (relative contraindications).

Pretreatment evaluation

The following are prerequisites that must be met before treatment with methotrexate can be considered:

1. A medical consultation with a history and physical examination;
2. A vaginal ultrasound examination;
3. Baseline laboratory work, including:
   (a) blood type and screen with the administration of Rhogam®, if indicated
   (b) CBC
   (c) platelet count
   (d) SGOT
   (e) β-hCG titer
   (f) creatinine;
4. Determination of the patient's height and weight;
5. A signed consent form prior to the initiation of treatment.

Administration

Methotrexate is a chemotherapeutic drug and special care must be taken with the administration and handling of this medication. We recommend that you talk about these issues with a pharmacist before using this medication. The standard dose of methotrexate to be administered is 50 mg/m^2. The dose is based on surface area (m^2), which is calculated from the patient's height and weight (see sample calculation). We recommend that the pharmacist verify the surface–area calculation and the dose to be administered. The injection is administered by intramuscular injection and is well tolerated by the patient.

Patient instructions

Following the injection, and until there is resolution, the patient should be instructed to avoid:

- Alcohol
- Folic acid and vitamins that contain folic acid

- Exposure to the sun, sun lamp, and tanning salons
- Non-steroidal inflammatory agents
- Immunizations
- Intercourse
- Contraception for 2 months following resolution.

Calculating the dose of methotrexate

The recommended dosage of methotrexate is 50 mg/m^2

Step 1 Calculate the surface area (m^2)

$$m^2 = \sqrt{\frac{\text{Height (inches)} \times \text{Weight (lbs)}}{3131}}$$

(Mosteller RD. Simplified calculation of body surface area. *N Engl J Med* 1987;317:1098)

Step 2 Calculate the total dose (mg) of methotrexate to be administered

Dose (mg) = surface area (m^2) × 50 mg/m^2

Step 3 Give these calculations to the pharmacist to verify the accuracy. The pharmacist will dispense the medication and the volume of the injection should not exceed more than 2 cc per injection site.

Sample calculations for a patient who weighs 152 lbs and is 5′ 2" (62") tall

Step 1 Calculate the surface area (m^2)

$$m^2 = \sqrt{\frac{62\,\text{inches} \times 152\,\text{lbs}}{3131}} = 1.73\,m^2$$

Step 2 Calculate the total dose (mg)

Dose (mg) = 1.73 m^2 × 50 mg/m^2 = 86.5 mg

Step 3 Methotrexate is available in a concentration of 25 mg/cc. For this particular patient, a total of 3.5 cc would be necessary to administer the 86.5 mg. This volume would be divided into two equal injections of 1.75 cc (44 mg each).

Postinjection follow-up

Following the administration of methotrexate a repeat β-hCG titer should be measured 4 and 7 days after the injection. In most cases, the titer obtained 4 days after the injection will continue to rise when compared to the titer obtained on the day of injection. The delayed effectiveness following the injection results from the gradual incorporation of methotrexate into the cell cycle of the trophoblastic tissue.

- If there is >15% decline between titers on postinjection days 4 and 7, then weekly β-hCG titers are obtained and followed until they are negative.
- If there is <15% decline between titers on postinjection days 4 and 7, a second dose of methotrexate 50 mg/m^2 can be administered and the titers are again assessed on days 4 and 7 after the injection.
- If there is *less* than a 15% decline between titers on post-treatment days 4 and 7, a third dose of methotrexate 50 mg/m^2 can be administered.
- Alternatively, laparoscopic evaluation may be an alternative (see below: *Surgical treatment*).

Because of the risk of tubal rupture, intercourse should be avoided until the β-hCG titer has become negative. However, those patients who choose to have intercourse should be counseled to use contraception.

Side-effects

Side-effects usually do not appear until 2–7 days after administration. Side-effects include nausea, vomiting, stomatitis, diarrhea, dizziness, and loss of appetite. Rarely, methotrexate can cause leukopenia and/or thrombocytopenia. Other very uncommon side-effects include hair loss, skin rash, dizziness, and liver dysfunction. Abdominal pain is another symptom that can be noted after administration of the drug;[12,13] this symptom is most likely the result of separation of the ectopic pregnancy from the tube. Others have theorized that some abdominal symptoms may be secondary to a transient toxic effect of methotrexate on the gastrointestinal tract. However, depending on the severity of the pain, the patient should be evaluated to rule out tubal rupture with a pelvic examination, vaginal ultrasound, and a β-hCG titer.

Clinical results

There have been several reports investigating the use of methotrexate for the treatment of ectopic pregnancy. The largest study reported on 320 women who underwent methotrexate treatment for an ectopic pregnancy.[16] Following medical treatment, 91% of patients had resolution of the ectopic pregnancies.

A total of 81% responded to one injection, 17% required two injections, and 2% required three injections. The mean time until resolution was 5 weeks. The medical treatment was well tolerated with few side-effects. The following factors were not predictors of success: the woman's age or parity, the size of the ectopic pregnancy, and the presence or absence of fluid in the peritoneal cavity. Fetal heart activity was present in 12% of the successfully treated cases and 30% of those in which methotrexate treatment was unsuccessful. Regression analysis confirmed that only the initial β-hCG titer was predictive of success. The authors concluded that methotrexate could be considered when the β-hCG titer was up to 10 000 mIU/ml. However, other reports suggest that a more conservative approach is warranted and medical treatment should only be considered when the titer is < 3000 mIU/ml.[17,18] Methotrexate failures and tubal rupture are more likely in cases when fetal heart activity is present, or the β-hCG titers were rising normally pretreatment, or the titers continue to rise following the first course of methotrexate.

Conclusion: medical therapy

Medical treatment with methotrexate offers another treatment option for patients with ectopic pregnancies. In selected cases, it has demonstrated its efficacy and safety, and it is cost-effective when compared to a surgical approach.

Surgical treatment

Surgical management of an ectopic pregnancy is indicated when medical therapy has failed or is contraindicated (see above*: Contraindications for methotrexate administration*). Surgery may also be the preferred approach even if the patient is a candidate for methotrexate. It allows the definitive diagnosis to be made. It also provides an opportunity to survey the condition of the other pelvic organs, which is helpful in the management of the patient who has infertility. Finally, if the patient is suffering from a recurrent ectopic pregnancy in the same tube or the patient is undergoing IVF treatment, serious consideration should be given to removing the tube.

Operative intervention is *absolutely* indicated as the initial approach to the treatment of a suspected ectopic pregnancy when the following clinical scenarios are present:

- Hemodynamic instability, i.e., hypotension, tachycardia;
- High index of suspicion of a pending or recent tubal rupture;
- Clinical symptoms of acute peritoneal irritation.

Operative intervention is the *preferred* initial approach to treatment when the following clinical scenarios are present:

- Signs of fetal cardiac activity within the adnexal mass;
- Serum β-hCG concentrations greater than 5000 mIU/ml;

- The confirmation of an adnexal mass measuring greater than 4 cm by transvaginal ultrasound;
- The confirmation of free fluid in the cul-de-sac and/or pelvis by transvaginal ultrasound.

Laparoscopy vs laparotomy

Conservative surgical treatment via operative laparoscopy is generally preferred to laparotomy, except for those cases in which the patient is unstable due to severe hypovolemia resulting from hemorrhage.

The advantages of laparoscopy over laparotomy include shorter hospital stays, quicker recovery, reduced blood loss and adhesion formation, and reduced cost.[19–21] Comparison of clinical outcomes between laparoscopy and laparotomy for the treatment of ectopic pregnancy show similar rates of subsequent tubal patency (80–90%), intrauterine pregnancy (55–75%), and recurrent ectopic pregnancy (10–15%).[22]

Laparoscopic salpingostomy vs salpingectomy

Eighty percent of ectopic pregnancies are located in the ampullary portion of the affected tube. The preferred surgical treatment of an unruptured ampullary ectopic pregnancy is a laparoscopic salpingostomy.

Indications for laparoscopic salpingectomy include:

- Rupture and extensive damage to the involved fallopian tube;
- Inability to achieve hemostasis of the involved fallopian tube;
- Recurrent ectopic pregnancy in the involved fallopian tube;
- The patient has clearly indicated that she has completed her childbearing.

In a prospective analysis of 143 laparoscopic procedures for the treatment of ectopic pregnancy, the authors determined that the subsequent intrauterine pregnancy rates for laparoscopic salpingostomy (60%) and laparoscopic salpingectomy (54%) were not significantly different.[23] However, a retrospective cohort study determined that the more conservative approach is more likely to preserve subsequent fertility. A multivariate analysis from this study showed a 3-year spontaneous intrauterine pregnancy rate following laparoscopic salpingostomy of 62%. The rate following laparoscopic salpingectomy was 38% ($p < 0.001$).[24]

Recurrent ectopic pregnancy rates following operative laparoscopic salpingostomy are 12–15.5%; the majority of these (85%) occur in the ipsilateral fallopian tube.[25,26] When the contralateral fallopian tube is left *in situ*, recurrence rates after laparoscopic salpingectomy are similar, but slightly lower at 9.8%.[27]

Certain factors have a negative impact on a patient's subsequent fertility following conservative operative treatment of an ectopic pregnancy. A history of infertility, salpingitis, prior ectopic pregnancy, or a solitary remaining fallopian

tube is associated with subsequent intrauterine pregnancy rates that are significantly lower than in patients without these characteristics (88.7% vs 56%, $p<0.001$).[25] Additionally, the presence of ipsilateral and contralateral periadnexal adhesions has a negative impact on subsequent successful pregnancy and conception rates following operative treatment of ectopic pregnancy by laparoscopic salpingostomy. In those patients found to have ipsilateral adhesions, the subsequent intrauterine pregnancy rate was significantly lower than the rate seen in patients with a normal ipsilateral fallopian tube (67.5% vs 45.7%, $p<0.02$). Patients found to have contralateral periadnexal adhesions and a blocked contralateral tube had low subsequent intrauterine pregnancy rates of 21.3%, and high recurrent ectopic rates of 21.3%. If the contralateral fallopian tube was patent, the presence of surrounding adhesions decreased subsequent intrauterine pregnancy rates from 82.8% to 41.9%, $p<0.001$.[25] These patients may consider *in vitro* fertilization for future conception, in that cumulative success rates from assisted reproductive technologies for the treatment of tubal factor infertility may exceed the rates cited in this study.

Persistent ectopic pregnancy

The most common complication of laparoscopic salpingostomy is a persistent ectopic pregnancy, occurring in 3–29% of women who have undergone this conservative surgical approach.[27] Risk factors for the development of a persistent ectopic pregnancy include:

- Small ectopic pregnancies, i.e., those measuring less than 2 cm;
- Early surgical intervention, occurring less than 42 days from the last menstrual period;[28]
- Preoperative serum β-hCG levels of 3000 mIU/ml or greater.[29]

A retrospective cohort study of 147 patients treated surgically for an ectopic pregnancy determined that a decline in the postop day 1 serum hCG of <50% from the preoperative value was predictive of a persistent ectopic, with a sensitivity of 42% and specificity of 88%. Declines of less than 50% were associated with a relative risk (RR) of 3.51 (CI 1.25–6.68) for a persistent ectopic gestation.[30]

It is imperative for the clinician to inform patients of the risk of having a persistent ectopic subsequent to conservative laparoscopic techniques. The need for postoperative surveillance and potential intervention with methotrexate should be discussed in detail during the preoperative informed consent process.

Postoperative surveillance includes:

- Measurement of the serum β-hCG on postoperative day 1:
  - a decline of >50% from the preoperative level requires a repeat measurement in 7 days

  - a decline of < 50% from the preoperative level requires a repeat measurement on postoperative day 3; repeat testing is required every 3–7 days until the serum hCG levels are no longer detectable.

- Patients with a plateau or rise in the serum β-hCG level are candidates for the single-dose methotrexate regimen (see above: *Indications for methotrexate administration*).

Surgical vs medical treatment

Success rates

A randomized prospective trial of 100 patients with laparoscopically confirmed unruptured tubal ectopic pregnancies showed similar success rates between those patients treated with methotrexate vs those who underwent attempted laparoscopic salpingostomy. Although patients with documented fetal heart activity were excluded from the study, the authors did not limit randomization based on either the initial serum hCG concentration or on the size of the ectopic gestation. Of the patients allocated to treatment with methotrexate, 82% were successfully treated with one course of treatment and 4% required an additional course of treatment for persistent trophoblast. In the remaining 14% surgical intervention was required, the majority of these required salpingectomy due to tubal rupture. In the group of patients who were randomized to attempted laparoscopic salpingostomy, 72% were successfully treated by this surgical approach. A salpingectomy was required in 8% of these patients, and 20% required methotrexate due to persistent trophoblast. Median serum hCG clearance times in the methotrexate group vs laparoscopic salpingostomy group were not statistically different: 19 days vs 14 days, $p = 0.64$. The outcome measures of tubal preservation and ipsilateral tubal patency were similar between the two groups. The affected tube was preserved in 90% of the patients in the methotrexate group vs 92% in the salpingostomy group. Hysterosalpingograms performed 3 months after the completion of therapy revealed ipsilateral tubal patency rates in the methotrexate vs laparoscopic salpingostomy groups of 62% vs 66% (rate ratio 0.93, CI 0.64–1.4).[31]

Quality of life

A randomized prospective trial of patients undergoing treatment for laparoscopically confirmed unruptured ectopic pregnancies investigated the differential impact of methotrexate and laparoscopic salpingostomy on quality of life. The authors noted that patients treated with repeated doses of systemic methotrexate were more likely to have limitations in physical functioning. Their overall quality of life, as determined by health perception, energy level, degree of pain, overall symptom complex, and psychologic depression, was deemed to be significantly inferior to that of the patients treated surgically.[32] However, in a

prospective randomized study comparing single-dose methotrexate with laparoscopic salpingostomy, the researchers noted that the patients treated medically had significantly better physical functioning scores compared to the women who were treated surgically. There were no differences in psychologic outcomes between the two treatment groups in this study.[33]

Cost-effectiveness

In an analytic model that accounted for varying resolution rates, complication rates, and cost-estimates, researchers determined significant cost-savings with single-dose methotrexate treatment protocols compared to the laparoscopic approach. Using meta-analysis results of studies comparing these treatments, the researchers estimated a cost saving of more than $3000 (US dollars in the year 2000) per resolved ectopic pregnancy in those patients treated with the single-dose methotrexate protocol.[34]

Unusual ectopic pregnancies

As mentioned above, the majority of ectopic pregnancies are located in the ampullary portion of the fallopian tube. Rarer loci include:[35]

- Isthmus of the fallopian tube
- Fimbrial end of the fallopian tube
- Uterine cornua/interstitial
- Abdominal
- Ovarian
- Cervical
- Cesarean scar ectopic.[36]

Treatment protocols for these clinical scenarios combine surgical and medical approaches. The specific therapy is dependent on the gestational age of the pregnancy and clinical status of the patient.

Heterotopic pregnancies are characterized by an intrauterine pregnancy occurring concomitantly with an ectopic gestation, the vast majority of the ectopics implant in the ampullary portion of the fallopian tube. The incidence of this condition is dependent on the mode of conception. Rates of 1/10 000–1/50 000 are seen among spontaneous pregnancies, versus an incidence of 1% among conceptions resulting from assisted reproductive technologies.[37] The treatment is surgical.

CONCLUSION

The increasing proficiency of transvaginal ultrasound combined with the enhanced accuracy of the radioimmunoassay for β-hCG allows a definitive and

early diagnosis of ectopic pregnancy. Treatment options in this setting include conservative medical (systemic methotrexate) and surgical (laparoscopic salpingostomy) approaches that minimize risk, intervention, cost, and time of recuperation. The relative risks and benefits of these treatment protocols with respect to both the success of treatment and restoration of future fertility have been outlined in this chapter. We hope that clinicians will use this information to determine the optimal treatment strategy for their patients.

REFERENCES

1. Kadar N, Caldwell BV, Romero R. A method of screening for ectopic pregnancy and its indications. Obstet Gynecol 1981; 58: 162–6.
2. Pittaway DE, Reish RL, Wentz AC. Doubling times of human chorionic gonadotropin increase in early viable intrauterine pregnancies. Am J Obstet Gynecol 1985; 152: 299–302.
3. Barnhart KT, Sammel MD, Rinaudo PF et al. Symptomatic patients with an early viable intrauterine pregnancy: hCG curves redefined. Obstet Gynecol 2004; 104: 50–5.
4. Kadar N, Caldwell BV, Romero R. A method of screening for ectopic pregnancy and its indications. Obstet Gynecol 1981; 58: 162–6.
5. Barnhart KT, Katz I, Hummel A, Gracia CR. Presumed diagnosis of ectopic pregnancy. Obstet Gynecol 2002; 100: 505–10.
6. Stovall TG, Ling FW, Carson, SA, Buster JE. Nonsurgical diagnosis and treatment of tubal pregnancy. Fertil Steril 1990; 54: 537–8.
7. Shalev E, Peleg D, Tsabari A et al. Spontaneous resolution of ectopic tubal pregnancy: natural history. Fertil Steril 1995; 63: 15–19.
8. Korhonen J, Stenman UH, Ylostalo P. Serum human chorionic gonadotropin dynamics during spontaneous resolution of ectopic pregnancy. Fertil Steril 1994; 61: 632–6.
9. Lipscomb GH, Stovall TG, Ling FW. Primary care: nonsurgical treatment of ectopic pregnancy. N Engl J Med 2000; 343: 1325–9.
10. Corsan GH, Karacan M, Qasim S et al. Identification of hormonal parameters for successful systemic single-dose methotrexate therapy in ectopic pregnancy. Hum Reprod 1995; 10: 2719–22.
11. Henry MA, Gentry WL. Single injection of methotrexate for treatment of ectopic pregnancies. Am J Obstet Gynecol 1994; 171: 1584–7.
12. Stika CS, Anderson L, Frederiksen MC. Single dose methotrexate for the treatment of ectopic pregnancy: Northwestern Memorial Hospital three-year experience. Am J Obstet Gynecol 1996; 174: 1840–6.
13. Stovall TG, Ling FW. Single dose methotrexate: an expanded clinical trial. Am J Obstet Gynecol 1993; 168: 1759–65.
14. Barnhart KT, Gosman G, Ashby R, Sammel M. The medical management of ectopic pregnancy: a meta-analysis comparing 'single dose' and 'multidose' regimens. Obstet Gynecol 2003; 101: 778–84.
15. Lipscomb GH, Givens VM, Meyer NL, Bran D. Comparison of multidose and single-dose methotrexate protocols for the treatment of ectopic pregnancy. Am J Obstet Gynecol 2005; 192: 1844–8.
16. Lipscomb GH, McCord ML, Stovall TG et al. Predictors of success of methotrexate treatment in women with tubal ectopic pregnancies. N Engl J Med 1999; 341: 1974–8.
17. Hajenius, PJ, Mol BW, Bossuyt PM et al. Interventions for tubal ectopic pregnancy. Cochrane Database Syst Rev 2000; CD000324.
18. Gamzu R, Almog B, Levin Y et al. Efficacy of methotrexate treatment in extrauterine pregnancies defined by stable or increasing human chorionic gonadotropin concentrations. Fertil Steril 2002; 77: 761–5.

19. Brumsted J, Kessler C, Gibson C et al. A comparison of laparoscopy and laparotomy for the treatment of ectopic pregnancy. Obstet Gynecol 1988; 71: 889–92.
20. Lundorff P, Hahlin M, Kallfelt B et al. Adhesion formation after laparoscopic surgery in tubal pregnancy: a randomized trial versus laparotomy. Fertil Steril 1991; 55: 911–15.
21. Vermesh M, Silva PD, Rosen GF et al. Management of unruptured ectopic gestation by linear salpingostomy: a prospective, randomized clinical trial of laparoscopy versus laparotomy. Obstet Gynecol 1989; 73: 400–3.
22. Hajenius PJ, Mol BWJ, Bossuyt PMM et al. Interventions for tubal ectopic pregnancy. Cochrane Database Syst Rev 2000; 1: CD000324.
23. Silva PD, Schaper AM, Rooney B. Reproductive outcome after 143 laparoscopic procedures for ectopic pregnancy. Obstet Gynecol 1993; 81: 710–15.
24. Job-Spira N, Bouyer J, Pouly J. Fertility after ectopic pregnancy: first results of a population-based cohort study in France. Hum Reprod 1996; 11: 99–104.
25. Pouly JL, Chapron C, Manhes H et al. Multifactorial analysis of fertility after conservative laparoscopic treatment of ectopic pregnancy in a series of 223 patients. Fertil Steril 1991; 56: 453–60.
26. Yao M, Tulandi T. Current status of surgical and nonsurgical management of ectopic pregnancy. Fertil Steril 1997; 67: 421–33.
27. Seifer DB. Persistent ectopic pregnancy: an argument for heightened vigilance and patient compliance. Fertil Steril 1997; 68: 402–3.
28. Seifer DB, Gutmann JN, Doyle MB et al. Persistent ectopic pregnancy following laparoscopic linear salpingostomy. Obstet Gynecol 1990; 76: 1121–5.
29. Lundorff P, Hahlin M, Sjoblom P, Lindblom B. Persistent trophoblast after conservative treatment of tubal pregnancy: prediction and detection. Obstet Gynecol 1991; 77: 129–33.
30. Spandorfer SD, Sawin SW, Benjamin I, Barnhart KT. Postoperative day 1 serum human chorionic gonadotropin level as a predictor of persistent ectopic pregnancy after conservative surgical management. Fertil Steril 1997; 68: 430–4.
31. Hajenius PJ, Engelsbel S, Mol BWJ et al. Randomized trial of systemic methotrexate versus laparoscopic salpingostomy in tubal pregnancy. Lancet 1997; 350: 774–9.
32. Nieuwkerk PT, Hajenius PJ, Ankum WM et al. Systemic methotrexate therapy versus laparoscopic salpingostomy in patients with tubal pregnancy, part I: impact on patients' health related quality of life. Fertil Steril 1998; 70: 511–17.
33. Sowter M, Farquhar C, Petrie K, Gudex G. A randomized trial comparing single dose systemic methotrexate and laparoscopic surgery for the treatment of unruptured tubal pregnancy. Br J Obstet Gynecol 2001; 108: 192–203.
34. Morlock RJ, Lafata JE, Eisenstein D. Cost-effectiveness of single-dose methotrexate compared with laparoscopic treatment of ectopic pregnancy. Obstet Gynecol 2000; 95: 407–12.
35. Breen JL. A 21 year survey of 654 ectopic pregnancies. Am J Obstet Gynecol 1970; 106: 1004–19.
36. Maymon R, Halperin R, Mendlovic S et al. Ectopic pregnancies in Caesarean section scars: the 8 year experience of one medical centre. Hum Reprod 2004; 19: 278–84.
37. Rizk B, Tan SL, Morcos S et al. Heterotopic pregnancies after in vitro fertilization and embryo transfer. Am J Obstet Gynecol 1991; 164: 161–4.

12.

Integrating quality management into a fertility practice

Michael M Alper

What is a quality management system (QMS) and what does it have to do with an infertility practice? If you have never heard the term QMS, you are not alone. I had not a clue what it meant just a few years ago. And I certainly had no idea of its relevance to medicine. The purpose of this chapter is not to give a detailed analysis of a QMS, but rather to understand how it relates (in simple terms) to what we do every day in our practice of medicine.

The underlying purpose of a QMS is simple – 'Say what you do and do what you say'. A QMS provides the tools to clearly delineate what everyone's responsibility is within your organization. It gets down to the core of your corporate essence – what you are about, why you do what you do, how you do it, and how you can do things better. The system is derived from the organization itself, and it is not something that is imposed from the outside. Therefore, part of the fun of developing a QMS is the creation of it. Sure, it is work. But it is also worthwhile, as I hope to explain in this chapter.

WHY IS QUALITY MANAGEMENT IMPORTANT?

Let me illustrate an example for the need of a QMS. I was visiting a highly respected *in vitro* fertilization (IVF) practice in the northeast United States. I asked the medical director what protocol they followed to replace frozen embryos. He precisely and carefully reviewed their technique to accomplish this. I then asked him for a written summary so I could discuss his technique with my colleagues back in Boston. After shuffling through his files, he came up with an overphotocopied and illegible summary of the protocol. He apologized and commented that 'most of what we do is in our heads'. So, what is wrong with this picture? How are new colleagues supposed to learn existing protocols at this IVF center? How do the nurses know what is expected of them? How can one keep track of changes in the protocol to observe resultant changes in outcome?

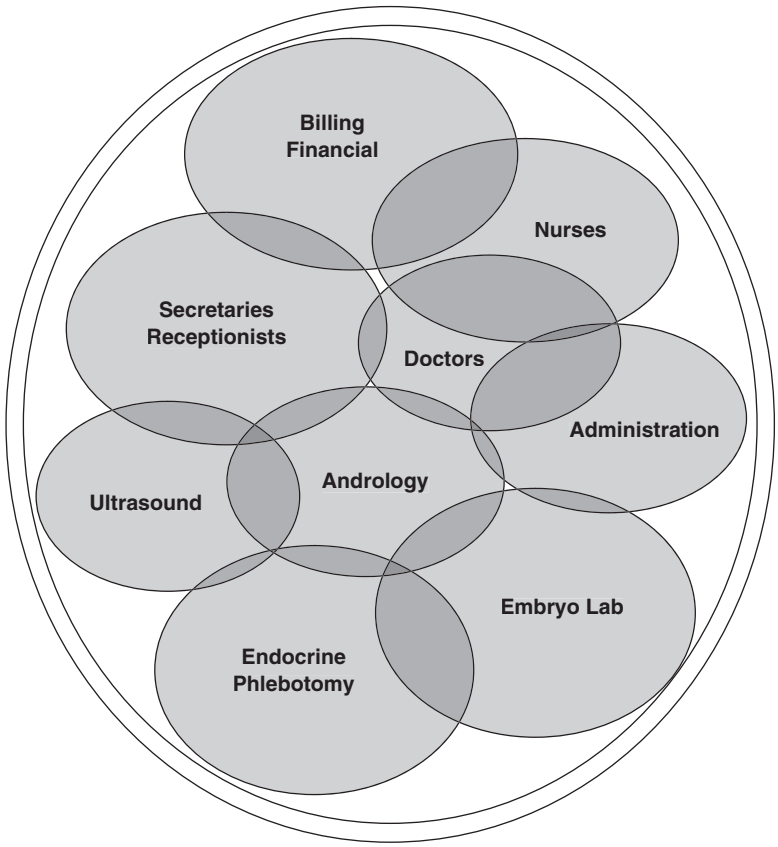

Figure 12.1 The IVF team must be a co-ordinated effort of many disciplines that must all communicate with one another

Documentation is the cornerstone of a QMS and this example illustrates the dire need for QMS in an infertility practice.

IVF centers are complex organizations. They involve the integration of many specialized professionals including physicians, nurses, scientists, administration, and others. In fact, it is a 'mini hospital'. These different entities have to work well as a team (Figure 12.1). They need to communicate well since a change in one area can quickly affect the others. The organization falls apart if any one area fails. A QMS assures that the infrastructure is set for all the players in the organization to communicate and achieve the common goals of the organization. Failure of an organization to function properly results in potentially serious errors at the very worst or corporate dysfunction at the very least.

ISO – AN EXAMPLE OF A QUALITY MANAGEMENT SYSTEM

The International Standard Organization, called ISO, is the most recognized standard for a QMS. This is a global organization with regional organizations in

How to get ISO certified:

1. Know the ISO standard
2. Document a quality management system
3. Implement the system
4. Be surveyed (assessed) by an accredited registrar
5. Be issued a Certificate of Conformity
6. Be listed in the Register of Certified Companies

Figure 12.2 Steps required for ISO certification

most countries to represent the international standard. ISO governs thousands of standards. For example, the specification for making a part such as a bolt needs to be standardized so that a particular sized bolt from company A could replace another from company B. So, these standards exist for several thousand products to keep some uniformity. Another important ISO function is to develop manufacturing standards. For example, if you are designing an aircraft for Boeing and wanted to install a particular aircraft part, you would purchase it only from a manufacturer that was ISO certified. This is one way to insure that the part comes from a company that meets certain manufacturing standards. Similarly, ISO standards exist for service industries. These are the 'ISO-9001' standards. It is these standards that can be applied to the health-care industry, and IVF in particular.

There are several steps for becoming ISO certified (Figure 12.2). For any service company to become ISO certified, it must first understand the standards that must be met. Typically, consultants with QMS experience work with the organization to understand and apply the standards. The time and expense for this process vary with the organization and its size, but typically it takes several months. The consultant must work with the employees to develop a QM system according to ISO standards. It must then be implemented to be sure it functions properly. A survey is conducted and, if successful, the certificate of conformity is issued.

The ISO standard is clearly laid out in a 23-page document of the elements required (Figure 12.3). These requirements are readily available from the ISO organizations (see http://www.asq.org/). These must be applied to the particular organization.

I have interpreted what ISO does for an organization to make them more understandable. A more detailed account can be found in the suggested reading at the end of the chapter. So, what does a QMS such as ISO teach us? Here are the main points: (1) documentation, (2) a process approach, (3) setting expectations for the staff, (4) never be happy with the status quo, (5) leadership, (6) communication, and (7) focus on the customer.

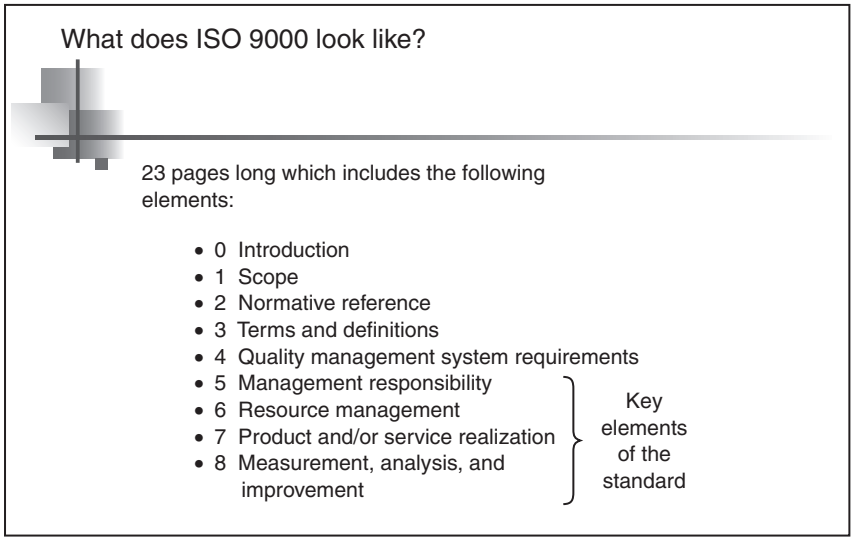

Figure 12.3 Elements required for ISO certification

DOCUMENTATION

Before implementing a QMS at Boston IVF we asked all employees to collect every single document that they have seen in the organization, no matter how old it was. These documents could include anything from the organization including protocols, handouts, marketing materials, etc. To my astonishment we had close to 3000 documents at Boston IVF! Some were older versions of documents (e.g. consent forms), instructions that few people ever knew existed, etc.

A QMS requires a company to organize and maintain its documents. All documents need to be clearly identified and assigned to someone in the organization to control. All revisions made to any document must be authorized and recorded. All employees must know where to find the latest version of the document. It sounds simple but it requires considerable effort to identify which items are important and forces the organization to revamp and revise outdated materials. The exercise of identifying and managing an organization's documents is an important part of 'cleaning house' resulting in a more organized and 'neat' approach. Our company found it extremely useful.

Documentation goes beyond collecting and organizing materials. Virtually everything that goes on in the organization that involves a process should be written down. What should happen when a potential patient calls requesting information? How are patient complaints handled? All these instructions should be clearly laid out.

A process approach to problem solving

So often in life and in business we make decisions based upon emotions and not on facts. A QMS should develop an organization's tools to solve problems based on the

analysis of facts. Sure, gut feeling are often important, but both major and minor corporate decisions require careful analysis and process. For example, what happens if an employee has an idea for improving a procedure? He may tell his supervisor, but the idea could die if not carefully evaluated. There needs to be a method developed for suggestions to be heard and analyzed. This would be a process for improvement within the organization. Another simple example is ordering. Who can order what in the organization? What process exists for purchasing that covers all departments? All this must be documented and flow charts developed for cetain processes so that all employees can clearly understand how things are done.

Setting expectations for the staff

It is typical for employees to want to succeed at their work. Human nature is to do a good job. Experience dictates that when an employee is failing at their work, it is commonly the result of a failure of the supervisor to clearly delineate the expectations, or the lack of training and tools that the employee receives.

It is vital for a clear job description and expectation to be presented to the employee. Also, we often fall short training staff on how to accomplish what we expect of them. And training does not start and end at the orientation. A QMS forces us to clearly identify how we manage staff training and competency. After all, a company's greatest asset is its employees and it is imperative that performance is constantly measured and accountability delineated.

Never be happy with the status quo

A fundamental requirement of a QMS system is to foster continual improvement. There is a rare task in any organization that cannot be done better. So, how does one foster the notion that continual improvement is critical? This corporate personality trait starts from the top to the bottom of the company. Every employee with an idea for improvement must be encouraged to share their ideas and know the steps to take when presenting their suggestions. It is the employees on the front line who often know how to make their jobs more effective or efficient.

Leadership

The mission of any organization needs to be developed and followed. For that to occur, management must take leadership. Physicians receive no instruction in leadership training. In fact, I would say that it is uncommon for physicians who spend most of their career learning how to care for individual patients to also have the skills to motivate and lead an organization. These skills are typically developed in business (and not medical schools). Typical fertility practices consist of several physicians practicing under one roof. A common frustration is bringing the group together to develop common practice patterns. It actually is not hard to accomplish this. But, there needs to be one person driving the process.

Books have been written on the skills required to be a leader. Some of these include, amongst others, good communication skills, belief in people, leading a balanced life, possessing a willingness to continually learn, and radiating positive energy. Leaders establish unity of purpose and direction. Leaders create an environment where people are fully involved in achieving the organization's objectives. Every manager needs to lead their department and a QMS focuses on responsibilities of management.

Communication

Proper communication both within the IVF center and with the outside world is of paramount importance. In fact, miscommunication can result in significant medical errors which are costly and can hurt the name of the IVF center. There must be an established method to handle patient complaints or suggestions.

IVF centers involve many disciplines. A change in one area typically affects another. For example, if the physicians decide to order an extra three blood tests during an IVF cycle, then nursing, phlebotomy, billing, and other physicians must all be aware of the change. How do these changes in procedure get communicated and followed?

Physicians are often perceived as having their own way of doing things and unwilling to change to develop a more uniform method of treatment. This is not the case when physicians have a way to discuss and debate their views. There must be an effective process to discuss protocols through meetings and discussions. We find that retreats away from the office are the perfect venue to review clinical matters.

The key to delivering optimal service to our patients is through effective communication. Do patients have trouble speaking to the nurse? Is voicemail preventing a patient from having the human touch? Frustration from inability of our patients to speak to the clinical staff in a timely manner is a frequently distressing issue for them.

Focus on the customer

A quality management system refocuses the organization on improving quality. But quality is not a vague concept or dream. If it cannot be measured, then it cannot be quality. The organization must be able to quantify and measure performance. Customer satisfaction is the tool that determines the ultimate success of an IVF center.

So, who are our customers? Certainly our patients are our primary customer. But for us to know if we are doing a good job, we must ask our patients how we are doing. Our product is not babies, but rather the resolution of infertility. Some patients leave our IVF centers with a baby but are dissatisfied with their experience with us. Is that a success? And vice versa, we have many patients without

success who are extremely appreciative of the efforts of our staff in helping them deal with and resolve their fertility issue. Our business is to provide a service, not a product. Since we cannot control whether the service will ultimately be successful in achieving a pregnancy, we must direct our efforts to helping our patients build their families by whichever means, or resolving their goals with comfort with child-free living.

We should not ask ourselves how we do at treating our patients; we must ask them. The best method is to survey them and follow the responses over time. Our surveys must be detailed enough to uncover deficiencies. All areas of the organization must be analyzed. Sometimes the results are surprising. How does a doctor know that he/she is effective at what they do? Ask the customer and you will find out.

But an IVF center has many customers beyond the patients. We have relationships with pharmacies, pharmaceutical companies, vendors, and insurance companies. These companies are also our customers and they must be managed as well.

Our employees are our internal customers. No company is effective with unhappy employees. The employees are one of the best marketing tools that the company has. These ambassadors must be satisfied to project the positive, excellent service provided.

SUGGESTED READING

1. Carson B, Alper M, Keck C. Quality Management Systems for Assisted Reproductive Technology. London, UK: Taylor and Francis, 2004.
2. Alper MM, Brinsden P, Fischer R, Wikland M. Is your IVF program good? Hum Reprod 2002; 17: 8–10.
3. Keck C. Quality Management in Assisted Reproduction. Czech Republic: KAP CZ, 2003.

13.

The true ART: how to deliver the best patient care

Merle J Berger

I have practiced in the field of infertility for 35 years and have been a part of a medical specialty that has undergone dramatic transformation. When I first entered the field in 1970, 8 years before the birth of Louise Brown, the first IVF success, the specialty was not practiced differently than any other medical specialty. The ratio of physicians to paramedic personnel was approximately 1:1.5, and the office facilities were little different from any other doctor's office. Finances were rarely an issue limiting care and all surgeries were major procedures and were performed in the hospital.

Following the inception of IVF the infertility practice has dramatically changed. Today, each one of our Boston IVF physicians needs approximately 10 paramedic people at their disposal in order to perform their specialty efficiently. Our facilities are in multiple locations, the largest of which encompasses almost 35 000 square feet of space including not only physician consultation and examination rooms, but administrators' space, laboratories, ultrasound rooms, operating rooms, and even a complementary care center for acupuncture, massage, and counseling. With all of these services in place, we can now offer a wide array of treatment options in a safe and efficient manner, but the inherent complexity in the discipline (and in the organization required to execute it) can appear emotionally and physically draining to many patients. While the infrastructure of an infertility practice has changed, the approach to caring for the patient has not. Over the years I have learned through trial and error the important ingredients to a successful infertility practice which I want to highlight in this chapter.

THE INITIAL ENCOUNTER

It all starts (and sometimes ends) with the first encounter we have with the couple. After we have seen a new couple at the initial consultation, we just assume that they follow our instructions, complete the evaluation, return for a follow-up consultation, and then proceed with our recommended treatment. However, it is

surprising with the successful treatment options that are currently available that many couples dropout and never return back to see us. For some it is based on the financial burden that is imposed, but this is not true for many others. Gleicher et al reported that 36% of HMO insured patients with full scale infertility coverage in place discontinued care after 6 months following their initial presentation.[1] Land et al performed a retrospective study of their IVF population in the Netherlands where IVF is a covered treatment.[2] They reported that almost half of patients voluntarily dropped out after three unsuccessful IVF cycles. These findings were also supported by a recent study out of Sweden that concluded that the dropout rate was 65% after three IVF cycles.[3] The most frequent underlying cause of the dropouts was the psychologic stress of the treatment. So the challenge that we all face is how to keep our patients engaged in the process long enough so that they can benefit from the successful treatments that we have to offer. We do this by minimizing the stress and inconvenience of the treatments, keeping them focused, and keeping tabs on how they are doing emotionally.

A STREAMLINED AND FOCUSED EVALUATION

In the past, couples would undergo an exhaustive and lengthy infertility evaluation that could last for months. The battery of diagnostic tests included multiple semen analyses, several blood tests, a hysterosalpingogram (HSG), BBT charts, endometrial biopsies, postcoital tests, various immune tests on cervical mucus and/or sperm, and a laparoscopy. Some of these procedures were not only painful and invasive but the results were often inconclusive so they had to be repeated frequently, thus prolonging the time of the workup and its associated discomforts and risks. Most of these tests are now considered unreliable and in retrospect were a waste of time.

Today, the infertility evaluation is streamlined and essentially encompasses only three basic tests: a cycle day 3 hormone assessment (FSH, E2), hysterosalpingogram (HSG), and semen analysis. All of these tests can be completed within a month so when the couple returns for a follow-up visit a treatment plan can be devised and instituted rather quickly after initial presentation. With regard to each of these tests, please note the following:

Semen analysis There is no need to prescribe coital instructions or limitations prior to the test. A random specimen will do even after only one day of abstinence. Furthermore, if desired and if geography permits, the specimen can be produced at home in a sterile container rather than in the laboratory, as long as it can be delivered within one hour after it is produced. During cold weather the sample should be kept at body temperature during transport.

Cycle day 3 hormone studies These studies can be obtained on either day 2 or day 4 of the cycle if day 3 is not convenient.

HSG This procedure can be performed quickly and with minimal discomfort. It is best if this procedure is performed by someone experienced with a pelvic exam such as a gynecologist or a nurse practitioner. My approach is to use a balloon catheter so that I can avoid the application of the tenaculum. However, if a tenaculum is necessary, to help reduce the discomfort it should be applied slowly. To further reduce the discomfort with the exam I inject the contrast material *very slowly* and administer a non-steroidal anti-inflammatory agent 1–2 hours before the procedure in order to avoid pain.

TREATMENT

At the follow-up consultation all of the test results are discussed and then I provide the couple with an overview of all treatment options from the most conservative to the most aggressive. For some couples the indicated treatment is IVF plus ICSI but for others, specifically those with unexplained infertility, there are conservative options to consider. An important part of the discussion focuses on the success rates and multiple pregnancy rates associated with the various treatments. Patients are always surprised at the low success rates of our treatments. To put it in proper perspective I educate them about the inefficiency of the human reproductive system and that in the best case scenario a normal *fertile* couple only has a 15–20% chance of achieving pregnancy during each month. I discuss with them how the woman's age impacts on the chance of pregnancy. I also want to know their views on a multiple pregnancy, which greatly helps in tailoring the treatment plan. Some couples want to do everything possible to avoid a multiple pregnancy, even twins. Alternatively, for many a multiple pregnancy is what they are looking for. If this occurs the couple has an instant family and would not have to return to undergo the painful process again. It is important to review with the couple all of the complications of a multiple pregnancy and emphasize that the goal of treatment is a healthy singleton pregnancy. Finally, during the discussion I try to get a feel for how aggressive the couple wants to be and what is their sense of urgency. For the timid who want to avoid a multiple or are overcome with the technology no treatment at all or conservative treatment with clomiphene citrate only may be their choice, whereas other couples may want to move on to more aggressive treatment with FSH ovulation induction plus intrauterine inseminations (IUI) or even IVF. My approach to the various treatments is as follows:

Level 1 – oral medications Clomiphene citrate (CC) has been used for almost 50 years and is the most widely prescribed fertility medication. It is tolerated by most patients but the most common side-effect I have noticed is mood changes and for some women it can be intolerable. CC is the first-line drug when treating ovulatory disorders and many times I will add in metformin to improve the response. CC is also an option for the couple with unexplained infertility. The dose appears to be important only when inducing ovulation, but it does not

seem to matter when used to superovulate the woman. Adding IUI may be considered in the case of unexplained infertility and may increase the chance of success by a few percentage points. If intercourse is chosen, there is no need to recommend frequent exposures since sperm will reside in the cervical mucus for many days before ovulation. During CC treatment consultations with the physician can be infrequent. A general rule is that if success is not obtained in 3 to 6 months, it is advisable to 'move on'.

Level 2 – injectable medications (FSH) As with CC, gonadotropins were originally used to correct anovulation but today are used primarily for superovulation as part of IUI or IVF treatment. To make the treatment easier, one should try to avoid unnecessary blood draws. If there is little likelihood of hyperstimulation, such as with patients who have had previous cycles on the same dose or in patients who are in the older reproductive age group, blood drawing can be minimized or even eliminated, and the decision when to trigger the ovulation with hCG is made based on ultrasound results alone. Similarly, there is no need to obtain any blood tests after ovulation has occurred to monitor progesterone levels. Since there is no evidence to support the existence of luteal phase deficiency there is no need for supplemental progesterone in any form, as well. For patients receiving FSH injections I perform an IUI but I question whether it truly increases the chance of pregnancy. In Massachusetts, we do it routinely but only because the insurance companies demand it before giving approval to move on to IVF. The approach to this treatment has changed over the years as IVF has developed into a more successful and safer option. In years past we would start with high doses of gonadotropins to superovulate the patient – the more follicles the better. The current approach is to avoid a high-order multiple pregnancy. Therefore we start out with lower doses and if the patient overresponds to the medication we either consider changing the cycle to IVF or canceling the cycle. This more conservative approach no doubt has decreased the success rate with this treatment and I predict that in 5–10 years this treatment will only rarely be used.

Level 3 – in vitro fertilization (IVF) In the past, IVF was considered a treatment of last resort because it was thought to be more difficult and more risky. However, over the years, all of the steps of IVF have been refined and it has evolved into the most successful and safest of the treatments we have to offer. Hence we are now encouraging patients to consider IVF much earlier in the treatment plan. IVF treatment was much different in years past as compared to how it is performed today. When IVF was performed in the past it was a commitment for our patients to say the least. Daily visits for monitoring were the norm. All medications were administered by intramuscular injections that would be continued for several months if pregnancy was established. Even after the embryo transfer it was routine to recommend several days of bed rest. Many of our patients had to stop working

just to go through an IVF cycle. In the past we were dealing with lower success rates than what we have today and every clinic had their own 'recipe' that they believed improved their success rate.

Despite all of the idiosyncrasies, IVF success rates have continued to go up which has allowed us to make the treatment easier. With more purified medications, most injections are now given subcutaneously. We limit the number of visits for monitoring – in some patients we have eliminated venipunctures since there are several studies concluding that ultrasound monitoring alone does not impair outcome or place the patient at risk for ovarian hyperstimulation. Several years ago at Boston IVF we made the decision to switch to using vaginal progesterone medications. There is no conclusive evidence that progesterone injections are better than vaginal preparations. We have noticed no decrease in success rates and have incredibly improved the patient acceptance rate. It must be realized that many patients stop treatment because of the pain associated with injections and venipunctures. There is little doubt that progesterone in oil is among the worst offenders causing discomfort and vaginal progesterone is clearly equally as effective. Even after embryo transfer, I tell my patients to resume normal activities immediately, including moderate exercise and intercourse. There is no evidence that a period of rest following the transfer improves outcome and it is our view that getting the patient back into their normal routine of life is advantageous. It is often reported that waiting for the pregnancy test is the most difficult part of the whole IVF process, so we provide them with a tip sheet which was prepared by our psychologist.

PATIENT INTERACTION

Since our patients are under a great deal of stress during treatment, more contact is better than less. After a patient starts a treatment program there is the possibility that the physician may not see the patient for months. Many patients can feel abandoned by their physicians even though the physician is supervising their care behind the scenes. Patients want to see their physicians. For patients undergoing an IUI or IVF cycle, it is best to see them during the treatment and after the cycle is completed, or at the very least speak to them by phone. The physician should also try to call their patients with daily decisions.

It is extremely important that we be honest with our patients about their chances of success. Infertility patients are desperate and vulnerable. It is important to respect the couple's wishes but if the treatment is futile – it is time to stop and move on to other options. These are always difficult conversations we have with our patients but they must take place. As long as we are supportive and compassionate with our patients we can help them move on. For those who struggle with a recommendation to stop treatment I refer them to one of my colleagues for a second opinion. Also getting a social worker involved will be of help to the couple.

COMMUNICATION

Effective communication is the foundation of any successful organization, especially a medical practice. Communication needs to be prompt, accurate, and consistent. Everyone on the medical team needs to be on the same page. Trust can be eroded if the patient gets different answers to the same question posed to different team members. Unlike other medical practices, there is more frequent communication between the patient and the medical practice during a treatment cycle and there is always a sense of urgency of the communication. Therefore, one should stress to all the staff that all calls have to be answered by the end of the day and all issues must be resolved. This is a challenge for our nurses who sometime field 50–100 calls on a daily basis. It is also important for the physician to be available when needed. Our nurses are extremely knowledgeable and resolve most issues. However, they all feel comfortable in getting the physician involved to resolve any particular issue if need be.

IT IS A TEAM EFFORT

I have been blessed over the years with a highly successful practice – in large part because of the excellent support staff. The success of any infertility practice is dependent on the skill and quality of the staff including the nurses, secretary, sonographers, phlebotomists, and other ancillary staff. You may be the greatest doctor but if you don't have a good staff to back you up – you are deemed to fail. Every physician must recognize the importance of the team and he/she must give each team member the respect they deserve.

KEEPING TABS ON THE EMOTIONS

As mentioned previously a major reason for patient dropout is the psychologic stress of the whole process. It is important to educate the staff about the stress the couples are under. Many times it is not the physician but other staff members that are the target and bear the brunt of the patient's stress and frustration. At the initial consultation I always survey how the couple is doing emotionally. I tell them that all couples struggling with infertility are stressed and feel anxious – this is normal. In some situations I refer a couple early in the process to our Mind & Body program for relaxation training or to one of our social workers for counseling. Other couples may not be ready or need a referral but may change their minds after they have been through a few unsuccessful cycles. It is vitally important that the medical team keeps tabs on the emotional health of the patients and intervenes when necessary. Otherwise it may be too late and discouragement sets in and the patient leaves the practice.

DON'T FORGET THE REFERRING PHYSICIAN

The lifeline for any specialty practice such as infertility is a constant stream of patients being referred from the referring physician. While the referring physician's goal is to have the patient return to their office pregnant they also need to be engaged in the process as well. I try to send frequent letters to referring physicians to keep them abreast of the progress. It does require time but these letters don't have to be elaborate – just a brief one is fine. If the patient needs a basic surgical procedure (i.e., D&E, laparoscopy for an ectopic pregnancy) I contact the gynecologist to see if that doctor is interested in performing it.

SUMMARY

Because of the nature of our specialty, patients must relate not only to their physicians and nurses, but to laboratory personnel, receptionists, ultrasonographers, phlebotomists, and even insurance and financial experts. The patients must be treated as customers but not made to feel like customers; so it is incumbent upon physicians who manage practices to learn skills never imagined in medical school, residency, or fellowship. With all this in mind and incorporating some or all of the suggestions described above, patients' acceptance rates can only improve which ultimately increases the chances of success as well as the popularity of the providers.

REFERENCES

1. Gleicher N, Vanderlaan B, Karande V et al. Infertility treatment dropout and insurance coverage. Obstet Gynecol 1996; 88: 289–93.
2. Land JA, Courtar DA, Evers JL. Patient dropout in an assisted reproductive technology program: implications for pregnancy rates. Fertil Steril 1997; 68: 278–81.
3. Olivius K, Friden B, Lundin K, Bergh C. Cumulative probability of live birth after three in vitro fertilization/intracytoplasmic sperm injection cycles. Fertil Steril 2002; 77: 505–10.

14.

Medical ethics in reproductive medicine

Steven R Bayer and Kim L Thornton

The advances in the field of reproductive medicine have created new treatment possibilities for infertile couples that previously did not exist. This progress has benefited many but has resulted in the emergence of challenging ethical dilemmas. In today's practice of reproductive medicine, ethics is playing an ever-increasing role. The specialty is ethically charged because of its focus on reproduction. Even though the concept of reproduction means something different to all of us, the ultimate goal is to produce an offspring and nurture that offspring. While nobody refutes this, the disagreement focuses on the means that may be required to achieve this goal. Society views the act of reproduction as a private, natural, and conjugal act between two people. In many cases, treatment with the available technology does everything but meet these criteria. Nevertheless, the right to procreate or reproduce is a liberty that is held sacred by all of us. As caregivers we must respect this right, but at the same time it is our responsibility to use the available technologies in a responsible manner. This is the role of ethics in reproductive medicine.

DEFINITION

Ethics is defined as a code of moral principles derived from a system of values and beliefs that helps define the correctness of our actions.

ETHICS IN MEDICINE AND NURSING

The practice of medicine and nursing is founded on ethics. Physicians take the Hippocratic Oath where it is stated 'I will follow that system of regimen which, according to my ability and judgment, I consider for the benefit of my patients, and abstain from whatever is deleterious and mischievous'. A similar statement is made in the nursing code of ethics, The Nightingale Pledge: 'I will abstain from whatever is deleterious and mischievous and will not take or knowingly administer

any harmful drug'. In society, it is implicit and expected that physicians and nurses practice ethically within the bounds of their profession and do what is in the best interest of their patients.

Therefore, it is our responsibility to administer treatment to the infertile patient in an ethical fashion. This is understood but who is the actual patient? It is complicated in the field of reproductive medicine where there can be many participants involved in the treatment. Obviously we have to look out for the interests of the woman undergoing treatment who is assuming the immediate risks of the treatment and the risks associated with the pregnancy. We also have to protect the rights of her partner who is not exposed to any risks of the treatment but he must first desire to become a parent and also be willing and able to care for any offspring that results from the treatment. As providers we must also determine the impact of our decisions on the yet unborn child. To further complicate matters there are other patients to be considered in cases of egg donation and gestational surrogacy. Therefore before any treatment is started all participants must be closely evaluated to insure their interests are not compromised as a result of the outcome of the treatment.

INTEGRATION OF ETHICS INTO CLINICAL PRACTICE

In every center there should be an opportunity to discuss ethical issues concerning the patient care that is provided. To integrate ethics into clinical practice there are four key components that must be in place, including open dialog, an ethics committee, resources, and ethical analysis.

Open dialog

When compared to most other medical problems, the treatment of infertility is unique because it can only be accomplished through a co-ordinated effort of a team made up of physicians, nurses, scientists, mental health professionals, and other key personnel. Every member of the team deserves respect since each plays a necessary role in the treatment of the couple. Each team member interacts with the couple at a different level, which gives him/her a unique perspective regarding the treatment that is being rendered. Each member must feel comfortable with the treatment that is being performed otherwise they must be able to voice their concern freely and it is taken seriously.

Ethics committee

To have an effective discussion on ethical issues, a group must be assembled. The committee can include a physician, nurse, mental health professional, and a representative from the laboratory. Depending on the topic that is being discussed, input from a lawyer, ethicist, or a member of the clergy may also be

helpful. While it is optimal to have regularly scheduled committee meetings it may be necessary to assemble the committee on short notice to resolve an emergent issue. One role of the committee is to review the ethical issues concerning a specific treatment (i.e., egg donation, gestational carrier treatment). If a decision is made to offer the treatment, the next step is to develop a comprehensive policy detailing how the treatment will be accomplished. Another role of the committee is to discuss ethical issues concerning individual cases. At the conclusion of any discussion by the committee, the goal is to establish a consensus regarding a resolution to the problem of concern.

Resources

For any ethical analysis there must be available resources. The resources come from the knowledge of individual members and from outside resources, as well. The ethics committee of the American Society of Reproductive Medicine (ASRM) has published papers entitled 'Ethical Considerations of Assisted Reproductive Technologies' as supplements to the journal Fertility and Sterility. The largest compilations of position papers of the ethics committee were published in 1994 and 1997, and cover over 20 different topics. In addition they have periodically published position papers on various topics. A sampling of positions published in the past few years is as follows:

- Fertility preservation and reproduction in cancer patients
- Fertility treatment when the prognosis is very poor or futile
- Child-rearing ability and the provision of fertility services
- Informing offspring of their conception by gamete donation
- Family members as gamete donors and surrogates
- Donating spare embryos for embryonic stem-cell research
- Human immunodeficiency virus and infertility treatment
- Preconception gender selection for non-medical reasons
- Financial incentives in recruitment of ooctye donors.

Copies of these guidelines can be printed from the ASRM website (www.asrm.org) or obtained by contacting the American Society for Reproductive Medicine, Attn: Ethics Committee, 1209 Montgomery Highway, Birmingham, Alabama 35216-2809, Phone: (205)-978-5000.

The ethical analysis

The framework that is used to perform an ethical analysis is based on several basic ethical principles and perspectives. These same principles are applied by the physician in day-to-day patient care. In order to perform an ethical analysis it must be done with compassion, integrity, and devoid of any bias or prejudice. The important ethical principles are discussed below.

Respect for patient autonomy

Patient autonomy is one of the most powerful and prevailing ethical principles. Autonomy is synonymous with independence or freedom. This ethical principle implies that it is the right of the patient to choose his/her treatment and this choice must be respected. However, it is the obligation of the physician to truthfully inform the patient of the consequences of any action including the benefits, risks, complications, and alternatives. This principle is founded on the concept of informed consent.

Beneficence

The principle of beneficence is the driving force of patient care. This principle refers to the ultimate goal of any treatment, which is to do something good for the patient. However, with any treatment there is always the possibility of a bad outcome. The decision to offer treatment is made after careful review of all of the potential good and bad outcomes. An important component of this principle is the *do no harm* concept or non-maleficence. While it is important that the harm or risk of any treatment be recognized, the complete avoidance of harm should not take precedence over the potential benefit of any treatment. Otherwise treatment would never be offered since every treatment has the potential for harm.

Paternalism

Paternalism refers to the action of a physician who in an authoritative and directive fashion influences the decision-making process. If this action is based on clinical knowledge and the physician does it without bias or prejudice it complements the principle of beneficence, but at the same time counters patient autonomy.

Standard of care

When examining any therapy it is important to determine whether this treatment falls within the standard of care for the community. This may have special importance if this treatment has never been offered and therefore a more critical assessment of all potential outcomes should be discussed before the treatment is offered. On the other hand, even if a treatment falls into the standard of care it does not necessarily mean that it is guaranteed to be safe. An example of this is the complications following the administration of diethylstilbestrol (DES) to pregnant women that was popular in the 1960s.

Justice/public stewardship

Public stewardship refers to the distribution of limited medical resources in the most effective manner. This allocation of medical resources is evident in socialized medical delivery systems and health maintenance organizations (HMOs).

Impact on the community

While any treatment may be ethically sound it is important to step back and envision the impact of the potential action on the community. The definition of community can vary. A narrow definition of community can be the center itself. Within any center, there may be some staff who have strong opinions for or against a proposed treatment. For instance, after careful analysis and deliberation it may be determined that sex selection is ethical. However, if team members are uncomfortable with this procedure then there should be reconsideration as to whether to offer sex selection at all or only offer it under certain conditions. A broader definition of community can be society at large. The pursuit of human cloning by a small group of scientists has drawn worldwide attention to our specialty. There has been public outcry that cloning crosses ethical boundaries and some countries have enacted laws against this practice.

CASE PRESENTATIONS

Case #1

A 35-year-old G0P0 female presents with a history of infertility. During the workup it was determined that both she and her husband were carriers of cystic fibrosis*. The couple was seen in consultation and they were informed that they had a 1/4 chance of having a child that would be affected by cystic fibrosis. Alternatives were discussed including IVF/PGD, genetic testing after pregnancy was established, and donor gametes. The couple could not afford IVF and basically were not overly concerned about having a child with the disease, in part because they had a friend with a 3-year-old daughter who was diagnosed with CF and she was 'doing just fine'. To provide further counseling the couple was referred to a cystic fibrosis specialist at a local children's hospital. The couple was seen in follow-up and further discussions ensued. Their desire was to start treatment with intrauterine inseminations. Prenatal genetic testing was again discussed but the patient was uncertain whether she could undergo a termination of the pregnancy. At this point it was concluded that the couple had been adequately informed and treatment was started.

This case highlights the important ethical principle of respect for patient autonomy which is founded on informed consent.

Case #2

A 40-year-old G1P0010 woman presents with a 5-year history of unexplained infertility. She was diagnosed with cerebral palsy at birth and is a paraplegic

*Cystic fibrosis is one of the most commonly inherited diseases in the Caucasian population. It results in thickened mucus production that can alter pulmonary and pancreatic function. The median life expectancy of affected individuals is the mid-thirties.

confined to a wheelchair. She had medical problems including hypertension and obesity. At another center she underwent treatment with clomiphene citrate plus intrauterine inseminations which were unsuccessful. She now presents for consideration of more aggressive treatment. Because of her medical state she was sent to a high risk obstetrician for counseling about the risk of a future pregnancy which could be a multiple gestation. She was given medical clearance to proceed. During the workup a hysterosalpingogram confirmed the presence of multiple filling defects in the uterine cavity. A decision was made to proceed with a hysteroscopy. The preoperative evaluation by the anesthesiologist confirmed that she had pulmonary hypertension. During pregnancy pulmonary hypertension results in a 50% rate of maternal mortality. The patient was seen in consult and the implications of her condition were discussed. However, she was not concerned and stated that 'I am a survivor and always beat the odds'. She wanted to move forward with the surgery and then ultimately treatment. A decision was made by the physician not to treat this patient based on medical reasons.

This case illustrates an example of paternalism. The decision not to treat this patient was done in an unbiased fashion and was based on medical fact. It was determined that the severity of a bad outcome as a result of the treatment far outweighed the benefit of the treatment. The decision not to treat countered patient autonomy.

Case #3

A 40-year-old woman presents with her husband with unexplained infertility. The couple has one daughter and they inquired about sex selection in their quest for a male offspring. They were told that it is the policy of the center that sex selection can only be done when there is another indication to do PGD. The topic of sex selection is never brought up again by the couple. The couple underwent several cycles of insemination treatment which were unsuccessful. They embarked on IVF treatment and requested that because of the woman's age they would like to have PGD performed with FISH to rule out aneuploidy. The couple underwent their first cycle of treatment. Eight embryos were biopsied and only two were found to be normal. The couple presented for the embryo transfer; when they find out that both embryos were female they chose to forego the transfer and discard the embryos. During the follow-up visit the couple was informed about the center's policy regarding sex selection. They never returned for another cycle.

Comment: A couple's desire for an offspring of a certain sex has been present since antiquity. There has been speculation that a woman's diet or the frequency or timing of intercourse can impact on whether she has a male or female infant. Over a decade ago sperm washing techniques were developed to select out the X or Y bearing sperm. In retrospect all of these techniques did little to give the couple what they wanted. The advances in IVF and PGD have given

the opportunity to sex embryos but is it the right thing to do? Sex selection is a slippery slope. Say a couple presents saying that they have three sons at home and would like to have a female infant. However, if they had another male infant they would be accepting of the outcome and love their son as much as they do their other children. This is a situation that most agree that sex selection should be offered. At the other extreme is the couple who requests that only male embryos can be transferred and if the PGD testing is incorrect and pregnancy is established they would terminate the pregnancy. This is obviously a situation where most would feel uncomfortable in proceeding with the desired treatment.

At Boston IVF a well thought out policy regarding sex selection was developed. Sex selection can only be performed for an infertile couple when they are undergoing PGD for aneuploidy screening. The couple must visit with a social worker and also agree to transfer embryos of the less desirable sex if they are the only ones available for transfer.

Case #4

A 46-year-old woman presents for IVF treatment. Her husband had a previous vasectomy. She has regular menstrual cycles and is in good health. The clomiphene citrate challenge test was normal. The physician had a long discussion about the impact of age on infertility and treatment success. The chance of an IVF cycle being successful in a woman of this age is 0–1%. Other treatment options were discussed with the couple including egg donation and adoption. The couple was adamant that they wanted to proceed with the treatment. The physician did not give in to their wishes and they left for a second opinion.

One of the major ethical principles is beneficence. The risks of IVF treatment are relatively low; however, in this particular case the risks outweighed the benefit and the right decision was made to not allow this patient to undergo treatment.

Case #5

A 56-year-old woman presents for consideration of egg donation. Her 18-year-old daughter, her only child, recently died from complications of leukemia. She has been menopausal for 5 years. She is in excellent health and was recently provided medical clearance from her internist to proceed with egg donation and an eventual pregnancy. The reproductive endocrinologist referred to the center's policy that the upper age limit for egg donation was 50 and therefore the patient could not undergo the treatment. After continued discussion it was clear that the patient was still grieving the loss of her daughter. She was referred to a social worker for further counseling.

Comment: The well publicized stories of older women including the 63-year-old woman who achieved pregnancy following egg donation give many a level of discomfort. Should there be an upper age limit for egg donation? There are medical concerns about the documented increased risks of pregnancy in older women. There are also ethical concerns for children being born to older women. An untimely death of the mother could place the potential offspring in jeopardy.

Boston IVF developed a policy setting the age limit at 50 for women undergoing egg donation. This decision was based on the documented medical risks to the older woman during pregnancy and ethical concerns for the unborn child. The other IVF centers in the Boston area were polled and the standard in the community was an age cut-off at 50.

HOW TO STAY OUT OF TROUBLE

Dealing with ethical issues involving individual patients can be time consuming and stressful. Being proactive will help avert some of the ethical dilemmas. Some tips are as follows.

Written policies and procedures It is important to have written policies and procedures in place for the treatments that are offered. These written documents should be developed by the team and represent a consensus of the group. These guidelines should be reviewed and updated on a regular basis. It is important that patients are made aware of specific criteria elaborated in these policies that impact on their care. Individual cases that fall outside of the guidelines can be reviewed by the treatment team.

Stop them at the gate When an ethical issue involving a couple is encountered it is of paramount importance that treatment is not initiated until the issue has been thoroughly investigated and there is a resolution. If treatment has been started it is much more difficult to halt the treatment if it is deemed necessary and from the patient's perspective the physician has already given approval for the patient to undergo treatment. As a physician we want to please our patients but in some situations the issue of concern must be investigated before proceeding.

Don't be the first The field of reproductive medicine is a highly competitive field and there is motivation to set yourself apart from your competitors in offering a new treatment modality. In some cases it may be better to be cautious and not offer the treatment until it has been accepted and all of the issues have been worked out. However, in some cases it may be worthwhile to proceed as long as all of the potential implications of the treatment have been researched and discussed.

Get legal input Don't be shy requesting legal input. There are lawyers who are well versed in reproductive law and they are also helpful in the development of consent forms.

Take a stand As physicians, we have the right to refuse treatment in situations where we feel uncomfortable or there is concern about the consequences of treatment. In these situations it is important that the physician maintain the high ground and do what is right. When discharging a patient from a practice it is important not to abandon the patient. An appropriate level of care must be provided that falls within the guidelines of the practice for a certain period of time, which allows the patient to establish care with another provider.

CONCLUSION

The technology in the field of reproductive medicine continues to make major advances and it is our obligation to use the new technology in a responsible and ethical fashion.

15.

The informed consent process

Steven R Bayer

Informed consent is at the foundation of medical practice and should precede any medical or surgical intervention. Lack of adequate informed consent has potential legal ramifications for the physician, but more importantly can be a violation of the ethical rights of the patient. One of the most important ethical principles is *respect for patient autonomy*, which is founded on informed consent. There are two important components of informed consent: comprehension and free consent. The patient must be provided with adequate information about her condition in language that she can understand along with the overall prognosis. All treatment options should be reviewed and the patient should be informed about the risks, benefits, and alternatives to the proposed treatment or procedure. One alternative to treatment that must be discussed with the patient is the option of no treatment at all along with its consequences. The patient should be discouraged in making a quick decision regarding treatment and ample time should be spent examining all aspects of the treatment options. It is also important that the patient makes a decision on her own free volition without any coercion. Therefore obtaining informed consent is a process and the signing of the consent is symbolic and represents a completion of the process. To this end, it is important for the physician to document in the chart any discussions that took place and pamphlets or other materials that were given to the patient in relation to the proposed intervention.

We have provided several sample consent forms (Chapter 20) for the following procedures and treatments:

- Laparoscopy
- Hysteroscopy
- Hysterosalpingogram
- Sonohysterogram
- Endometrial biopsy
- Ovulation induction
- Methotrexate

ADDITIONAL RESOURCES

1. Bayer SR. Informed Consent, Ethics in Obstetrics and Gynecology. The American College of Obstetrics and Gynecology, Washington DC, January 2004.
2. Braddock CH, Edwards KA, Hasenberg NM et al. Informed decision making in outpatient practice: time to get back to basics. J Am Med Assoc 1999; 282: 2313–20.

16.

The mind/body connection

Alice D Domar

INTRODUCTION

Every woman who is experiencing infertility has been told at some point to 'just relax', 'go on vacation', 'stop trying so hard', or the old favorite, 'just adopt and then it will happen'. The assumption behind all of these comments is that the woman's stress level is in some way preventing conception. But is that true? Are infertile women more stressed than fertile women? And if so, does their stress level preclude pregnancy? Can it truly prevent infertile women from benefiting from the advances in reproductive technologies? And will relaxing indeed lead to conception? These are the questions which will be answered in the following pages.

THE PSYCHOLOGIC IMPACT OF INFERTILITY

One of the problems with assessing the distress levels of infertile women, or many other kinds of patients facing medical treatment for that matter, is that the typical way to assess distress is with self-report psychologic questionnaires. And in order to get accurate data, one needs to collect accurate responses. However, many patients feel an intense need to come across as a 'good patient', and may thus underestimate their level of distress. This phenomenon was highlighted in a recent study in Sweden on IVF patients.[1] Women were psychologically assessed several times during an IVF cycle and their well-being scores were in the normal range and consistently comparable with Swedish reference values. The authors theorized that the reason why patients tested so well is that they 'kept their worries and anxieties to themselves because they had great expectations regarding both themselves and the anticipated treatment. Perhaps they also wanted to show how well they felt and that they could handle the treatment'. Several other studies with infertility patients have come to similar conclusions; self-report measures in the infertile population may well underestimate the level of distress.

Despite this concern, there have been numerous studies using self-report measures which have shown that infertile women have more symptoms of depression and anxiety than in the general population. Research has shown that the prevalence of depressive symptoms in the infertile population is twice that

of the general population.[2] In addition, infertile women have comparable levels of anxiety and depression to women with heart disease, HIV+ status, or metastatic cancer.[3]

However, the gold standard in psychologic testing is not a self-report measure but instead a structured psychiatric interview. A recent study on 112 patients presenting to an infertility clinic for the first time included such an interview.[4] A total of 40.2% of the women met the criteria for a psychiatric disorder; the most common was anxiety disorder (23.2%), followed by depressive disorder (17%). This compares with a community sample prevalence of 3%.

It is obvious that infertile women are suffering. If almost half of new infertility patients report significant psychologic symptoms, since the level of distress tends to rise as duration increases, and to intensify as treatment becomes more complex, it is reasonable to theorize that more than half of patients actively receiving treatment are experiencing a diagnosable level of anxiety and/or depression.

There are many reasons why infertile women experience such high levels of distress – the process impacts their relationship with their partner, their sex life, their relationships with family and friends, their job, their financial security, and their relationship with God. Men and women do not react to infertility in the same way, at the same time, or with the same level of commitment. In most cases, the infertile couple is surrounded by the fertility of their siblings, friends, neighbors, and co-workers. Imagine the couple who start trying the same time as a sibling or close friend, then find themselves 2 or 3 years later still childless while the other couple announces their second pregnancy. Many jobs involve structured meetings and travel, neither of which is conducive to invasive and unexpected infertility treatments. Money is already an issue for most couples; the thought of spending $12 000 on a treatment which has less than a 40% chance of succeeding will force many couples into conflict. Finally, the issue of religiosity needs to be addressed. The majority of individuals in this country pray and believe in a higher power. For many, this is the first time that God has not answered their prayers, leading many to question either their own level of goodness, or the existence of God.

Whether a particular couple experiences conflict in one of these areas, or more likely in all seven, it is not surprising that infertility can cause such emotional upheaval. To top it off, the comments from well-meaning family and friends, such as the ones which introduced this chapter, can contribute to a 'blame the victim' mentality.

THE IMPACT OF STRESS ON TREATMENT OUTCOME

Since *in vitro* fertilization involves a relatively similar protocol throughout the world, research on the impact of stress on reproductive outcome has focused mainly on IVF patients. There have been 21 studies which include adequate data on the relationship between stress prior to or during an IVF cycle, and subsequent pregnancy rates.[5] Fifteen of these studies show a significant relationship between distress and pregnancy (i.e. the most distressed patients have the lowest

pregnancy rates), two studies found a trend in that direction, and four did not find any relationship.

Perhaps the best designed study was one on 151 women prior to beginning an IVF or GIFT cycle.[6,7] The strength of this study was the fact that they collected numerous psychologic factors, including not only how stressed the patients reported feeling, but what factors about the treatment were the most stressful, as well as a number of physical factors, such as number and quality of oocytes retrieved, pregnancy outcomes, and birth weight. The baseline level of stress was significantly related to outcome; stress levels were correlated to number of retrieved oocytes, percentage fertilized, pregnancy rates, live birth rate, and birth weight. The strength of the correlation between distress and pregnancy was strong – the subjects who expressed the least baseline level of distress were 93% more likely to give birth than the patients who reported the most baseline level of distress.

The majority of research to date supports the hypothesis that stress hampers the effectiveness of reproductive technologies. The mechanism of action, however, is unknown.

THE IMPACT OF PSYCHOLOGIC DISTRESS ON DROPOUT RATES

Until recently, it was assumed that patients would pursue infertility treatment until one of two events occurred – their physician told them that further treatment was inadvisable (so called active censoring) or they ran out of money. This theory was well accepted by most health-care professionals in the infertility field, simply because the patients they saw on a day-to-day basis were the ones who chose to continue treatment. The ones who dropped out of treatment came to no one's attention, and were thus forgotten. However, research conducted in the past few years reveals a completely different scenario – patients drop out in large numbers. And since the new research is coming from countries where IVF is covered by insurance, money was clearly not the motivation to terminate treatment. Anywhere from 40 to 65% of insurance-covered non-pregnant patients discontinue treatment prior to completing their covered cycles.

As it turns out, active censoring is relatively rare – a study from the Netherlands, in which there was a cumulative dropout rate of 62% after three cycles, found that only 14% of the patients who dropped out of treatment did so because of physician recommendation.[8] The most recent research shows that the primary reason why patients drop out of IVF treatment is psychologic stress. In a Swedish study of 974 couples, the patients reported that 'psychologic burden' was the reason they discontinued treatment.[9] An Australian study showed the same results – 66% of couples who dropped out of IVF cited the emotional strain as their reason for terminating treatment.[10] In a study of 211 couples who dropped out for reasons other than active censoring, the most commonly cited reason was psychologic burden, followed by the perception of a poor prognosis.[11]

This study also revealed that the couples who dropped out of treatment were as satisfied with their care as couples who remained in treatment, so the quality of care does not seem to be a contributing factor in patients' stress levels.

Obviously, couples who drop out of treatment are likely to sacrifice their chance of pregnancy. A retrospective German study on 2130 IVF patients analyzed the cumulative pregnancy rate and found a 31.4% rate for couples after three cycles; however, if couples had undergone one more cycle, the rate would have increased to 41%.[12] If a couple had undergone the six insurance-covered cycles, the rate would have climbed to 60%.

Finally, it appears to be possible to predict which patients are more likely to drop out of treatment. In a prospective study of women beginning IVF, it was determined that pretreatment levels of depression were significantly predictive of patient treatment termination after only one cycle.[13]

Thus, it is obvious that psychologic distress plays a large role in IVF retention. Patients who are depressed prior to treatment are more likely to drop out after only one cycle and, throughout the IVF process, patients cite psychologic burden as the primary reason for dropping out of treatment. Obviously, premature termination limits a couple's ability to get pregnant. What is not known, however, is if it is possible to psychologically intervene with distressed patients, in order to support them to continue treatment.

THE IMPACT OF PSYCHOLOGIC INTERVENTIONS ON INFERTILE WOMEN

If one accepts the theory that distress is associated with lower pregnancy rates in infertile women, then interventions designed to decrease distress should lead to higher pregnancy rates. And in fact, the majority of the research to date supports this notion. Although there are only a handful of randomized, controlled prospective studies, most do indeed show a positive effect from psychologic interventions. In a recent meta-analysis of the literature,[14] the authors concluded that group as well as individual and couples' psychotherapy is associated with the alleviation of anxiety and depressive symptoms. In addition, the meta-analysis also indicated evidence for the enhancement of conception rates through psychologic therapy.

Psychologic interventions can take many forms, ranging from individual therapy to stress management programs. The term counseling can take many forms. Most would assume that would involve treatment for an individual or couple. But counseling can apply to many forms of intervention. For example, a randomized, controlled, prospective study was performed on 60 IVF patients in Turkey to assess the impact of 'counseling' on IVF patients.[15] In this case, counseling was provided by the IVF nurses and included several hours of personal attention and support. The couples who received this intervention reported lower anxiety and depression scores as well as a 43% pregnancy rate, compared to a 17% rate in the control group who received routine nursing care.

There has not been solid data to support the use of brief psychotherapy with infertile individuals or couples. And in fact, the most recent research does not show any benefit.[16] In a study of 265 couples in the Netherlands, 84 of the couples agreed to be randomized to either a routine care control group or to an intervention which included three sessions with a social worker. There were no differences in psychologic parameters or pregnancy rates between the two groups. This is the most recent of several studies which have not shown any definitive benefit of brief counseling.

Research on other interventions has shown more promise. In one randomized, controlled prospective study, 185 infertile women were assigned to either a 10 session mind/body group, a 10 session support group, or a routine care control group.[17,18] The mind/body intervention included instruction in relaxation techniques, stress management strategies, and lifestyle modifications. The support group included time for members both to voice their concerns about the impact that infertility was having on their lives as well as to provide support to each other. All subjects continued to receive routine infertility care. During the one-year follow-up study period, 55% of the mind/body patients and 54% of the support group patients experienced a live birth, compared to only 20% of the control subjects. In addition, there were differences in psychologic health. The mind/body patients experienced a decrease in negative symptoms such as anxiety and depression, the support patients remained the same, while the control patients experienced a worsening of symptoms.

In a subsequent study in Japan, 74 subjects were randomized to either a five-session mind/body group or a routine care control group.[19] The mind/body subjects experienced a significant decrease in psychologic distress and natural killer cell activity while the control subjects experienced no change. In addition, 38% of the mind/body subjects became pregnant during the study period compared to 13.5% of the control subjects.

The data thus far on the effectiveness of psychologic interventions point to a stress-management kind of approach, rather than the more traditional use of individual or couples' counseling. Mind/body interventions have been well researched; their effectiveness has been established with a variety of medical and psychologic conditions, including hypertension, menopausal symptoms, premenstrual symptoms, insomnia, chronic pain, anxiety, cardiac arrhythmias, chemotherapy side-effects, depressive symptoms, and gastrointestinal problems. The application of mind/body techniques to infertility began in 1986 and the clinical use is increasingly rapidly.

THE MIND/BODY PROGRAM FOR INFERTILITY

The first mind/body infertility program opened in 1987 and was designed to teach relaxation and cognitive strategies to infertile women. The goal of the program was psychologic symptom reduction, not pregnancy, and this message was disseminated to all interested patients. After the first 50 women completed

the program, it was noted that they were experiencing significant psychologic symptom reduction as well as a higher than anticipated pregnancy rate.[20]

At this point in time, after 18 years of clinical practice, pregnancy rates within 6 months of program completion average 45–50% and every psychologic parameter measured, including anxiety, depression, hostility, and confusion, decreases significantly. In addition, patients report significant reductions in physical symptoms such as insomnia, headaches, abdominal pain, and gastrointestinal symptoms. Health-care professionals from around the world have been trained as group leaders and uniformly report the same positive changes.

All potential participants must attend an intake appointment with the group leader. They are mailed a long questionnaire which they are instructed to bring to the intake. There are multiple goals for this session. It provides an opportunity for the two of them to get to know each other better, the group leader obtains a comprehensive medical, psychologic, social, and lifestyle history, the group leader can explain how the program is run, and it gives the patient an opportunity to ask questions.

Groups are normally led by a mental health professional with extensive knowledge of infertility. Each group leader is supported by two 'peer counselors' who are graduates of the program; peer counselors are chosen because as program participants, they experienced excellent symptom relief and successfully incorporated the mind/body skills into their lives. They serve as role models as well as being a liaison between the leader and the patients. The mind/body program also includes a buddy system. Patients are paired with another patient the first night. If there are two patients with similar circumstances (for example secondary infertility, recurrent miscarriages, or a history of a stillbirth), they are paired up; otherwise it is done on a geographic basis. Buddies are asked to speak to one another at least once per week and each buddy pair brings in a snack for the group once.

Patients with any kind of infertility diagnosis may attend including endometriosis, ovarian dysfunction, advanced age, male factor, premature ovarian failure, recurrent miscarriage, tubal blockage, and unexplained infertility. The groups include married heterosexual women, single women, lesbian women, and women with secondary infertility (although secondary patients may only have one child – women with more than one child are referred for individual counseling since their presence would be likely to upset the primary patients).

Table 16.1 outlines each session of the program and every session follows a similar schedule, as can be seen in Table 16.2. Each session incorporates relaxation training, social support, and a new stress management strategy. Despite the fact that the first half hour of social support is optional, virtually all participants choose to attend. This is their time to share their stories, compare experiences, and complain about their husbands/mothers-in-law/doctors.

The program is designed to treat patients' anxiety first so the first two sessions are dedicated to relaxation training. The next one is focused on self-nurturance, after which lifestyle habits are addressed. The current research on the impact of lifestyle behaviors is presented, such as the impact of smoking on IVF outcome,

Table 16.1 Sessions of the mind/body program for infertility

1. Group leader and peer counselor introductions, research on the stress/infertility connection, the physiology of the relaxation response, participant and partner introductions, program mechanics*
2. Physiology of diaphragmatic breathing, mini relaxation exercises, effective communication
3. The art of self-nurturance, how to reintroduce joy into one's life
4. The impact of lifestyle behaviors on fertility: weight, smoking, alcohol, exercise; the safety and efficacy of alternative medicine approaches
5. Introduction and experiential exercise of hatha yoga
6. Introduction to cognitive restructuring
7. All day Sunday session – couples' yoga, the use of humor to reduce stress, goal setting, couples' communication*
8. Completion of cognitive restructuring
9. The impact of emotional expression on health, journaling; guest lectures from prior participants who went on to adopt or do donor egg*
10. Assertiveness, goal setting, summary, goodbyes

*Husbands/partners attend these sessions

Table 16.2 Outline of each mind/body session

30 minutes	Optional sharing support time
15 minutes	Relaxation exercise (different one each week)
10 minutes	Patients pair up to discuss individual progress
30 minutes	Group discussion on how members are doing incorporating mind/body skills into their lives, review of previous week's assignment
10 minutes	Brief lecture by the group leader on the topic of the evening
30 minutes	Experiential exercise on evening's topic
20 minutes	Group discussion on topic, Q&A
5 minutes	Mini relaxation exercise

and participants are encouraged to discontinue smoking, limit their alcohol and caffeine intake, decrease the intensity of their exercise routine, maintain a healthy weight, and avoid alternative medicine methods such as herbs. The next sessions are dedicated to cognitive approaches to stress reduction, such as cognitive restructuring, journaling to express negative emotions, and effective communication strategies. One of the sessions includes guest lectures by prior participants who moved on to either adoption or egg donation.

Husbands/partners attend three of the ten sessions; the first introductory session, the Sunday session which is focused on couples' communication and pleasure, and the ninth session where the men meet as a group with a male therapist to discuss how they are handling the crisis of infertility.

At the first session, each participant is asked to describe what they hope to get out of the program, i.e. where they hope to be by the tenth session. Thus, at the tenth session, each patient is asked whether or not they reached their goal.

This tends to be a very emotional time, since each patient recounts her emotional state a mere 10 weeks ago and thanks the group, and group leader, for helping her get to such a much healthier place.

At the tenth session, participants complete a similar but shorter questionnaire to the one they completed prior to the intake. Each patient is offered an appointment with the group leader to review their progress, compare their pre- with their post-program status, and set goals for their continued improvement.

Patients consistently experience statistically significant reductions in all measured physical and psychologic symptoms. But perhaps more important, their attitude towards their infertility changes. As opposed to their sole identity as an infertile woman at the intake, they leave being a healthy active woman who happens to be experiencing infertility. They don't cry for days when they start to menstruate, they tolerate pregnancy announcements from others, and they feel more comfortable meeting their own needs, such as skipping baby showers or not visiting friends with newborns. Perhaps one of the most unexpected side-effects of the program is the participants' willingness to try avenues which did not feel tolerable prior to participation, such as trying IVF or deciding to pursue donor egg, or adoption.

SUMMARY

Women experiencing infertility report significant levels of emotional distress. Their distress can make them difficult to treat, may make treatment less effective, and increases their tendency to drop out of treatment which might have been successful for them. Psychologic interventions can decrease psychologic symptoms and are associated with increases in pregnancy rates. A mind/body approach can satisfy the numerous needs of patients, including decreasing distress, increasing social support, increasing the chance of pregnancy, and helping them move on to alternative treatments, including the ARTs and third-party reproduction.

REFERENCES

1. Anderheim L, Holter H, Bergh C, Moller A. Does psychological stress affect the outcome of in vitro fertilization? Hum Reprod 2005; 20: 2969–75.
2. Domar AD, Broome A. The prevalence and predicatibility of depression in infertile women. Fertil Steril 1992; 58: 1158–63.
3. Domar AD, Zuttermeister PC, Friedman R. The psychological impact of infertility: a comparison to women with other medical conditions. J Psychosom Obstet Gynaecol 1993; 14: 45–52.
4. Chen TH, Chang SP, Tsai CF, Juang KD. Prevalence of depressive and anxiety disorders in an assisted reproductive technique clinic. Hum Reprod 2004; 19: 2313–18.
5. Domar AD. Infertility and the mind/body connection. The Female Patient 2005; 30: 24–8.
6. Klonoff-Cohen H, Chu E, Natarajan L, Sieber W. A prospective study of stress among women undergoing in vitro fertilization or gamete intrafallopian transfer. Fertil Steril 2001; 76: 675–87.

7. Klonoff-Cohen H, Natarajan L. The Concerns During Assisted Reproduction Technologies (CART) scale and pregnancy outcomes. Fertil Steril 2004; 4: 982–8.
8. Land JA, Courtar DA, Evers JL. Patient dropout in an assisted reproductive technology program: implications for pregnancy rates. Fertil Steril 1997; 68: 278–81.
9. Olivius K, Friden B, Lundin K, Bergh C. Cumulative probability of live birth after three in vitro fertilization/intracytoplasmic sperm injection cycles. Fertil Steril 2002; 77: 505–10.
10. Hammarberg K, Astbury J, Baker H. Women's experiences of IVF: a follow-up study. Hum Reprod 2001; 16: 374–83.
11. Olivius C, Friden B, Borg G, Bergh C. Why do couples discontinue in vitro fertilization treatment? A cohort study. Fertil Steril 2004; 81: 258–61.
12. Shroder AK, Katalinic A, Diedrich K, Ludwig M. Cumulative pregnancy rates and drop out rates in a German IVF programme: 4102 cycles in 2130 patients. Repro Biomed Online 2004; 5: 600–6.
13. Smeenk JM, Verhaak CM, Stolwijk AM, Kremer JA, Braat DD. Reasons for dropout in an in vitro fertilization/intracytoplasmic sperm injection program. Fertil Steril 2004; 81: 262–8.
14. de Liz TM, Strauss B. Differential efficacy of group and individual/couple psychotherapy with infertile patients. Hum Reprod 2005; 20: 1324–32.
15. Terzioglu F. Investigation into the effectiveness of counseling on assisted reproductive techniques in Turkey. J Psychosom Obstet Gynaecol 2001; 22: 133–41.
16. de Klerk, Hunfeld JA, Duivenvoorden MA et al. Effectiveness of a psychological counseling intervention for first-time IVF couples: a randomized controlled trial. Hum Reprod 2005; 20: 1333–8.
17. Domar AD, Clapp D, Slawsby EA et al. Impact of group psychological interventions on pregnancy rates in infertile women. Fertil Steril 2000; 73: 805–11.
18. Domar AD, Clapp D, Orav J, Kessel B, Freizinger M. The impact of group psychological interventions on distress in infertile women. Health Psychol 2000; 19: 568–75.
19. Hosaka T, Matsubayashi H, Sugiyama Y, Izumi S, Makino T. Effect of psychiatric group intervention on natural-killer cell activity and pregnancy rate. Gen Hosp Psychiatr 2002; 24: 353–6.
20. Domar AD, Seibel MM, Benson H. The mind/body program for infertility: a new behavioral treatment approach for women with infertility. Fertil Steril 1990; 53: 246–9.

17.

Infertility counseling: the role of the social worker

Jeanie Ungerleider, Terry Chen Rothchild, and Lynn Nichols

INFERTILITY AS A CRISIS

Infertility is a medical condition which can affect every part of an individual's or couple's life. It may challenge the ways in which people feel about themselves and their relationships with their partner, family, and friends. It often impacts their work environment and general outlook on life. Few situations in life are as challenging and overwhelming. Because of this, infertility is considered a life crisis.

For those going through infertility, this often is the first time that an experience in life may feel totally beyond their control. Most people assume that if they only work hard enough, they will succeed and achieve their goals, including when to become parents. Being faced with infertility often runs counter to individual's and couples' experiences and expectations about life. Not being able to get pregnant when they want to and feeling a lack of control in this area can be frustrating and frightening. These feelings can then get amplified by the disappointment of repeated failed treatment. Indeed, the uncertainty as to whether they will ever conceive and have a healthy baby can create mounting anxiety. The infertile couple is surrounded by peers who are pregnant with their first, second, or third child, while they struggle with infertility treatments and feeling increasingly resentful, angry, and isolated from their usual supports.

Infertility is a crisis of identity that can challenge one's sense of self and self-worth. It can impair one's definition of who one is and whether one will ever have a meaningful place in the world. For women, infertility challenges their long-held assumptions of being mothers someday. The more that a woman's self-identity is defined by being a mother, the more at risk is she for psychologic distress and feelings of inadequacy. The longer that infertility continues, the more a sense of helplessness and hopelessness can take over, which can lead to greater depression. A diagnosis of male factor problem can feel devastating for the man. This finding can challenge his sense of masculinity, potency, and identity.

Factors contributing to different people's coping styles include personality differences, family history, and life experiences. These factors can shape how

people experience and handle this particular life crisis. Moreover, women and men can demonstrate very different ways of coping with the diagnosis of infertility. Women often feel anxious and depressed because they are mindful of the limits of their biologic clock. There is the heightened awareness of the urgency of time and a painful reminder of disappointment each month when there is no pregnancy. Women are sometimes angry with themselves or their partners for not starting to build their family sooner. They are burdened with feelings of guilt and regret about their delay. In some cases, for women who had a prior termination of pregnancy, they may come to feel that their infertility is a punishment for having had an earlier abortion.

Women who are faced with infertility often want to discuss their feelings and concerns with their partners, which can dominate their conversations when the couple spends time together. Generally speaking, men may tend to respond with optimism, assuring their partner of a positive outcome. Not wanting to fuel or add to their partner's distress, they may wish to limit or avoid conversation about infertility. The couple's growing sense of feeling disconnected from each other can add to an already existing sense of isolation and alienation from the outside world. Tensions such as these often interfere with the couple's sexual relationship. No longer is their lovemaking pleasurable and intimate. Sex becomes a task to accomplish the goal of conception. When the woman's and man's styles are in such contrast, it can interfere with their going forward with infertility treatment as a couple.

Case 1

A couple was referred to the infertility counselor by their physician because they expressed conflict over how aggressive they wanted their infertility treatment to be and showed difficulty with decision-making. The husband, age 36, was annoyed by his wife's insistence on seeking infertility treatment just 6 months into their marriage. His wife, age 39, was convinced that she would have problems conceiving because of her history of erratic menstrual cycles. The husband complained that his wife had become totally obsessed and preoccupied with having a baby to the exclusion of his needs. The counselor met weekly with the couple, helping them to communicate more effectively with each other. Their increased ability to partner together and to appreciate each of their different coping styles allowed this couple to proceed more effectively with infertility treatment.

THE ROLE OF THE COUNSELOR IN AN INFERTILITY PRACTICE

Most major infertility practices have licensed independent clinical social workers (LICSWs) or psychologists available who specialize in infertility counseling.

Many of these clinicians are members of the American Society for Reproductive Medicine (ASRM) and the Mental Health Professional Group of ASRM which offer practice guidelines and guidance for the mental health professionals. The role of the infertility counselor is multi-faceted and ever-changing depending on the request of the physician, the expressed needs of the individual or couple, and the level of distress and crisis in their life. The counselor can serve the role of a clinical evaluator, consulting member of the health-care team, supportive counselor, bereavement counselor, patient advocate, or more broadly, psychotherapist. The infertility counselor can make referrals to resources in the community and be a liaison to other mental health professionals, such as psychopharmacologists and psychotherapists, on behalf of the health-care team. The roles of the infertility counselor can shift with the individual or couple over time and reflect the complex process of infertility treatment as well as people's responses to their treatment and changing needs.

Counseling can offer support in dealing with the unique stresses of ongoing medical treatments and the uncertainty of outcome, including the possibility of unsuccessful treatment cycles. If an individual or couple is having a difficult time going through the medical process, seeing a counselor one-on-one can help address the issues that are specific to the individual or couple and provide the needed support and strategies.

Counseling is helpful for those who are having difficulty making informed treatment decisions or choosing treatment options. It is useful for those who have experienced a miscarriage and are grieving this very powerful and real loss.

Counseling is also recommended for people who are facing the end of medical treatment and are having difficulty making this decision, or wishing to discuss other options and alternatives, such as the use of donor egg or donor sperm, gestational care arrangement, adoption, or childfree living.

If the individual or couple is experiencing stress, depression, or anxiety to a degree that is significantly affecting their life or making it hard to enjoy life, it is advisable to refer them to a counselor before any medical treatment begins. As outlined in the ASRM Fact Sheet on Infertility Counseling and Support, signs and symptoms to consider include:

- Persistent feelings of sadness, guilt, or worthlessness;
- Loss of interest in usual activities and relationships;
- Agitation and anxiety;
- Constant preoccupation with infertility;
- Difficulty concentrating and remembering;
- Change in appetite, weight, or sleep patterns;
- Social isolation;
- Increased use of alcohol or drugs;
- Increased mood swings;
- Marital conflicts;
- Other current or past stress that heightens infertility distress.

In making a clinical assessment of the individual's or couple's needs, the counselor can determine the most appropriate treatment modality. This can be in the form of individual counseling, couples' counseling, a support group, a mind/body program, or a combination of these options. In individual and couples' counseling, the counselor can help sort out feelings of how their infertility has impacted them and their partner as well as help them deal with family, friends, and the fertile society. Couples learn ways to strengthen their relationship and develop skills to navigate the emotional roller coaster of infertility. A peer support group can help reduce the feelings of isolation and provide a support network, and additionally, a mind/body program can teach self-care skills and address lifestyle changes that can have beneficial effects for a lifetime. It is generally agreed that the outcome for those people who seek out professional help in some form is much better than those who choose to remain socially isolated and grieve alone, especially if infertility treatment is prolonged and disappointing.

The following case demonstrates the various roles that an infertility counselor can provide over time in helping a person with their emotional needs and assisting as part of the health-care team.

Case 2

A 37-year-old married woman presented with depression and crying whenever she got her period. She was obsessed about getting pregnant for the last 1½ years. While quite motivated, she stated that she was very anxious about the medical process and reported a history of panic reactions based on childhood fears. There were 'worriers' in her family, and her own anxiety had worsened as each treatment cycle was met with failure. The counselor offered her opportunities to safely talk about and examine her fears, helped her gain perspective on overwhelming feelings and issues, helped her identify what resources and assistance she needed most at each stage of her cycle, and shared relevant information with her physician and nurse co-ordinator so that she felt well cared for by her whole team. Based on ongoing discussions and increasing trust with the counselor, this woman was able to see how incapable she was at advocating for herself in the initial stages of medical treatment given her overwhelming level of distress, which was in sharp contrast to her effectiveness as a manager at her job. During counseling sessions, she also gained insight into how, by not allowing her husband to participate in her treatment, served to undermine herself and protect her husband, which she recognized as a pattern that was counterproductive to them both. After undergoing four IVF cycles with the needed emotional support from her whole health-care team and husband, she went on to have a successful pregnancy and delivery.

A woman can bring a complicated history, such as a trauma history or other past stress, which can heighten infertility distress. In the counselor's understanding

of the cause of her distress, the counselor can effectively help to facilitate the woman's care with her health-care team and intervene when necessary in a particular area of concern in order to assist her in going forward with treatment.

Case 3

A woman presented with anxiety and stress as her first IVF procedure approached and questioned whether she could go forward. She was increasingly having difficulty sleeping and concentrating at work. In the assessment with the counselor, she revealed a history of emotional and sexual abuse. She realized that she was terrified of having the procedure done by a physician whom she would not know and was not scheduled to meet until the day of the procedure. She was also fearful of having anesthesia, which she had never experienced. The counselor was able to advocate on behalf of the woman and arranged for her to meet briefly with the physician, operating room nurse, and anesthesiologist prior to the day of her IVF procedure. This helped diminish her anxiety considerably and made her feel well cared for. The staff also benefited from the advanced meeting and understanding of this special situation.

THE ROLE OF THE INFERTILITY COUNSELOR IN ASSISTED CONCEPTION

Newer ways of having a family with the use of donor egg, donor sperm, or gestational carrier arrangement have become increasingly successful for individuals and couples to have a child. This choice of family building raises unique social, emotional, and ethical issues. As part of most IVF programs, it is considered invaluable for people to meet with an infertility counselor to discuss these complex issues.

The topics covered in the psycho-educational consultation may include: transitioning from a traditional form of treatment to the use of a third party; the feelings involved in making this decision; choosing an anonymous or known donor and the benefits and challenges associated to either choice; issues of disclosure, including when and how to tell the child, the notion of privacy versus secrecy, and how to discuss disclosure with family and friends; transitioning to parenthood and parenting at an older age, if applicable; and the possibility of treatment failure and alternatives for future planning.

In instances where a known donor is considered, it is important to explore and discuss with the recipients and donor their feelings about the relationship and future expectations between all parties, including with the future child. It is essential that everyone involved be in agreement with decisions that have the potential to affect a future family.

When third party reproduction is recommended to infertile individuals and couples, new sets of concerns and feelings arise. This includes feelings about the medical condition that necessitated the use of a donor. Additionally, the loss of the genetic tie to the mother or father and its meaning may become central. Practical issues such as disclosure must also be addressed. While the decision to tell the child about its genetic origins is a personal one, it is an issue that should be explored with the couple before treatment begins. Those coming into infertility clinics with the hopes of creating their own child have often gone through and continue to go through a multitude of emotional experiences from positive anticipation to frustration, disappointment, and continued loss. Here the counselor can continue to assist couples to manage the emotional roller coaster associated with infertility treatment.

In contrast to this group of infertile couples, there are also single adults, gay, and lesbian couples who are entering infertility practices and looking to the donor process or gestational care arrangement as a way of becoming parents. These groups of people, who have not experienced problems with infertility by and large, may not necessarily go through the same emotional experiences as the infertility group. The issue of loss, mourning, and grief work may be quite different depending on their reason for treatment. Nonetheless, the use of a third party in the reproductive process does raise certain unique social, emotional, and ethical issues for all recipients, donors, and children. Additionally, with both of these groups, the infertility counselor has an opportunity to address concerns about how to raise these children as healthy and wholesome beings and help children deal with information about their assisted conception in their various life stages.

SUMMARY

While the infertility counselor cannot predict or guarantee the outcome of the woman's infertility treatments, the counselor can help make the process as supportive and helpful as possible. The individual or couple generally values the team approach and expresses appreciation for their health-care providers' attention to their medical, physical, and emotional well-being.

In the near future, assisted reproductive technologies will become even more sophisticated, with the availability of ovum freezing and more extensive use of preimplantation genetic testing. These new advances will open up more complex ethical, emotional, and psychosocial issues. With the increased success of the assisted reproductive technologies, there are new ways to create families. It is possible to have numerous people involved in the creation of a child. They can include the ovum donor, the sperm donor, the gestational carrier, and the intended parents who will be raising the child. Such complex options for family building necessitate careful understanding of the issues involved and exploration of their implications for the individual, couple, and future child. The infertility counselor's role is ever-expanding as patients make use of these new pathways to parenthood.

WHERE TO FIND AN INFERTILITY COUNSELOR?

Mental health professionals, including social workers, psychologists, and psychiatrists, are trained to evaluate and treat individuals and couples who are in crisis. Because of the complexities of infertility and the treatment options that are available, individuals and couples would benefit most from a referral to a mental health professional with expertise in the field of infertility. Besides getting a referral from their own physician who specializes in infertility treatment, people can turn to RESOLVE, the American Fertility Association (AFA), and the American Society for Reproductive Medicine (ASRM) as valuable resources for seeking out qualified mental health professionals in their community.

RESOLVE National Office
1310 Broadway
Somerville, MA 02144-1731
617-623-1156
www.resolve.org

The American Society for Reproductive Medicine (ASRM)
1209 Montgomery Highway
Birmingham, AL 35216
205-978-5000
www.asrm.org

American Fertility Association (AFA)
666 Fifth Avenue, Suite 278
New York, NY 10103-0004
888-917-3777
www.americanfertilityassociation.org

HOW TO LEARN MORE ABOUT ADOPTION?

The first step is to follow up with a mental health professional to discuss the emotional and practical issues about the process. There are many different variations of the adoption process including anonymous and identified adoption; national and international opportunities also exist. The couple can be referred to the following resources for additional information and learn more about the process:

National Adoption Information Clearinghouse
Children's Bureau/ACYF
1250 Maryland Avenue, SW
Washington, DC 20024
Phone: 703.352.3488 or 888.251.0075
http: //naic.acf.hhs.gov/parents/index.cfm

National Council for Adoption
225 N. Washington Street
Alexandria, VA 22314-2561
Phone: (703) 299-6633
www.ncfa-usa.org/

RESOLVE National Office
1310 Broadway
Somerville, MA 02144-1731
617-623-1156
www.resolve.org

18.

Insurance and coding issues

Steven R Bayer and Karen Parlee

Before any medical services are provided, it is essential that the patient's insurance coverage be investigated. This is a dual responsibility of both the patient and the medical practice. This will help to insure that any services that are rendered will be properly reimbursed and will eliminate the chance that the patient will receive any unexpected bills. Some of the important insurance issues in the US regarding infertility services are discussed below. In addition, guidelines for current procedural terminology (CPT) coding for infertility services are presented.

WHEN SHOULD THERE BE AN INVESTIGATION OF THE INSURANCE COVERAGE?

When the first appointment is made we encourage all of our patients to educate themselves on the limits of their insurance coverage for infertility services. At the initial consultation documentation of medical insurance coverage for both partners should be reviewed and verified. An updated insurance card should be copied and placed in the patient's chart. Verification of infertility benefits should be obtained by contacting the insurance company or reviewing the insurance policy. The extent and the limitations of coverage should also be determined. If there are any restrictions in the insurance coverage, it is important that this is discussed with the couple before they undergo any medical services. This information needs to be conveyed to the medical team as well so that treatment can be tailored according to their coverage. For instance, if there is a cap on coverage it may be worthwhile to try a few cycles of clomiphene citrate with intrauterine insemination treatment but bypass the more costly FSH–IUI treatment and go directly to IVF. Any conversations that our financial co-ordinators have with insurance companies and patients regarding coverage are documented in the medical record so that they can be referred to in the future. At our center we have the patient sign a waiver that they are responsible to know their benefits and they are financially responsible for any uncovered services (Figure 18.1).

If the couple wants to challenge limitations of their insurance coverage then they have recourse. The first option is that the couple can present their case in front of the appeals board of the insurance company. In some cases legal representation will

Understanding Your Insurance Benefits

We know that insurance and financial matters can be complicated. This document is designed to outline important insurance and financial information that you need to know while receiving services at our center.

- Please contact your insurance company as it is your responsibility to obtain your infertility benefits. Your insurance company customer service representative will help you to understand your plan**, what it covers and what it does not.**
- Your insurance company may require referrals from your primary care physician for your visits. It is your responsibility to obtain these referrals. If you are not able to obtain a referral from your primary care physician you will be charged for that visit.
- If your insurance plan imposes a dollar limit on your treatment, you are responsible for keeping track of the money paid by your insurance. Once you have met this dollar maximum, you will be responsible for the cost of services that are provided to you.
- Please notify us **immediately** of any changes to your insurance. If your coverage terminates while you are undergoing treatment, you will be financially responsible for charges incurred during your lapse in coverage. Due to the pre-authorization requirements of the insurance companies, if you change insurance plans while undergoing a treatment cycle, your cycle may be delayed or cancelled and you may be responsible for the cost of that treatment cycle. If you proceed with any treatment that has not been approved by your insurance company, you will be responsible for those charges.
- Many patients choose to freeze sperm and/or embryos at our facility. This may or may not be a covered benefit under your plan. Please check with your insurance company to determine if these services are a covered benefit for you.
- There are annual storage charges for frozen embryos as well as frozen sperm that are not covered by insurance. Your financial counselor can provide you with our current prices for these services if they apply to you.
- We require 24 hours' notice if you are canceling your appointment. If you do not cancel your appointment with 24 hours' notice or if you do not appear for your appointment you may be responsible for a cancellation fee of up to the full cost of the visit.

MY SIGNATURE BELOW INDICATES THAT I HAVE READ AND UNDERSTAND THE INFORMATION PROVIDED IN THIS DOCUMENT.

Please bring this document with you to your appointment and give to your financial counselor.

_____ _____

(Print Name) (Date)

_____

(Signature)

Figure 18.1

maximize the results of the appeals process. The other option is that the couple can contact the state insurance commissioner, who acts on behalf of consumers. Finally, couples who do not have any insurance benefits should be encouraged to look for other insurance plans that may provide coverage for infertility services.

It is also important to keep tabs on the patient's insurance plan. Many change jobs or their employer changes the insurance plans that they offer. At every visit it is our policy that the patient is asked if their current insurance plan is still in effect.

Table 18.1 The extent of infertility coverage in states where mandated benefits is presented. Data obtained from the American Society for Reproductive Medicine; Birmingham, AL www.asrm.org

Tx, treatment; HMO, Health maintenance organizations

		Mandate to:		*IVF coverage*		*IVF Tx*
STATE	*Enacted*	*Cover*	*Offer*	*Included*	*Excluded*	*ONLY*
Arkansas	1987	X[1]				X
California	1989		X		X[2]	
Connecticut	1989	X		X		
Hawaii	1987	X				X[3]
Illinois	1991	X		X[4]		
Maryland	1985	X[5]				X
Massachusetts	1987	X		X		
Montana	1987	X[6]				
New Jersey	2001	X		X		
New York	1990				X[7]	
Ohio	1991	X[6]				
Rhode Island	1989	X		X		
Texas	1987		X			X
West Virginia	1977	X[6]				

[1] Lifetime maximum benefit of not less than $15 000
[2] Excludes IVF but covers GIFT
[3] A one-time benefit covering all outpatient IVF expenses
[4] Limits first-time attempts to four oocyte retrievals. If a child is born, two complete oocyte retrievals are covered. Businesses with 25 or fewer employees are exempt
[5] Businesses with 50 or fewer employees are exempt
[6] Applies to HMOs only
[7] Provides coverage for the 'diagnosis and treatment of correctable medical conditions'. Does not consider IVF a corrective treatment

WHAT STATES HAVE MANDATED INFERTILITY BENEFITS?

Infertility treatment has been viewed as elective and many insurance companies have chosen not to pay for it. In 1987, Massachusetts passed a bill that defined infertility as a medical diagnosis and therefore mandated insurance companies in the state to pay for infertility treatment. Other states have insurance mandates in place including: Arkansas, California, Connecticut, Hawaii, Illinois, Maryland, Montana, New Jersey, New York, Ohio, Rhode Island, Texas, and West Virginia. Detailed state-specific information can be obtained by visiting the web site of the American Society for Reproductive Medicine (www.asrm.org). If you reside in a state that does not have mandated insurance benefits for infertility, you can contact RESOLVE, a patient advocacy organization (see Chapter 19) to find out if there is any pending legislation. Even if your state does have mandated benefits, restrictions can still exist regarding the extent and types of infertility treatment that are covered (Table 18.1). In addition, within mandated states, privately insured companies often can eliminate infertility services as a covered benefit.

CODING AND BILLING ISSUES

After medical services have been provided, the next step is to get reimbursed from the insurance company in an expeditious fashion. This is achieved by submitting a claim to the insurance company describing the procedures that were performed along with supporting diagnosis codes. The reference for diagnostic coding is 'The International Classification of Diseases, 9th Revision, Clinical Modification' (ICD–9–CM). Complete Procedure Terminology (CPT) coding is based on a numeric system that identifies the procedure that was performed. These references are revised on an annual basis. Accurate CPT coding helps to maximize reimbursements and to avoid costly audits by insurance companies. A complete review of CPT coding is beyond the scope of this handbook. CPT coding is a complicated process that is constantly changing. All physicians need to be educated on the intricacies of the coding process. The American Medical Association (AMA) publishes an annual update on CPT coding. In addition the American College of Obstetrics and Gynecology (ACOG) publishes an annual update of changes in the specialty. The coding for specific procedures regarding infertility treatments is discussed below.

Evaluation and management (E/M) CPT codes

The E/M CPT codes are applied to office visits. The E/M services include new patient office visits (CPT codes 99241–99245, 99201–99205) and repeat visits (CPT codes 99211–99215). A new patient is one that has not been seen in consultation by the treating physician or by another physician in his/her group in the past 3 years. There are two choices for coding after a new patient office visit:

(1) If a physician or other appropriate authority has requested an opinion regarding the evaluation and treatment of a particular medical problem then the consultation CPT codes are used (99241–99245). After the consultation a letter needs to be sent to the referring physician. These consultation codes can only be used once. After a physician has assumed care of the patient for any follow-up consultations, the repeat visit codes should be used (99211–99215).
(2) If a new patient has not been referred by another physician the CPT codes 99201–99205 should be used.

The key components of the E/M codes include the history, physical examination, medical decision-making, counseling, coordination of care, nature of presenting problem, and time. The first three components of this list (history, physical examination, and medical decision-making) are the key components that determine the level of coding.

(1) For the new patient visits (99241–99245, 99201–99205) all three key components need to be performed and documented.
(2) For repeat visits (99211–99215) two out of the three key components should be performed and documented.

However, in many cases at the time of the office visit the majority of the physician's time is spent counseling the couple and the key components necessary for the coding are not performed. In these situations, the time spent can be the controlling factor to determine the level of the coding but it needs to be documented in the chart. An excerpt from the AMA CPT coding manual addresses this issue:

> 'In the case when counseling and/or coordination of care dominates (more than 50%) the physician/patient encounter (face-to-face time in the office or other outpatient setting or floor/unit time in the hospital), then time may be considered the key or controlling factor to qualify for a particular level of E/M services. The extent of counseling and/or coordination of care must be documented in the medical record.'

Therefore we document in our medical records the following statement: 'A total of _____ minutes was spent face to face with the patient and >50% of the time was spent in counseling'.

The amount of face-to-face time (in minutes) needed to determine the level of coding is described in the AMA CPT handbook and is as follows:

99241 15'	99201 10'	99211 5'
99242 30'	99202 20'	99212 10'
99243 40'	99203 30'	99213 15'
99244 60'	99204 45'	99214 25'
99245 80'	99205 60'	99215 40'

To aid our physicians with correct CPT coding we have the encounter times next to the correct CPT code on the fee ticket which is filled out after the office visit (Figure 18.2).

Coding for specific office procedures

The CPT codes that can be used for various office procedures are listed below. If a consultation takes place either before or after the procedure is performed then the appropriate E/M code should be selected but a modifier (–25) must be added. Time spent discussing the procedure or reviewing the consent with the patient is felt to be inclusive in the code of the procedure and should not be billed separately.

A. Endometrial biopsy†

   81025 – urine pregnancy testing
   58100 – performance of endometrial biopsy

B. Hysterosalpingogram†

   81025 – urine pregnancy testing
   58340 – induction of dye

Name:		**DOB**	**Clinician**		**Site:**		
Service Date:		**Primary Insurance:**			**Referral #**		
Reason:		**Initials:**		**Is there a co-pay? Y / N**	**Amount-**		
Outstanding balance:		**Global: Y / N**		**How was it paid?**			
		Initials:		**Any change in address/insurance? Y / N**	**Initials**		
OFFICE VISITS			DIAGNOSIS		DIAGNOSIS		
New (referred)	**PE or Time**		**INFERTILITY**		**GYNECOLOGY**		
LEVEL 1	(15)	99241	Anovulation	628.0	Pain		
LEVEL 2	(30)	99242	Cervical	628.4	Abdominal		789.67
LEVEL 3	(40)	99243	Male factor	628.8	Dysmenorrhea		625.3
* LEVEL 4	(60)	99244	Tubal factor	628.2	Dyspareunia		625.0
LEVEL 5	(80)	99245	Uterine factor	628.3	Pelvic		625.9
New (not referred)	**PE or Time**		Unexplained	628.9	PCO		256.4
LEVEL 2	(20)	99202	Other, specified origin	628.8	Premenstrual symptom		625.4
LEVEL 3	(30)	99203			Polyp Ð endometrial		621.0
LEVEL 4	(45)	99204	**ENDOCRINE**		Ð cervical		622.7
* LEVEL 5	(60)	99205	Amenorrhea	626.0	Vaginitis		616.10
Repeat office visit	**Time**		Hirsutism	704.1	**PREGNANCY**		
LEVEL 1	(5)	99211	Hyperprolactinemia	253.1	Supervision		V23.0
LEVEL 2	(10)	99212	Other ovarian dysfunction	256.8	Twin pregnancy		651.00
LEVEL 3	(15)	99213	PCO	256.4	Triplet pregnancy		651.10
* LEVEL 4	(25)	99214	Premature ovarian failure	256.31	Miscarriage: SAB		634.90
LEVEL 5	(40)	99215	**GYNECOLOGY**		Threatened		640.03
Prenatal visit	(15)	99213	Adenomyosis	617.0	Missed		632
	(25)	99214	Adhesions Ð tubal/pelvic	614.6	Habitual AB		629.9
			Annual gyn exam	V72.31	Ectopic pregnancy (tubal		633.10
Post-op visit		99024	Asherman syndrome	21.5	Ectopic pregnancy (presumed)		633.90
Annual GYN Exam			Bleeding		**OTHER DIAGNOSES**		
18-39YRS	NEW PATIENT	99385	Menorrhagia	626.2	Egg donor		V99.9
	ESTABLISHED	99395	Abnormal uterine bleeding	626.6	Genetic counseling		V26.3
40-64YRS	NEW PATIENT	99386	Unspecified	626.9	Gestational carrier		V99.9
	ESTABLISHED	99396	Cervical polyp	622.7	TDI Ð single Ð female		V26.8
			Cervical stenosis	622.4	Other specified procreative mgt		V26.8
CANCELLATION		CAN	Cervical dysplasia	622.10	Previous tubal ligation		V26.51
NO SHOW		NO SHOW	Chronic anovulation	626.1	Previous vasectomy		V26.52
			Dysmenorrhea	625.3	**Ultrasound procedures**		**Diagnosis**
Hospital Care Services			Dyspareunia	625.0	Follicle Ð initial complete	76830	628.9
Initial inpatient visit	(50)	99222	Dysuria	788.1	Follicle-F/U	76857	628.9
Repeat inpatient visit	(25)	99232	Endometrial hyperplasia	621.30	Prenatal (initial)	76817	V23.0
Discharge day	(30)	99238	Endometrial polyp	621.0	Prenatal (follow-up)		
Emergency room visit			Endometriosis:		Bleeding	76815	640.03
Level 3 (Pt discharged)		99283	of ovary	617.1	? Miscarriage	76815	632
Level 4 (Pt admitted)		99284	of fallopian tube	617.2	Twin	76815	651.00
			of pelvic peritoneum	617.3	Triplet	76815	651.10
OFFICE PROCEDURES			Herpes genitalia	054.10	Age > 34 years	76817	659.53
Cervical dilation		57800	Leiomyoma	218.9	R/O ectopic	76817	633.90
Cervical polyp removal		57500	Menopause	627.2	Other	76815	V23.0
Endometrial Bx		58100	Menstrual irregularity	626.4	Gyn US	76830	
HSG		58340	Mittleschmirtz	625.2	**Please circle any special situations:**		
Injections	IM	90772	Mullerian anomaly				
	IV	90784	Didelphys	752.2	A consultation takes place on the		–25
IUI treatment	Natural-IUI	58322	Mullerian agenesis	752.49	day of the procedure		
	CC-IUI	58322	Sept/bico/unic:	752.3			
	FSH-IUI	58322	Ovarian cyst		A decision is made to do		–57
Sonohysterogram		58340/76831	Luteal	620.1	major surgery in 1Ð2 days		
Other Services			Follicular	620.0			
Urine pregnancy test **DX V72.4**		81025	Endometrioma	617.1	A procedure is started but can		–53
Urine analysis		81000	Unspecified	620.2	not be completed		
Specimen handling		99000	Ovarian hyperstimulation	256.9/789.67			
Wet smears		87205	Ovarian torsion	620.5	Unrelated service during surgical		–24
Paracervical block		64435	PID Ð chronic	614.9	global		

Figure 18.2

C. Sonohysterogram†

81025 – urine pregnancy testing
76831 – hysterosonography
58340 – induction of saline

D. Insemination treatments

(1) Intracervical (donor insemination) – 58321
(2) Intrauterine insemination
  (a) sperm washing – 58323
  (b) limited semen analysis – 89310
  (c) performance of the insemination – 58322

E. Injections (i.e. hCG, methotrexate) – 90772

†In some cases a paracervical block (CPT code – 64435) and/or a cervical dilation (CPT code – 57800) are necessary to complete these procedures. If so, these procedure codes should be submitted for reimbursement.

Billing for surgical procedures

There are several important points concerning billing for surgical procedures, which are described below. It is important that the physician work with the billing personnel to make sure the coding is done correctly.

Relative value units

Insurance companies base reimbursement for a procedure on the number of relative value units (RVU). The Medicare Resource Based Relative Value Scale (RBRVS) was implemented in 1992 as a means to determine physician reimbursement for services on Medicare patients but all insurance companies have adopted it as well. The system is updated every 5 years and the most recent update was in 2002 and the next update is scheduled for 2007. The RVU is a measure of the time and intensity of the procedure that is performed. For instance, a diagnostic hysteroscopy has 5.93 RVU while a hysteroscopic resection of a uterine septum has 10.92 RVU. The number of RVU for a procedure is directly related to the level of reimbursement. If multiple procedures are performed it is important that the primary procedure (with the most RVU) is listed first then all secondary procedures are listed in descending order of decreasing RVU with a modifier (–51). Generally the primary procedure is reimbursed at 100%, and then the secondary procedures are reimbursed at a lower percentage. For a list of the current RVU visit the Center for Medicare and Medicaid Services (CMS) website http://www.cms.hhs.gov/PhysicianFeeSched/.

Bundling

Bundling is a process whereby the CPT codes of multiple procedures are combined into one. For example, a patient who underwent a hysteroscopy with a polypectomy would be assigned the CPT code 58558. During the procedure a cervical dilation (57800), a diagnostic hysteroscopy (58120), and a D&C (58120) were performed. All of these procedures have separate CPT codes. However, these procedures cannot be separately billed because the CPT code for the operative hysteroscopy (58558) is bundled and includes these procedures.

Global reimbursement

Payment for a surgical service is a global type reimbursement that covers a period of time prior to and following the surgery. The global payment may include the time spent doing the preoperative history and physical examination. Following the surgery, any routine follow-up care during the postoperative period (ranging from 0 to 90 days depending on the procedure) may also be included in the global period. The definition of the global period can vary depending on the surgery performed and is defined by the CMS.

Using modifiers

Modifiers are ways to redefine a surgical procedure or an evaluation and management code under special circumstances. The use of modifiers is necessary to be reimbursed for the extent of the services provided. The ACOG and the AMA coding manuals provide a description of these modifiers. There are several situations that make it necessary to use modifiers to get reimbursed. Examples of some of these situations are as follows:

- A consultation with the patient occurs on the same day of an office procedure (i.e. endometrial biopsy). *(Modifier –25)*
- An office visit takes place and a decision is made to perform the surgery that same day. *(Modifier –57)*
- The surgical procedure is more complicated and takes additional time. *(Modifier –22)*
- An open laparoscopy is performed. *(Modifier –22)*
- At the time of surgery bilateral procedures are performed on the ovaries (or tubes). *(Modifier –50)*
- Multiple surgeries are performed on the same day. *(Modifier –51)*
- A repeat procedure is performed by the same physician within the global period. *(Modifier –76)*
- A surgical assistant is used when a resident is unavailable. *(Modifier –80/82)*
- A procedure is started but aborted. *(Modifier –53)*

ICD–9–CM diagnostic codes

The CPT code for any E/M or procedure must be accompanied by a compatible diagnosis. The current system in use is the International Classification of Diseases, 9th Revision, Clinical Modification (ICD–9–CM). Some of the commonly used diagnostic codes for infertility services are presented below:

Infertility		Endocrine		Other	
Anovulation	628.0	Hyperprolactinemia	253.1	Pelvic adhesions	614.6
Cervical factor	628.4	Hyperandrogenism	256.1	Cervical stenosis	622.4
Male factor		Premature ovarian failure	256.3	Endometriosis	617.3
azoospermia	606.0			Endometrioma	617.1
oligospermia	606.1	Anovulation	628.0	Leiomyoma	218.9
Tubal blockage	628.2	Amenorrhea	626.0		
Unexplained	628.9				
Non-specified	628.8				

Note: If the patient does not have insurance coverage for infertility services, then it is not appropriate to submit a diagnosis such as endometriosis or uterine fibroids to obtain reimbursement from the insurance company. One must use infertility diagnosis codes if infertility services are being provided.

Available resources for coding issues

(1) Publications by the American Medical Association (www.ama-asn.org/catalog). (Call 1–800–621–8335 to order.)
(2) International Classifications of Diseases, 9th Revision; Clinical Modification (ICD–9–CM), 5th edition; published by INGENIX (1-800-464-3649).
(3) American College of Obstetricians and Gynecologists (ACOG) (www.acog.com).
    (a) CPT Coding in Obstetrics and Gynecology, 2006 edition. ACOG web site.
    (b) Online discussion – CPT/ICD9 Coding and Reimbursement section – questions can be posted and answered by their coding experts.
(4) The American Society for Reproductive Medicine (www.asrm.org) – the web site has a section entitled 'Coding Q&A'. Questions can be posted and then answered by their coding experts.

19.

Educational resources

Steven R Bayer

BOSTON IVF

130 Second Avenue
Waltham, MA 02541

- Phone 1–781–434–6500
- Web site – ***www.bostonivf.com***

Our web site provides a comprehensive overview of infertility that can benefit patients and those in the health-care field. Topics that are discussed include the causes, diagnostic testing, and treatment options for the infertile couple.

AMERICAN SOCIETY FOR REPRODUCTIVE MEDICINE (ASRM)

1209 Montgomery Highway
Birmingham, AL 35216

- Phone 1–205–978–5000
- Web site – ***www.asrm.org***

ASRM has been a leader in the field of reproductive medicine. Membership is available to all health-care professionals. The web site provides committee opinions, bulletins, and ethics reports that benefit the physician. The ASRM web site also has a section for patients that provides fact sheets, information booklets, and information on adoption.

RESOLVE

7910 Woodmont Avenue
Suite 1350
Bethesda, MD 20814

- Phone: 1–301–652–8585
- Web site – ***www.resolve.org***

RESOLVE was established in 1974 and is a non-profit organization with the only established, nationwide network of chapters mandated to promote reproductive health and to ensure equal access to all family building options for men and women experiencing infertility or other reproductive disorders. The mission of RESOLVE is to provide timely, compassionate support and information to people who are experiencing infertility and to increase awareness of infertility issues through public education and advocacy.

THE AMERICAN FERTILITY ASSOCIATION

666 Fifth Avenue, Suite 278
New York, NY 10103

- Phone: 1–718–621–5083
- Web site – ***www.theafa.org***

The American Fertility Association (AFA) is a national non-profit organization that was founded in 1999. AFA works to transform the lives of couples faced with infertility, to raise awareness, and to fight for social and legislative change around infertility issues. AFA's purpose is to educate the public about reproductive disease, and support families during struggles with infertility and adoption. AFA provides a range of services designed to help people gather information about medical treatments, options, coping techniques, legal and insurance issues, and other concerns.

THE INTERNATIONAL COUNCIL FOR INFERTILITY

Information Dissemination (INCIID)
PO Box 6836
Arlington, Virginia 22206

- Phone: (703) 379-9178
- Web site – ***www.inciid.org***

INCIID (pronounced 'inside') is a non-profit organization that helps individuals and couples explore their family-building options. INCIID provides current information and immediate support regarding the diagnosis, treatment, and prevention of infertility and pregnancy loss, and offers guidance to those considering adoption or childfree lifestyles.

20.

Forms and documents

Steven R Bayer

Following years of experience at Boston IVF we have developed documents that aid in the delivery of efficient care to the infertile patient. This chapter contains documents that can be tailored and used in your own practice.

1. **History forms** The female and male history forms provide a comprehensive assessment of medical, social, environmental, genetic, and occupational factors that are of importance. In addition, an extensive fertility history is also included in the history forms. To maximize efficiency these forms can be sent to the couple to be completed in advance of the initial consultation. The nurse/physician reviewing these forms can make additional notes in the comments section along the side of the forms. After the forms are filled out they can become part of the permanent medical record. These history forms were developed in part to support the documentation that is necessary for the CPT coding of initial consultation visits.
3. **BMI sheet** This sheet provides an easy calculation of the body mass index (BMI).
4. **Things you must know before you get pregnant** This narrative is given to all of our patients at the initial consultation. It provides the patient with recommendations on lifestyle issues as they relate to fertility and pregnancy.
5. **Infertility evaluation**
   (a) **Infertility evaluation** narrative. This from can be given to the couple after the initial consultation. A check mark can be made next to the tests that will be performed. Within the narrative there is a discussion of the rationale, performance and risks of the tests. Information is also provided for the patient regarding the scheduling of the tests.
   (b) **Evaluation Summary**. Test results can be entered on this form for review.
6. **Methotrexate administration**
   (a) Administration sheet – this sheet provides the formula for calculating the methotrexate dose and a log to follow the β-hCG titers;
   (b) Patient instruction sheet.

7. **Consent Forms**
   (a) Ovulation induction/intrauterine inseminations;
   (b) Hysterosalpingogram;
   (c) Sonohysterogram;
   (d) Endometrial biopsy;
   (e) Laparoscopy;
   (f) Hysteroscopy;
   (g) Methotrexate.
8. **Billing**
   (a) Office fee ticket – this fee ticket has been specifically tailored to an infertility practice;
   (b) CPT coding tip sheet for physicians;
   (c) Understanding your insurance benefits – this form is signed by patients at the initial consultation.

Boston IVF

FEMALE INTAKE FORM

TODAY'S DATE: ___/___/___
month day year

Patients – please complete all pages of this form.

NAME: _____ _____ AGE: _____ DOB: ___/___/___
Last First month day year

OCCUPATION: _____

PARTNER'S NAME: _____ _____ AGE: _____ DOB: ___/___/___
Last First month day year

REFERRING PHYSICIAN: _____ PRIMARY CARE PHYSICIAN: _____

ADDRESS _____ ADDRESS _____

PHONE NO.: _____ PHONE NO.: _____

MARITAL STATUS: ❒ Single ❒ Separated ❒ Divorced ❒ Married _____ years

REASON FOR VISIT: _____

TRYING TO CONCEIVE? ❒ No ❒ Yes If so, how long without protection? _____ Years _____ months

***Please answer the following questions. Do not write in shaded areas. Enter additional comments on reverse side under section* "Patient Comments."**

Menstrual History

Age you started to have periods	_____ yrs
Are your periods regular?	❒ Yes ❒ No
If cycles irregular, number cycles/year	_____ cycles
On average, how many days between periods?	_____ days
How long do your periods last?	_____ days
Menstrual flow:	❒ Normal ❒ Light ❒ Heavy
Pain with your periods?	❒ None ❒ Mild ❒ Mod ❒ Severe
Pain not associated with your periods?	❒ Yes ❒ No
Bleeding between periods?	❒ Yes ❒ No
Date of last menstrual period	___/___/___
Frequency of intercourse (per week)	_____

Comments:

Gynecological History

Gonorrhea	❒ Yes ❒ No	Chlamydia	❒ Yes ❒ No
Pelvic infection	❒ Yes ❒ No	Herpes	❒ Yes ❒ No
Painful sex	❒ Yes ❒ No	Excessive hair	❒ Yes ❒ No
Breast discharge	❒ Yes ❒ No	Prior IUD use	❒ Yes ❒ No
Birth control pill	❒ Yes ❒ No	Mom took DES	❒ Yes ❒ No
Vaginal lubricants	❒ Yes ❒ No	Douche	❒ Yes ❒ No
Sexual abuse	❒ Yes ❒ No	Physical abuse	❒ Yes ❒ No
Abnormal Pap	❒ Yes ❒ No	Mammogram	❒ Yes ❒ No
Date last Pap: ___/___/___		Acne	❒ Yes ❒ No

Obstetric History

Date *(mo/yr)* Outcome *(circle one)* *Comments/Complications?*

____/____ Miscar/Nml deliv/Cesar/Tubal/Abortion _____

____/____ Miscar/Nml deliv/Cesar/Tubal/Abortion _____

____/____ Miscar/Nml deliv/Cesar/Tubal/Abortion _____

____/____ Miscar/Nml deliv/Cesar/Tubal/Abortion _____

Prior Infertility Evaluation (if applicable)

		Year	**Result**	
Basal temp records	❒ No	____	❒ Normal	❒ Abnormal
Urine ovulation kits	❒ No	____	❒ Normal	❒ Abnormal
Endometrial biopsy	❒ No	____	❒ Normal	❒ Abnormal
Semen analysis	❒ No	____	❒ Normal	❒ Abnormal
Hysterosalpingogram	❒ No	____	❒ Normal	❒ Abnormal
Postcoital test	❒ No	____	❒ Normal	❒ Abnormal
Laparoscopy	❒ No	____	❒ Normal	❒ Abnormal
Hysteroscopy	❒ No	____	❒ Normal	❒ Abnormal
FSH blood test	❒ No	____	❒ Normal	❒ Abnormal

Prior Infertility Treatments (if applicable)

			Year	
Clomid or Serophene	❒ No	❒ Yes:	____	# cycles _____
FSH injectable meds.	❒ No	❒ Yes:	____	# cycles _____
hCG injectable med.	❒ No	❒ Yes:	____	# cycles _____
Intrauterine insemin.	❒ No	❒ Yes:	____	# cycles _____
IVF or GIFT	❒ No	❒ Yes:	____	# cycles _____

Take Medications ❒ Yes ❒ No

If yes, which ones: _____

_____

Do you take folic acid or vitamins? ❒ Yes ❒ No

Do you take herbal remedies? ❒ Yes ❒ No

Allergies ❒ Yes ❒ No

If yes, describe: _____

_____

What is your blood type? ❒ Unknown ❒ Blood type _____

Past Surgeries ❒ Yes ❒ Yes

If yes, state type, date, hospital:

_____

_____

_____

_____

Social

Smoke	❒ Yes	❒ No	Alcohol weekly	❒ Yes	❒ No
Cocaine	❒ Yes	❒ No	Marijuana	❒ Yes	❒ No
IV drugs	❒ Yes	❒ No	Weight change	❒ Yes	❒ No
Regular exercise	❒ Yes	❒ No	Caffeine	❒ Yes	❒ No

Comments:

Family History

Has anybody in your family had any of the following?

Early menopause	❒ Yes	❒ No	Breast cancer	❒ Yes	❒ No
Ovarian cancer	❒ Yes	❒ No	Muscular dystrophy	❒ Yes	❒ No
Stillbirth	❒ Yes	❒ No	Sickle-cell anemia	❒ Yes	❒ No
Cystic fibrosis	❒ Yes	❒ No	Mental retardation	❒ Yes	❒ No
Tay-Sachs	❒ Yes	❒ No	Spina bifida	❒ Yes	❒ No
Down's syndrome	❒ Yes	❒ No	Tuberous sclerosis	❒ Yes	❒ No
Birth defects	❒ Yes	❒ No	Heart attack (< 50 yrs)	❒ Yes	❒ No
Thyroid disease	❒ Yes	❒ No	Psychiatric disease	❒ Yes	❒ No
Diabetes	❒ Yes	❒ No	Blindness	❒ Yes	❒ No
High blood press.	❒ Yes	❒ No	Chromosome problem	❒ Yes	❒ No
Hemophilia	❒ Yes	❒ No	Recurrent miscarriage	❒ Yes	❒ No
Deafness	❒ Yes	❒ No	Other genetic disorders:	❒ Yes	❒ No
Polycystic kidneys	❒ Yes	❒ No	_____		
Bleeding disorders	❒ Yes	❒ No	_____		

Ancestral Background

There are certain ancestral backgrounds that have an increased frequency of some genetic diseases. Please indicate if either your mother or father are of any of the following backgrounds:

❒ African ❒ Caribbean ❒ Jewish ❒ Indian ❒ Native American
❒ French-Canadian ❒ Latin-American ❒ Mediterranean ❒ Asian

Medical History (Review of Systems)

Have you ever had any of the following?

Abdominal pains	❒ Yes	❒ No	Epilepsy	❒ Yes	❒ No
Anemia	❒ Yes	❒ No	Excessive thirst	❒ Yes	❒ No
Antibiotics	❒ Yes	❒ No	Fainting	❒ Yes	❒ No
Appendicitis	❒ Yes	❒ No	Fibroids	❒ Yes	❒ No
Arthritis	❒ Yes	❒ No	Exces. Constipation	❒ Yes	❒ No
Asthma	❒ Yes	❒ No	Severe headaches	❒ Yes	❒ No
Blood clots	❒ Yes	❒ No	Urinary infections	❒ Yes	❒ No
Blood in stool	❒ Yes	❒ No	Heart disease	❒ Yes	❒ No
Blood transfusion	❒ Yes	❒ No	Heat/cold intolerance	❒ Yes	❒ No
Problem with vision	❒ Yes	❒ No	Hepatitis, liver prob.	❒ Yes	❒ No
Breast discharge	❒ Yes	❒ No	High blood pressure	❒ Yes	❒ No
Cancer	❒ Yes	❒ No	Hot flashes, sweats	❒ Yes	❒ No
Diabetes	❒ Yes	❒ No	Lack bladder control	❒ Yes	❒ No
Dizziness	❒ Yes	❒ No	Anxiety	❒ Yes	❒ No
Easy bruising	❒ Yes	❒ No	Kidney problems	❒ Yes	❒ No
Endometriosis	❒ Yes	❒ No	Mitral valve prolapse	❒ Yes	❒ No
Neck/back pain	❒ Yes	❒ No	Thrombophlebitis	❒ Yes	❒ No
Neurological prob.	❒ Yes	❒ No	Thyroid problem	❒ Yes	❒ No
Nose/gum bleeds	❒ Yes	❒ No	Tuberculosis	❒ Yes	❒ No
Palpitations	❒ Yes	❒ No	Shortness of breath	❒ Yes	❒ No
Stomach problems	❒ Yes	❒ No	Swollen joints	❒ Yes	❒ No
German measles	❒ Yes	❒ No	Chicken pox	❒ Yes	❒ No

Comments:

Boston IVF

MALE INTAKE FORM

TODAY'S DATE: ____/____/____
month day year

NAME: _____ _____ AGE: _____ DOB: ____/____/____
Last First month day year

PARTNER'S NAME: _____ _____ AGE: _____ DOB: ____/____/____
Last First month day year

REFERRING PHYSICIAN: _____ PRIMARY CARE PHYSICIAN: _____

REASON FOR VISIT: ❒ Infertility ❒ Other _____

IF TRYING TO CONCEIVE, HOW LONG? ❒ Yes _____ years OCCUPATION _____

Please answer the following questions on the front and back of this page. Make any comments in the comments section at the bottom of this page.

Number of pregnancies with current partner: _____

Number of years married: ____ years

Number of prior marriages: Husband: ____ Wife: ___

Number of pregnancies with previous partner(s): _____

Age(s) of children, if any: _____

Past Medical History

Do you have any heart problems? ❒ Yes ❒ No

Do you have any lung problems (asthma, etc.)? ❒ Yes ❒ No

Do you have bowel or stomach problems? ❒ Yes ❒ No

Problems with muscles or joints? ❒ Yes ❒ No

Ever had mumps? ❒ Yes ❒ No

Do you have any neurological problems? ❒ Yes ❒ No

Any hormonal problems (thyroid, diabetes, etc.)? ❒ Yes ❒ No

Do you have any other medical problems?

_____

_____

_____

Have you had any other surgery?

_____

_____

List medications you are now taking:

_____

_____

ALLERGY to medications: ❒ Yes ❒ No _____

Urological History

Have you ever had undescended testicles? ❒ Yes ❒ No

Have you ever suffered an injury to the testicles? ❒ Yes ❒ No

Have you ever had a hernia repair? ❒ Yes ❒ No

Have you been diagnosed with a varicocele? ❒ Yes ❒ No

Have you had a vasectomy? ❒ Yes ❒ No

Have you had bladder or prostate surgery? ❒ Yes ❒ No

Do you have a problem with achieving erections? ❒ Yes ❒ No

Have you had epididymitis? ❒ Yes ❒ No

Ever had a urinary tract infection? ❒ Yes ❒ No

Ever had a sexually transmitted disease? ❒ Yes ❒ No

Any problems with ejaculation? ❒ Yes ❒ No

Any problems with sex drive? ❒ Yes ❒ No

Did you have early puberty (before 12 yrs)? ❒ Yes ❒ No

Did you have late puberty? ❒ Yes ❒ No

Have you had abnormal sexual development? ❒ Yes ❒ No

Have you had a fever within the last 3 months? ❒ Yes ❒ No

Other family member have a fertility problem? ❒ Yes ❒ No

Social

Any special exposure to heat on a regular basis (sauna, baths, Jacuzzi)? ❒ Yes ❒ No

Do you use recreational drugs? ❒ Yes ❒ No

Do you smoke? ❒ Yes ❒ No

Have you been exposed to any chemicals? ❒ Yes ❒ No

Have you been exposed to radiation (not routine x-rays)? ❒ Yes ❒ No

How many drinks of alcohol per week? _____

_____

Comments on any of the above:

_____

_____

_____

Family History

Has anybody in your family had any of the following?

Breast cancer	❒ Yes	❒ No	Stillbirth	❒ Yes	❒ No	Tuberous sclerosis	❒ Yes	❒ No
Cystic fibrosis	❒ Yes	❒ No	Muscular dystrophy	❒ Yes	❒ No	Tay-Sachs	❒ Yes	❒ No
Sickle-cell anemia	❒ Yes	❒ No	Down's syndrome	❒ Yes	❒ No	Mental retardation	❒ Yes	❒ No
Birth defects	❒ Yes	❒ No	Spina bifida	❒ Yes	❒ No	Thyroid disease	❒ Yes	❒ No
High blood press.	❒ Yes	❒ No	Diabetes	❒ Yes	❒ No	Heart attack (< 50 yrs)	❒ Yes	❒ No
Blindness	❒ Yes	❒ No	Psychiatric disease	❒ Yes	❒ No	Hemophilia	❒ Yes	❒ No
Polycystic kidneys	❒ Yes	❒ No	Deafness	❒ Yes	❒ No	Chromosome problem	❒ Yes	❒ No
Ovarian cancer	❒ Yes	❒ No	Bleeding disorders	❒ Yes	❒ No	Other genetic disorders	❒ Yes	❒ No

Ancestral Background

There are certain ancestral backgrounds that have an increased frequency of some genetic diseases. Please indicate if either your mother or father are of any of the following backgrounds:

❒ African ❒ Caribbean ❒ Jewish ❒ Indian ❒ Native American ❒ French-Canadian ❒ Latin-American ❒ Mediterranean ❒ Asian

This section to be completed by your Physician

Laboratory Results

Semen Analysis	***Date***	***Date***	***Date***	***Other test results***
COUNT	_____	_____	_____	FSH _____
MOTILITY	_____	_____	_____	LH _____
MORPHOLOGY	_____	_____	_____	PRL _____
VOLUME	_____	_____	_____	TESTO/FT _____
Other Comments	_____	_____	_____	TSH _____

Physical Examination

GENERAL		❒ Normal	❒ Abnl: _____	
ABDOMEN		❒ Normal	❒ Abnl: _____	
PENIS		❒ Normal	❒ Abnl: _____	
Meatus		❒ Normal	❒ Abnl: _____	
TESTES	Left	❒ Normal	❒ Abnl: _____	
	Right	❒ Normal	❒ Abnl: _____	
VASA	Left	❒ Normal	❒ Abnl: _____	
	Right	❒ Normal	❒ Abnl: _____	
EPID	Left	❒ Normal	❒ Abnl: _____	
	Right	❒ Normal	❒ Abnl: _____	
PROSTATE		❒ Normal	❒ Abnl: _____	
VARICO	Left	❒ No	❒ Mild	❒ Mod ❒ Large
	Right	❒ No	❒ Mild	❒ Mod ❒ Large
Other Findings:	_____			
U/A:	Dip	❒ Normal	❒ Abnl: _____	
	pH:	_____		

Impression and Plan

_____

_____

_____

_____

_____

Chromosomal abnormalities in liveborn infants and maternal age*

Maternal age	Risk for Down's syndrome	Total risk for chromosomal anomalies†
20	1/1667	1/526
21	1/1667	1/526
22	1/1429	1/500
23	1/1429	1/500
24	1/1250	1/476
25	1/1250	1/476
26	1/1176	1/476
27	1/1111	1/455
28	1/1053	1/435
29	1/1000	1/417
30	1/952	1/385
31	1/909	1/385
32	1/769	1/322
33	1/602	1/286
34	1/485	1/238
35	1/378	1/192
36	1/289	1/156
37	1/224	1/127
38	1/173	1/102
39	1/136	1/83
40	1/106	1/66
41	1/82	1/53
42	1/63	1/42
43	1/49	1/33
44	1/38	1/26
45	1/30	1/21
46	1/23	1/16
47	1/18	1/13
48	1/14	1/10
49	1/11	1/8

* The data presented above were modified from Hook DB, Cross PK, Schreinemachers DM. Chromosomal abnormality rates at amniocentesis and in live-born infants. J Am Med Assoc 1983; 249: 2034–8, and Hook EB. Rates of chromosomal abnormalities at different maternal ages. Obstet Gynecol 1981; 58: 282–5

†The other chromosomal anomalies that are increased with maternal age in addition to 47,+21 (Down's syndrome) are 47,+18; and 47,+13; 47,XYY (Klinefelter's syndrome); 47,XYY and 47,XXX. The incidence of 47,XXX for women between the ages of 20 and 32 years is not available

BODY MASS INDEX

	NORMAL						OVERWEIGHT					OBESITY										EXTREME OBESITY					
	19	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36**	**37**	**38**	**39**	**40**	**41**	**42**	**43**	**44**	**45**
4' 10"	91	96	100	105	110	115	119	124	129	134	138	143	148	153	158	162	167	172	177	181	186	191	196	201	205	210	215
4' 11"	94	99	104	109	114	119	124	128	133	138	143	148	153	158	163	168	173	178	183	188	193	198	203	208	212	215	222
5' 0"	97	102	107	112	118	123	128	133	138	143	148	153	158	163	169	173	179	184	189	194	199	204	209	215	220	225	230
5' 1"	100	106	111	116	122	127	132	137	143	148	153	158	164	169	174	180	185	190	195	201	206	211	217	222	227	232	238
5' 2"	104	109	115	120	126	131	136	142	147	153	158	164	169	174	180	185	191	196	202	207	213	218	224	229	235	240	246
5' 3"	107	113	118	124	130	135	141	146	152	158	163	169	175	180	186	192	197	203	208	214	220	225	231	237	242	248	254
5' 4"	110	116	122	128	134	140	145	151	157	163	169	174	180	186	192	197	204	209	215	221	227	232	238	244	250	256	262
5' 5"	114	120	126	132	138	144	150	156	162	168	174	180	186	192	198	204	210	216	222	228	234	240	246	252	258	264	270
5' 6"	118	124	130	136	142	148	155	161	167	173	179	186	192	198	204	210	216	223	229	235	241	247	253	260	266	272	278
5' 7"	121	127	134	140	146	153	159	166	172	178	185	191	198	204	210	217	223	230	236	242	249	255	261	268	274	280	287
5' 8"	125	131	138	144	151	158	164	171	177	184	190	197	203	210	216	223	230	236	243	249	256	262	269	276	282	289	295
5' 9"	128	135	142	149	155	162	169	176	182	189	196	203	209	216	223	230	236	243	250	257	263	270	277	284	291	297	304
5' 10"	132	139	146	153	160	167	174	181	188	195	202	209	216	222	229	236	243	250	257	264	271	278	285	292	299	306	313
5' 11"	136	143	150	157	165	172	179	186	193	200	208	215	222	229	236	243	250	257	265	272	279	286	293	301	308	315	322
6' 0"	140	147	154	162	169	177	184	191	199	206	213	221	228	235	243	250	258	265	272	279	287	294	302	309	316	324	331
6' 1"	144	151	159	166	174	182	189	197	204	212	219	227	235	242	250	257	265	272	280	288	295	302	310	318	325	333	340
6' 2"	148	155	163	171	179	186	194	202	210	218	225	233	241	249	256	264	272	280	287	295	303	311	319	326	334	342	350
6' 3"	152	160	168	176	184	192	200	208	216	224	232	240	248	256	264	272	279	287	295	303	311	319	327	335	343	351	359
6' 4"	156	164	172	180	189	197	205	213	221	230	238	246	254	263	271	279	287	295	304	312	320	326	339	344	353	361	369

Instructions: This chart provides a simple way to calculate body mass index (BMI). Find your patient's height on the far left column then move to the right to find the weight (lbs.) in the corresponding row. Then ascend the column to determine the BMI. For instance, a woman who is 5'6" tall and weighs 229 lbs has a BMI of 37

THINGS YOU MUST KNOW BEFORE YOU GET PREGNANT

We have two goals for your treatment. The first goal is to help you achieve a pregnancy. The second goal is that the pregnancy is uncomplicated and results in the delivery of a healthy baby. To this end, there are certain things that you can do to help achieve this goal, which are discussed below.

Smoking

The detrimental effects of smoking on general health are well established (e.g., heart disease, cancer, and chronic lung disease). Smoking also impacts on reproductive health, as well. Women who smoke during pregnancy are at increased risk for premature labor, decreased fetal growth, and other complications. In addition, studies have demonstrated that men and women who smoke have a decreased chance of achieving a pregnancy either naturally or following infertility treatment. Therefore, if you smoke, we feel strongly that for general and reproductive health concerns, you must stop. If you are unable to stop on your own then you should contact your primary care physician to get enrolled in a smoking cessation program.

Alcohol

Alcohol should be completely avoided during pregnancy because it increases the chance of birth defects. In addition, alcohol can interfere with the establishment of pregnancy. A previous study concluded that any amount of alcohol ingested by the woman decreased the chance of pregnancy and increased the chance of a miscarriage. Therefore, we recommend that if a woman is attempting pregnancy she should completely avoid alcohol or limit intake to the first week of the menstrual cycle. There is no detriment of mild to moderate alcohol intake on male fertility.

Caffeine intake

Several studies have concluded that caffeine intake by the woman decreases the chance of establishing a pregnancy and increases the chance of a miscarriage. Caffeine is present in coffee, tea, some soft drinks, and chocolate. It is our recommendation that you should avoid caffeine altogether or limit intake to one caffeinated beverage per day. There is no detrimental effect of caffeine on male fertility.

Recreational drug use

The use of recreational drugs is contraindicated while attempting to conceive and during pregnancy. Some drugs, such as marijuana, may decrease sperm production. Drug use by the woman during pregnancy, such as cocaine and heroin, may lead to severe withdrawal reactions in the baby after it is born. Further, the use of intravenous drugs increases the risk of acquiring an HIV and hepatitis infection.

Medication use

All non-fertility medications that have been prescribed should be discussed with your physician. It is also important that you contact the physician who originally prescribed these medications to make sure he/she is aware that you are attempting pregnancy. You should avoid taking aspirin and aspirin-like compounds (e.g., Advil, Aleve, Ibuprofen, and Motrin) around the time of ovulation, since these medications can interfere with ovulation. Tylenol® is a suitable alternative. Herbal remedies should be completely avoided since their effects on fertility and pregnancy are unknown.

Vitamin supplementation

Neural tube defects are abnormal developments of the spine and skull. One type of neural tube defect is spina bifida. Several studies have confirmed that folic acid supplementation started before conception will reduce the occurrence of neural tube defects in infants by almost half. It is now recommended that all women who are attempting pregnancy ingest at least 0.400 mg of folic acid per day for this protection. Folic acid supplementation can be achieved by taking an over-the-counter multivitamin or a prenatal vitamin on a daily basis.

There are published data that have confirmed that excessive intake of vitamin A increases the chance of birth defects. Prenatal vitamins and over-the-counter multivitamins contain 5000 IU of vitamin A, which is a safe dose. However, daily intake should *not* exceed 10 000 IU.

THINGS YOU MUST KNOW BEFORE YOU GET PREGNANT

Nutrition

Our general health is influenced by what we eat, how much we eat, and how much energy we expend with activity and exercise. In addition, our nutritional state can impact on reproductive health, as well, and can influence the establishment and maintenance of a pregnancy. As a general recommendation, women should be encouraged to maintain a balanced diet of fruits, vegetables, breads, meats, and dairy products. Foods with a high content of fats and oils should be used at a minimum. During pregnancy, ingestion of some fish which contain higher amounts of mercury can affect the development of the nervous system of a fetus. Before and after pregnancy is established a woman should avoid eating these fish – shark, swordfish, king mackerel, tilefish and tuna fish. In addition, the ingestion of all other fish should be limited to 12 oz per week.

Body weight

A major concern about increased weight is the higher chance of complications during pregnancy, including diabetes, high blood pressure, and clot formation. Women who are overweight tend to have larger babies, more difficult deliveries, and a higher chance of requiring a Cesarean section. Further, a Cesarean section that is performed on a woman who is overweight is associated with a higher incidence of anesthetic and surgical complications that could jeopardize the health of the mother and baby.

The body mass index (BMI) is a standard to determine whether a person's weight is appropriate for their height. It is a calculation that takes into account the weight and height [weight (kg)/height (m^2)]. An easy way to calculate the BMI is as follows: multiply the weight in pounds by 704 then divide by height (in inches) squared.

Example: A woman is 5' (60") tall and weighs 207 lb; her BMI would be calculated as follows:

$$207 \times 704/60^2 = \underline{40.5}$$

An optimal BMI is 20–24. All women with a BMI of >30 should be encouraged to lose weight. For women who have a BMI >40 it is recommended to lose weight prior to attempting pregnancy or undergoing infertility treatment.

Exercise

The benefits of exercise on general health and mental well-being are established. Further, exercise during pregnancy has also been shown to be beneficial. If you are already in an exercise program, we would encourage you to continue. However, the medications used to stimulate the ovaries as part of your treatment can cause temporary ovarian cysts to form. Therefore, we would advise you to avoid exercise activities that result in a lot of vertical movement (i.e., running, step aerobics). Exercise activities such as swimming, bicycle riding, walking, and using the treadmill or step exercise are acceptable.

Routine gynecologic care

During your infertility treatment, it is important for you to continue your routine care with your gynecologist or primary care physician. This should include a yearly blood pressure check, physical examination, pelvic examination, and Pap smear. A baseline mammogram is recommended for every woman at age 40 and every 1–2 years thereafter.

THE INFERTILITY EVALUATION

The infertility evaluation consists of a series of tests that evaluates male and female reproductive function. The objective of the evaluation is to identify potential causes of infertility. Accordingly, your doctor may order some or all of the following tests, as it is important that a complete evaluation be performed. To help familiarize you with these tests and what can be learned from them, a description of each appears below.

☐ Semen analysis

The semen analysis is the standard test for the evaluation of the male partner. The semen analysis includes an assessment of the sperm concentration, motility (or activity of sperm), and a determination of the percentage of normally shaped sperm. If the initial semen analysis is found to be abnormal, then a repeat analysis may be requested.

Scheduling

You will be instructed to set up an appointment for the test.

Please read carefully and follow these instructions. If you have any questions, feel free to discuss them with us.

1. The physician should be informed of all medications that you are taking.
2. Exposure of the testes to high temperatures (saunas, hot baths) should be avoided since this will decrease the sperm count.
3. You should abstain from ejaculation for 24 hours before the test. Decreasing the frequency of ejaculation *'to save sperm'* does not improve the results of the semen analysis.
4. The specimen is produced by masturbation into a sterile container that will be provided. The sample can be produced at the laboratory or at home then brought in immediately. For the latter, the specimen should arrive at the laboratory no later than 30 minutes after it is produced. During transport, the specimen should be kept at body temperature and not exposed to extreme heat or cold. If the sample is to be produced at home, a container to collect the sample will be provided.

The results of the analysis will be discussed with you at the follow-up consultation or you will receive a letter from your physician. If for any reason the test must be repeated, you will be contacted.

☐ Hormone testing of ovarian function

An important factor that influences a woman's fertility is the number and quality of eggs, which can be assessed by hormone testing. Between days 2–4 of the menstrual cycle, a blood sample can be obtained for the measurement of follicle-stimulating hormone (FSH) and estradiol (E2) hormone. FSH is made by the pituitary gland (located at the base of the brain). FSH stimulates the development of ovarian follicles, which are the fluid-filled cysts that contain the eggs. Estradiol is an estrogen hormone, which is produced by the developing follicle. An elevation in the FSH and/or estradiol levels suggests a reduction in the supply of eggs within the ovaries. In this circumstance, there may be a reduced chance of achieving pregnancy.

Scheduling

On the first day of your menstrual period (cycle day 1) contact your physician's office and arrange for the blood test, which can be performed between cycle days 2–4. If your period occurs on the weekend, please call first thing Monday morning to schedule the test.

☐ Hysterosalpingogram (HSG)

A hysterosalpingogram (also called *tubogram* or *hysterogram*) is an x-ray that is performed to examine the uterine cavity and determine whether the fallopian tubes are open.

Scheduling

On the first day of your menstrual period (cycle day 1) contact your physician's office to schedule the test. If your period occurs on the weekend, please call Monday morning to schedule the test. The test is performed in a radiologist's office and usually done between cycle days 5–12.

THE INFERTILITY EVALUATION

Performance of the test

First, a speculum is placed in the vagina to visualize the cervix. A small tube is then placed into the cervical canal. An iodine containing fluid is injected gently through this tube into the uterine cavity. The progress of the dye is followed by viewing a television monitor. Generally, the test is completed within 4–5 minutes and is sometimes associated with temporary lower abdominal cramping which resolves after completion of the test. *You may benefit from taking 2–3 tablets (200 mg) of ibuprofen (Advil, Motrin) one hour before your test.*

The complication rate from this procedure is less than 2%. Some of the risks include the following:

Pelvic infection – The performance of this test can result in an infection that could produce abdominal pain and fever. A consequence of this infection may be scarred fallopian tubes and infertility. An infection is more likely to occur in women who already have damaged fallopian tubes.

Allergic reaction – The contrast medium used contains iodine. *If you have had any allergic reaction to iodine, a reaction following another radiologic procedure (e.g., CT scans, IVP) or if you have had a reaction to fish or shellfish, please notify your physician.* This could be suggestive of an iodine allergy.

Exposure to potential pregnancy – Please notify your physician if you feel that your previous menstrual period was not normal. In this circumstance a pregnancy test can be done before the procedure.

Upon completion of the test the results will be discussed with you. Following the x-ray you are ready to resume your normal activities and can return to work. A discharge of clear fluid and vaginal spotting may be noted for the next day. You should refrain from intercourse for 2 days.

☐ Sonohysterogram

The sonohysterogram is a test that examines the uterine cavity and is sometimes done *in lieu* of or in conjunction with the hysterosalpingogram.

Scheduling

On the first day of your menstrual period (cycle day 1) contact your physician's office to schedule the test. If your period occurs on the weekend, please call Monday morning to schedule the test. The test is usually done between cycle days 5–12.

Performance of the test

First, a speculum is placed in the vagina to visualize the cervix. A small catheter is then placed through the cervical canal into the uterine cavity. The vaginal ultrasound probe is inserted into the vagina. Once the uterus is brought into view, a saline solution is injected into the cavity through the catheter. Generally, the test is completed within 4–5 minutes. The test is sometimes associated with lower abdominal cramping. *You may benefit from taking 2–3 tablets (200 mg) of ibuprofen (Advil, Motrin) one hour before your test.*

The complication rate from this procedure is less that 2%. Some of the risks include the following:

Pelvic infection – The performance of this test can result in an infection that could produce lower abdominal pain and fever. A consequence of this infection may be scarred fallopian tubes and infertility. An infection is more likely to occur in women who already have damaged fallopian tubes.

Exposure to potential pregnancy – Please notify your physician if you feel that your previous menstrual period was not normal. In this circumstance a pregnancy test can be done before the procedure.

Upon completion of the test the results will be discussed with you. Following the test you are ready to resume your normal activities and can return to work. A discharge of clear fluid and vaginal spotting may be noted for the next day. You should refrain from intercourse for 2 days.

☐ Endometrial biopsy

An endometrial biopsy is an office procedure that involves the removal of a small amount of tissue from the uterine cavity. A pathologist will then examine the biopsy. Any woman who has a history of abnormal bleeding, irregular or absence of menstrual periods, or a history of a biopsy confirming an infection may benefit from the performance of an endometrial biopsy. The endometrial biopsy *is not a routine test* and is done in selected cases.

(Continued)

THE INFERTILITY EVALUATION

Scheduling

Your physician will discuss with you the appropriate timing of the biopsy.

Performance of the test

First, a speculum is placed in the vagina to visualize the cervix. A small plastic catheter is placed into the cervical canal into the uterine cavity. The biopsy is obtained with this catheter. Generally, the biopsy is completed within a few minutes. The test is associated with some lower cramping. *You may benefit from taking 2–3 tablets (200 mg) of ibuprofen (Advil, Motrin) one hour before your test.*

The complication rate from this procedure is less that 2%. Some of the risks include the following:

Pelvic infection **–** The performance of this test can result in an infection that could produce lower abdominal pain and fever. A consequence of this infection may be scarred fallopian tubes and infertility. An infection is more likely to occur in women who already have damaged fallopian tubes.

Exposure to potential pregnancy **–** Please notify your physician if you feel that your previous menstrual period was not normal. In this circumstance a pregnancy test can be done before the procedure.

You are ready to resume your normal activities and may return to work one hour after the endometrial biopsy is performed. Results should be available one week after the performance of the biopsy.

☐ Surgery

☐ **Laparoscopy –** This is an outpatient surgical procedure that is performed under general anesthesia. This procedure involves the placement of a telescopic instrument through a small incision and into the abdominal cavity, which allows the visualization of the pelvic organs. The objective of the laparoscopy is to identify and treat any conditions involving pelvic organs (i.e., endometriosis, adhesions) that might be playing a role in your infertility. Following the surgery, you will need to be transported home. Usually, you are ready to return to normal activities approximately 2–3 days after the surgery.

☐ **Hysteroscopy –** This is an outpatient surgical procedure. It can be performed by itself but many times is done in conjunction with a laparoscopy. The procedure involves the placement of a telescope through the cervical canal and into the uterine cavity. The cavity is distended with saline and then examined. The objective of this procedure is to identify and treat conditions in the uterine cavity (i.e., endometrial polyps, and fibroids) that might be contributing to your infertility. Following the surgery, you will need to be transported home. Usually, you are ready to return to normal activities the day after your surgery.

☐ **Counseling**

Dealing with infertility can be stressful. To help you deal with the stress, we can refer you to one of our social workers who have experience with infertile couples. Most psychologic services are covered under the mental health benefit section of insurance plans. Please check with your insurance company regarding your benefits.

☐ Medical records

Review of medical records from previous testing and treatment will help in the development of a treatment plan. Please obtain the following records.

☐ ***Hysterosalpingogram films*** **–** Contact the radiology department of the hospital where the x-ray was performed. *Please specify that the x-ray films and the report should be sent to us for review.*

☐ ***Operative reports*** **–** Contact the medical records department of the hospital where the surgery was performed and ask that the medical records pertaining to the surgery be sent to us.

☐ ***Office notes*** **–** Obtain all office records from physicians who have evaluated or treated you for infertility.

☐ Follow-up consultation

After all of the tests have been completed, please set up a consultation. At that time the test results will be reviewed and a treatment plan will be developed.

EVALUATION SUMMARY

FEMALE PARTNER TESTING

Date	Test	Result	Date	Test	Result
☐ / /	CD3 FSH		☐ / /	CD3 FSH	
☐ / /	CD3 E2		☐ / /	CD3 E2	
☐ / /	CD10 FSH		☐ / /	CD10 FSH	
☐ / /	CD10 E2		☐ / /	CD10 E2	
☐ / /	Prolactin		☐ / /	Prolactin	
☐ / /	TSH		☐ / /	TSH	
☐ / /	Thyroid antibodies		☐ / /		
☐ / /	Testosterone		**MALE PARTNER TESTING**		
☐ / /	DHEA-S				
☐ / /	17-OH-Progesterone		**Date**	**Test**	
☐ / /	Hemoglobin A1C		☐ / /	HIV	
☐ / /	Fasting glucose		☐ / /	Hepatitis screen	
☐ / /	2° GTT		☐ / /	Karyotype	
☐ / /	CBC		☐ / /	Y deletion study	
☐ / /	Type & screen		☐ / /	FSH	
☐ / /	Rubella screen		☐ / /	LH	
☐ / /	Varicella screen		☐ / /	Testosterone	
☐ / /	RPR		☐ / /	Prolactin	
☐ / /	Hepatitis screen		☐ / /	Cystic fibrosis	
☐ / /	HIV screen		☐ / /	Fam dysautonomia	
☐ / /	Karyotype		☐ / /	Canavan	
☐ / /	Lupus anticoagulant		☐ / /	Tay-Sachs	
☐ / /	Anti-cardiolipin ab		☐ / /	Hgb electro	
☐ / /	Thrombophilia w/u		☐ / /		
☐ / /	Cystic fibrosis		**SEMEN ANALYSIS**		
☐ / /	Fam dysautonomia				
☐ / /	Canavan		☐ / /		
☐ / /	Tay-Sachs		Count	Motility	Morphology
☐ / /	Hgb electrophoresis				
☐ / /	BUN/creatinine				
☐ / /	SGOT/SGPT		☐ / /		
☐ / /			Count	Motility	Morphology
☐ / /					
☐ / /					
☐ / /	**Test**				
☐ / /	HSG				
☐ / /	SonoHSG				
☐ / /	Lap/hyst				
☐ / /	Endometrial biopsy				
☐ / /	Vaginal ultrasound				

METHOTREXATE ADMINISTRATION FLOW SHEET

Name _____ Physician _____ Height _____

Date of birth _____ LMP _____ Weight _____

Diagnosis: ☐ Proven ectopic ☐ Presumed ectopic ☐ Persistent ectopic

Day 0: **CBC**: nl abnl **SGOT**: nl abnl **CREAT**: nl abnl **Blood type** _____

REPEAT: **CBC**: nl abnl **SGOT**: nl abnl **CREAT**: nl abnl

Calculating the dose of Methotrexate (verify calculations with pharmacist)

$$\text{Dose (mg)} = \text{surface area (m}^2) \times 50\,\text{mg/m}^2$$

$$= \sqrt{\frac{(\text{inches}) \times (\text{lbs})}{3131}} \times 50 = \_\_\_\_\,\text{mg}$$

Date	β-hCG titer	Ultrasound results	MTX dose	Comments

Protocol for following β-hCG titers after methotrexate administration:

Following the administration of methotrexate a repeat β-hCG titer will be measured 4 and 7 days after the injection. It is important to realize that in most cases the β-hCG titer performed 4 days after the injection will continue to go up. It takes several days before the methotrexate gets incorporated into the cell cycle.

1. If there is greater than a 10% decline between post-treatment days 4 and 7, then weekly β-hCG titers are obtained and the levels will be followed until they are negative.
2. If there is less than a 10% decline between post-treatment days 4 and 7, a second dose of methotrexate 50 mg/m^2 can be administered and β-hCG are assessed on days 11 and 14.
3. If there is less than 5% decline between days 11 and 14, a third dose may be considered. Laparoscopic evaluation may be an alternative.

Instructions Following Methotrexate Administration

Over the next two weeks you should:

- ❑ Not drink alcohol.
- ❑ Not take folic acid or vitamins that contain folic acid.
- ❑ Avoid excessive exposure to the sun and you should not use a sun lamp.
- ❑ Avoid the use of aspirin-like compounds, including: Advil, Motrin, Ibuprofen, Naprosyn, Aleve, etc.
- ❑ Avoid any immunizations or vaccines since methotrexate can affect your immune system.
- ❑ Otherwise continue with your normal activities and if you have any other symptoms, including abdominal pain, or pain at the injection site, please contact us immediately.
- ❑ Oral contraceptives or barrier contraception are recommended until the pregnancy level is negative.

CONSENT FORM FOR TREATMENT WITH OVULATION INDUCTION MEDICATIONS AND INTRAUTERINE INSEMINATIONS

INTRODUCTION

Ovulation induction medications can help an infertile woman achieve a pregnancy by stimulating the ovulation of eggs from the ovaries. Ovulation inducing medications are often used in conjunction with intrauterine inseminations. Sometimes intrauterine inseminations are used without any preceding medications. This document explains ovulation inducing medications and intrauterine insemination treatment.

This consent is valid for a period of one calendar year after it has been signed. Please make a copy for your records. It is recommended that you review the consent prior to each treatment cycle. If you have any questions about your treatment then it is your responsibility to speak with your physician.

Pretreatment recommendations:

During treatment a woman should avoid any activity, behavior, and medications that could reduce her chance of conceiving and having a healthy baby. In addition, the recommendations listed below should be followed.

1. A prenatal vitamin should be taken on a daily basis before the treatment is begun. This will reduce the chance that a baby will be born with a neural tube defect (e.g. spina bifida), which is a birth defect that effects the development of the spine.
2. Smoking must be avoided before and during treatment. It is also contraindicated during pregnancy.
3. Recreational drugs are absolutely contraindicated.
4. Ingestion of aspirin or aspirin-like products (e.g. Motrin, Advil, Anaprox, Naprosyn, Aleve, etc.) should be avoided during treatment. However, in certain circumstances your doctor may prescribe low dose aspirin (baby aspirin, 81 mg). Tylenol is safe to take before and during pregnancy.
5. The use of alcohol should be avoided during treatment and after pregnancy is established.
6. The use of all prescription and over-the-counter medications (including herbal remedies) should be discussed with a physician before starting a treatment cycle.
7. HIV (human immunodeficiency virus) screening is strongly recommended for all couples undergoing infertility treatment. HIV is the virus that causes acquired immunodeficiency syndrome (AIDS). A woman infected with HIV can pass the virus to her unborn child. Please talk to your physician about having this test performed.
8. Ingestion of some fish, which contain higher amounts of mercury, can affect the development of the nervous system of a fetus. During the treatment and after pregnancy is established you should avoid eating these fish – shark, swordfish, king mackerel, tilefish, and canned tuna fish. You should limit the intake of all other fish to 12 oz per week.

DESCRIPTION OF TREATMENT

This treatment involves several steps as outlined below. Patients are not guaranteed success at any or all of these steps. If optimal results are not achieved at any step, it may be recommended that the treatment is stopped and the cycle cancelled.

I. Ovulation induction

The eggs are present in the ovaries within fluid-filled cysts called follicles. During a woman's menstrual cycle, usually one mature follicle develops, which results in the ovulation of a single egg. Several hormones including follicle stimulating hormone (FSH) and luteinizing hormone (LH) influence the growth of the ovarian follicle. These hormones are produced by the pituitary gland, which is located at the base of the brain. FSH is the main hormone that stimulates the growth of the follicle, which produces an estrogen hormone called *estradiol*. When the follicle is mature, a large amount of LH is released by the pituitary gland. This surge of LH helps to mature the egg and leads to ovulation 36–40 hours after its initiation.

There are two approaches for ovulation induction that are detailed below:

Medicated approach – This is the most common approach to ovulation induction in women undergoing IUI. Medications are administered to increase the number of follicles that develop, which will increase the number of eggs that are released. There are several medications that can be used for this phase of treatment.

1. *Gonadotropins* – these are injectable medications commonly prescribed to stimulate the ovaries of women undergoing IVF treatment. Two types of gonadotropins can be prescribed and are discussed below.

   (a) FSH (Gonal-F®, Follistim®, Fertinex®, Bravelle®) – these medications contain only FSH and are administered on a daily basis by injection.

   (b) LH (Luveris®) – this medication contains only LH and is administered by injection. It is used in combination with FSH containing medications.

   (c) Human menopausal gonadotropins (Pergonal®, Repronex®) – these medications contain equal amounts of FSH and LH, and are administered on a daily basis by injection.

2. *GnRH agonist (Lupron®)* – this synthetic hormone is administered by an injection. The administration of Lupron initially causes release of FSH and LH from the pituitary gland. However, with continued administration there is a temporary depletion of FSH and LH, which suppresses an LH surge, thereby preventing ovulation. Lupron is administered in conjunction with gonadotropins.

   There are several ovulation induction protocols that utilize Lupron. The first involves the daily administration of Lupron beginning approximately one week before the anticipated menstrual period. Lupron is administered by itself until the menstrual period occurs, generally 7–21 days later. After the menstrual period occurs, the dose of Lupron is decreased and gonadotropins are started. When this protocol is used it is advised that contraception be used following the menstrual period until the start of Lupron. For those women with irregular menstrual cycles the Lupron can be started after a period is induced by progesterone or birth control pills. The second protocol involves a combination of a dilute dose of Lupron and gonadotropins started soon after the menstrual period has begun.

   Although Lupron is approved by the Food and Drug Administration (FDA) for treatment of endometriosis, uterine fibroids, precocious puberty, and prostate cancer in men, it is not FDA approved for the treatment of infertility. However, most fertility centers in the United States and the world have used Lupron (or other GnRH agonists) for many years for this purpose.

3. *GnRH antagonist (Cetrotide®, Ganirelix®)* – GnRH antagonists are medications that reversibly bind to GnRH receptors in the pituitary gland and prevent release of FSH and LH. GnRH antagonists are administered in combination with gonadotropins. The major benefit of a GnRH antagonist is that it suppresses an LH surge, thereby preventing ovulation.

4. *Clomiphene citrate (Clomid®, Serophene®)* and letrozole *(Famara®)* – these medications are synthetic hormones that are taken orally for a period of 5 days and cause the release of FSH and LH, which stimulate the development of follicles. These medications are used in combination with injectable medications.

5. Human chorionic gonadotropin [hCG] (Profasi®, Ovidrel®, Pregnyl®, Novarel®) – this medication contains the pregnancy hormone hCG, which functions similarly to LH. It is administered approximately 36 hours before the IUI by subcutaneous injection and matures the eggs, which will allow them to become fertilized.

Note: Many of the medications that are used are administered by an injection. The patient or another person can be instructed to give these injections.

(Continued)

Side-effects

The use of the above listed medications can cause side-effects such as nausea, vomiting, hot flashes, headaches, mood swings, visual symptoms, memory difficulties, joint problems, weight gain, and weight loss, all of which are temporary. Rare allergic reactions are also possible. Other possible side-effects include the following:

- *Ovarian hyperstimulation* – After ovulation the follicles can fill up with fluid and form cysts. The formation of cysts will result in ovarian enlargement and can lead to lower abdominal discomfort, bloating, and distention. These symptoms generally occur within 2 weeks after hCG administration. The symptoms usually resolve within 1–2 weeks without intervention. If ovarian hyperstimulation occurs your physician may recommend a period of reduced activity and bed rest. Pregnancy can worsen the symptoms of ovarian hyperstimulation. Severe ovarian hyperstimulation is characterized by the development of large ovarian cysts and fluid in the abdominal and, sometimes, chest cavities. Symptoms of severe ovarian hyperstimulation include abdominal distention and bloating along with weight gain, shortness of breath, nausea, vomiting, and decreased urine output. Approximately 1–2% of women will develop severe ovarian hyperstimulation and may need to be admitted to the hospital for observation and treatment. To help alleviate the symptoms of severe ovarian hyperstimulation an ultrasound-guided paracentesis can be performed which results in the removal of fluid from the abdominal cavity. Rare, but serious consequences of severe ovarian hyperstimulation include formation of blood clots that can lead to a stroke, kidney damage, and possibly death. Every woman who takes these medications can develop ovarian hyperstimulation, but the chance is higher in a woman with a high blood estradiol level and a large number of ovarian follicles. In some cases when the estradiol level is significantly elevated, the cycle may be cancelled or possible converted to IVF.
- *Ovarian torsion (twisting)* – In less than 1% of cases, a fluid filled cyst(s) in the ovary can cause the ovary to twist on itself. This can decrease the blood supply to the ovary and result in significant lower abdominal pain. Surgery may be required to untwist or possibly remove the ovary.
- *Ovarian cancer* – In the general population, every woman has a 1 in 70 chance of developing ovarian cancer during her lifetime. Studies have shown that infertile women have a higher chance of developing ovarian cancer than fertile women. Controversial data exist that associate the use of ovulation induction drugs (e.g., clomiphene citrate, gonadotropins) with an increased risk of ovarian cancer. However, presently a cause and effect relationship has not been clearly established.

Non-medicated approach – Non-medicated IUI treatment is less commonly used than the medicated approach. If a woman has regular menstrual cycles, a non-medicated cycle may be considered. With this approach, the development of the single follicle is monitored with an ovulation predictor kit or blood tests and ultrasound examinations. When the follicle is mature and ovulation is imminent, the IUI treatment will be planned. In contrast to the medicated approach, there is a lower chance of pregnancy because only one egg is released for possible fertilization.

Monitoring – During the ovulation induction phase of treatment, monitoring of follicular development is performed with periodic blood hormone tests and/or vaginal ultrasound exams. Monitoring helps the physician to determine the appropriate dose of the medications and the timing of the egg retrieval. Vaginal ultrasound examinations are usually painless and generally considered to be safe. However, the possibility of harm cannot be excluded. Blood drawing may be associated with mild discomfort and, possibly, bruising, bleeding, infection, or scar at the needle sites. The need for repeated ultrasound examinations and/or blood drawing on a frequent basis requires the woman's presence in the vicinity of a monitoring site.

II. Intrauterine insemination

Around the time of ovulation, a woman receiving ovulation inducing medications will be instructed to either have intercourse or an intrauterine insemination (IUI) with a washed sperm sample. On the day of the IUI treatment, the male partner will be asked to produce a semen specimen at the center. The semen sample can be produced at home as long as it can be brought into the center within one hour after it is produced.

(Continued)

It is important that the semen sample is kept at body temperature during transport. The semen sample will then be washed and prepared. In some cases the woman (or couple) may elect to use a donor sperm sample.

To perform an IUI a speculum is placed in the vagina and the cervix is visualized. Sperm are loaded into a catheter, which is inserted through the cervical canal and into the uterine cavity. Following the insemination normal activity can be resumed. Because a catheter is inserted into the uterine cavity during the insemination treatment, there is always the risk of a pelvic infection following the treatment. Symptoms of an infection include fever, vaginal bleeding, chills, and abdominal pain. If any of these symptoms occur you should contact your physician. If you should have any difficulty in contacting your physician you should proceed to the emergency department of the nearest hospital. In rare cases, hospitalization with intravenous antibiotics and/or surgery (to remove ovaries, fallopian tubes, or the uterus) may be necessary. As a result fertility may be impaired in some cases.

III. Treatment following ovulation

Fourteen days after ovulation has occurred, a blood pregnancy test can be performed. If this test is found to be positive, a repeat pregnancy test may be done 2–3 days later. If the test results are encouraging, a vaginal ultrasound will be done approximately 4 weeks after the treatment to determine the status of the pregnancy. Because of the potential for complications following ovulation induction, the woman should have access to medical care up to the time of the pregnancy test, and beyond if pregnancy is established. If travel is absolutely necessary, it should be discussed with a physician.

TREATMENT OUTCOMES

The success (the delivery of a live born infant) following a cycle of treatment with the administration of ovulation induction medications is between 5–20% per cycle. The development of a pregnancy following this treatment is dependent on many factors, some of which include: the age of the woman, the infertility diagnosis, the number of previous cycles of treatment, the number of follicles that develop, and the quality of the sperm.

The following is a list of common events when pregnancy does not lead to the birth of a single baby:

Miscarriage – The risk of miscarriage in the general population is 15–20%. The risk of miscarriage increases with the age of the woman and for women over 40 years of age, the risk may exceed 50%. Studies have shown either no increase or a slight increase in the risk of miscarriage in women who conceive with this treatment. Most miscarriages are associated with lower abdominal cramping and bleeding, but do not necessarily require treatment. In some cases, however, complete removal of the pregnancy tissue must be accomplished by a surgical procedure called a dilatation and curettage (D&C). This procedure is usually performed under anesthesia in the operating room and involves placing a suction tube into the uterine cavity to remove the pregnancy tissue.

Tubal (ectopic) pregnancy – An ectopic pregnancy may develop as a result of this treatment. The majority of ectopic pregnancies are present in the fallopian tube. The chance of tubal pregnancy is greater in a woman with damaged tubes. If a woman has a tubal pregnancy, she may need surgical treatment, which may involve the removal of the involved tube. Medical treatment with methotrexate may be an option in selected cases.

Multiple pregnancy – The administration of ovulation induction medications can result in the ovulation of more than one egg, which increases the chance of a multiple pregnancy. The chance of multiple pregnancy ranges from 8–25%, which is in part dependent on the medication that is used. For instance, following clomiphene citrate treatment the multiple pregnancy rate ranges between 8–12%. When the injectable medications are used (gonadotropins) the multiple pregnancy rate is between 20–25%. Of the multiple pregnancies, approximately 80% are twins and the remainder (20%) are triplets and quadruplets. The chance of quadruplets is less than 2% of all pregnancies. Rarely, more than quadruplets can result.

(Continued)

All multiple pregnancies are associated with an increased risk of most complications of pregnancy including, but not limited to, miscarriage, toxemia, congenital anomalies, gestational diabetes in the mother, and premature labor and birth. Premature birth is the single greatest cause of death or disability in newborn infants. In contrast to a single intrauterine pregnancy, a multiple pregnancy may pose increased emotional and financial hardship.

If a multiple pregnancy develops, the couple may consider being referred to a specialist who can perform a multifetal reduction procedure. This procedure, which is performed at approximately 3 months of pregnancy, is done to reduce the number of pregnancy sacs to a lower and safer number. Although this procedure is successful 90–95% of the time, a complete miscarriage may result. The best time to discuss the risks of multiple pregnancy and multifetal pregnancy reduction with your physician is before your treatment cycle begins.

Other risks – Most infants who have been born following fertility treatment are normal. The rate of congenital abnormalities (birth defects) in the general population is 2–3% and is not different in babies conceived following this treatment. It is important to be aware that genetic abnormalities, structural abnormalities, mental retardation, and other abnormalities may occur following this treatment or as they do in pregnancies conceived naturally.

Psychological risks – Undergoing infertility treatment can be psychologically stressful. Anxiety and disappointment may occur at any point during and after treatment. Significant commitment of time and at times finances may be required. All couples are encouraged to meet with a counselor.

There are many complex and sometimes unknown factors, which may prevent the establishment of pregnancy. Known factors, which may prevent the establishment of pregnancy, include, but are not limited to, the following:

1. The ovaries may not respond to the medications or the ovarian follicles may not develop during the treatment.
2. The ovaries may over respond to the medication and the cycle may be cancelled because of the increased risk of ovarian hyperstimulation and/or multiple pregnancy.
3. The male partner may be unable to ejaculate or the semen sample may be of poor quality.
4. The passage of the catheter into the uterus may be technically difficult or impossible.
5. Even if the insemination is successfully performed, pregnancy may not result.
6. If a pregnancy is established, it may not develop normally.
7. Equipment failure, infection, technical problems, human errors, and/or other unforeseen factors may result in loss or damage to the semen sample.

The foregoing general information is based upon the experience and knowledge of the physicians. It is based, in part, upon a review of the literature pertaining to reproductive medicine. This information is generally accurate and comprehensive, however medicine is a dynamic discipline and reproductive medicine in particular is constantly evolving. Estimates of risks factors and the relative benefits of alternative treatment that have been discussed with you represent the best professional judgment of your physicians and caregivers taking into account your specific needs and circumstances.

ACKNOWLEDGEMENT OF INFORMED CONSENT AND AUTHORIZATION

We acknowledge that we, the undersigned, are voluntarily seeking treatment with **Ovulation Induction Medications and Intrauterine Inseminations** in order to conceive a child. We will acknowledge our natural parentage of any child or children born through this treatment.

We have discussed this treatment in detail with our physician and caregivers in language that we understand. We understand the purpose, risks, and benefit of the treatment. **We acknowledge that we have read all pages of this consent form and all of our questions concerning the treatment have been fully answered to our satisfaction.**

By consenting to treatment we accept the responsibilities, conditions, and risks involved as set out in this document and as explained by the staff. In addition, we consent to the techniques and procedures used to accomplish this treatment described in this document and as explained by the physicians and staff.

We understand and acknowledge that medicine is not an exact science and that in cases of doubt our physicians and caregivers will exercise their best professional judgment.

We acknowledge and agree that acceptance into treatment and our continued participation is within the sole discretion of our physicians. We understand that should this cycle be unsuccessful, it may be determined that further treatment may not be indicated.

We agree to notify BIVF immediately in writing of any change in our marital status including separation or divorce.

We also understand that we are financially responsible for any medical expenses that are not covered by our insurance policy.

By signing this document we acknowledge that we have had a thorough discussion with our physician and caregivers. This discussion included information on the risks, benefits, side-effects, and complications of the treatment. Furthermore, we acknowledge that the discussion with our physician provided sufficient information to allow us to make an informed decision whether or not to proceed with treatment. The discussion with our physician included alternatives including the option of having no treatment.

By signing this document we acknowledge that our physician and caregivers have obtained from us informed consent to proceed with Ovulation Induction Medications and Intrauterine Inseminations

_____	_____	_____
Signature of Patient	Signature of Partner	Signature of Physician
_____	_____	_____
Printed Name	Printed Name	Witness
_____	_____	
Date of Birth	Date of Birth	
_____	_____	
Date	Date	

CONSENT FORM FOR A HYSTEROSALPINGOGRAM

A hysterosalpingogram is an x-ray procedure that is performed to examine the uterine cavity and to determine whether the fallopian tubes are open. This procedure is commonly performed to identify potential causes of infertility. In addition, it can be performed to examine the uterine cavity in women who have irregular or heavy menstrual periods.

PROCEDURE

First, a pelvic examination is performed and a speculum is inserted into the vagina to visualize the cervix. An instrument is attached to the cervix and then a small tube is placed in the outer opening of the cervix. Through this tube an iodine-containing solution is injected into the uterine cavity. The progress of the injected solution into the uterine cavity and the fallopian tubes is followed by viewing a television monitor. Generally, the test is completed within 4–5 minutes. The test can be associated with lower abdominal cramping that subsides after the test is completed.

COMPLICATIONS

The complication rate from this procedure is less than 2%. Some of the complications include the following:

1. **Pelvic infection** – The performance of this test can result in an infection that could produce lower abdominal pain and fever that develop within a few days following completion of the procedure. A consequence of this infection may be scarred fallopian tubes and infertility. Infections are more likely to occur in women who have already had a previous pelvic infection and/or damaged tubes. If an infection develops, hospitalization with IV antibiotics and, potentially, surgery may be indicated.
2. **Allergic reaction** – The contrast medium that is used contains iodine. **If you have had any allergic reaction to iodine, a reaction following a radiologic procedure [i.e. Cat (CT) scan, intravenous pylogram (IVP)] please notify the physician.** This could be suggestive of an iodine allergy.
3. **Exposure of potential pregnancy** – Despite your perception of a normal menstrual period, there is always the possibility of a potential pregnancy. If your last menstrual period was abnormal, either delayed or lighter, you should notify your physician.

INSTRUCTIONS FOLLOWING THE TEST

Following the completion of the test you can return to your normal routine. If you develop any fever, chills, severe abdominal pain, or heavy vaginal bleeding, you should contact the physician immediately. If you should have any difficulty in contacting your physician you should proceed to the emergency department of your nearest hospital.

ACKNOWLEDGEMENT OF INFORMED CONSENT AND AUTHORIZATION

I acknowledge that I have read and understand this written material. I understand the purpose, risks, and benefits of this procedure. I am aware that there may be other risks and complications not discussed that may occur. I also understand that during the course of the procedure, unforeseen conditions may be revealed requiring the performance of additional procedures. I also understand that technical problems with the instrumentation may prevent the completion of the procedure. I acknowledge that no guarantees or promises have been made to me concerning the results of this procedure or any treatment that may be required as a result of this procedure. This procedure has been explained to me in language that I understand. **I have been given the opportunity to ask questions which have been answered to my satisfaction.** I have also considered other options and alternatives**. I consent to the performance of the procedure described above**.

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Signature of Patient Signature of Physician

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Printed Name

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Date

CONSENT FORM FOR A SONOHYSTEROGRAM

A sonohysterogram is a procedure that is performed to examine the uterine cavity. This procedure may help to determine the cause of a woman's infertility or abnormal bleeding. For women with uterine fibroids, the sonohysterogram is helpful to determine whether the fibroids have entered the uterine cavity.

PROCEDURE

The procedure is performed in the office. First, a pelvic examination is performed with insertion of a speculum into the vagina to visualize the cervix. Next, a small catheter is inserted through the cervical canal into the uterine cavity. After the catheter is put in place, a vaginal ultrasound probe is inserted into the vagina. Once the uterus is visualized saline is injected through the catheter into the uterine cavity. The progress of the saline into the uterine cavity is followed by viewing the ultrasound screen. Generally, the test is completed within 4–5 minutes. The test can be associated with mild lower abdominal cramping that subsides after the test is completed.

COMPLICATIONS

Complications following this procedure are uncommon. Some of the risks include the following:

1. **Pelvic infection** – The performance of this test can result in an infection that could produce lower abdominal pain and fever that develop within a few days following completion of the procedure. A consequence of this infection may be scarred fallopian tubes and infertility. Infections are more likely to occur in women who have already had a previous pelvic infection and damaged tubes. If an infection develops, hospitalization with IV antibiotics and, potentially, surgery may be indicated.
2. **Exposure of potential pregnancy** – If your last menstrual period was not normal or there is a possibility that you could be pregnant please request that a pregnancy test be performed before the procedure.

INSTRUCTIONS FOLLOWING THE TEST

Following the completion of the test you can return to your normal routine. If you develop any fever, chills, severe abdominal pain, or heavy vaginal bleeding, you should contact the physician immediately. If you should have any difficulty in contacting your physician you should proceed to the emergency department of your nearest hospital.

ACKNOWLEDGEMENT OF INFORMED CONSENT

I acknowledge that I have read and understand this written material. I understand the purpose, risks, and benefits of this procedure. I am aware that there may be other risks and complications not discussed that may occur. I also understand that during the course of the procedure, unforeseen conditions may be revealed requiring the performance of additional procedures. I also understand that technical problems with the instrumentation may prevent the completion of the procedure. I acknowledge that no guarantees or promises have been made to me concerning the results of this procedure or any treatment that may be required as a result of this procedure. This procedure has been explained to me in language that I understand. **I have been given the opportunity to ask questions which have been answered to my satisfaction.** I have also considered other options and alternatives**. I consent to the performance of the procedure described above**.

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Signature of Patient Signature of Physician

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Printed Name

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Date

CONSENT FORM FOR AN ENDOMETRIAL BIOPSY

An endometrial biopsy is a procedure that involves the removal of endometrial tissue from the uterine cavity for examination. The endometrial biopsy can be performed as part of an infertility evaluation to assess the adequacy of the uterine lining, which is influenced by progesterone levels in the blood. In addition, women who have a history of abnormal bleeding, irregular or absent menstrual periods, or have had a previous endometrial biopsy demonstrating the presence of infection, may benefit from the performance of an endometrial biopsy.

PROCEDURE

The procedure is performed in the office. First, a speculum is placed in the vagina to visualize the cervix. A small plastic catheter is then inserted into the cervical canal and into the uterine cavity. In some cases, it may be necessary to attach an instrument to the cervix to help pass the biopsy catheter into the uterine cavity. After the catheter is inserted, a biopsy of the endometrium is aspirated into the catheter, which is then removed. In most cases, the biopsy is completed within 4–5 minutes. This procedure can be associated with some lower abdominal cramping which will subside after the biopsy is completed. The endometrial biopsy is then sent to the laboratory for an examination by a pathologist. Results of the biopsy are available approximately one week after it is performed.

COMPLICATIONS

Complications following this procedure are uncommon. Some of the complications include the following:

1. **Pelvic infection** – The performance of this test can result in an infection that could produce lower abdominal pain and fever that develop within a few days following completion of the procedure. A consequence of this infection may be scarred fallopian tubes and infertility. If an infection develops, hospitalization with IV antibiotics and surgery may be indicated.
2. **Exposure of potential pregnancy** – If your last menstrual period was not normal or there is a possibility that you could be pregnant please request that a pregnancy test be performed before the procedure. However, if the pregnancy is too early the pregnancy test may be negative. If the endometrial biopsy is performed during an early pregnancy there is a possibility that the performance of the biopsy could increase the chance of a miscarriage.
3. **Uterine perforation** – An uncommon complication of this procedure is uterine perforation. If this occurs, the procedure is stopped. Perforation can result in injury to other organs including the intestines, bladder, uterus, and blood vessels. Injury to these organs could result in a hospitalization and additional treatment that could include surgery to repair the injury.

INSTRUCTIONS FOLLOWING THE TEST

Following the completion of the test, you can return to your normal routine. If you develop any fever, chills, severe abdominal pain, or heavy vaginal bleeding, you should contact the physician immediately. If you should have any difficulty in contacting your physician you should proceed to the emergency department of the nearest hospital.

ACKNOWLEDGEMENT OF INFORMED CONSENT

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Signature of Patient Signature of Physician

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Printed Name

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Date

CONSENT FORM FOR A LAPAROSCOPY

A laparoscopy is an outpatient surgical procedure that is performed to diagnose and treat conditions of the pelvic organs such as infertility, pelvic pain, pelvic masses, and other disorders.

PROCEDURE

During the evening before the procedure it is important that you do not eat or drink anything after midnight. When you arrive at the surgical suite, an anesthesiologist will place an intravenous line. You will then be taken to the operating room and general anesthesia will be administered. At the start of the procedure a pelvic examination is performed and an instrument is inserted into the uterine cavity that allows manipulation of the uterus during the procedure. Next, a small incision (1–2 cm) is made just below the navel through which a small telescopic instrument, called a laparoscope, is inserted into the abdominal cavity. Usually, one to three additional incisions are made in the lower abdomen through which other instruments can be inserted. After all the instruments are in place, a systematic inspection of the pelvis is performed including an examination of the uterus, fallopian tubes, ovaries, and all other surrounding organs. If either pelvic adhesions or endometriosis is identified, a decision may be made to treat these conditions at the time of the surgery with the laser, electrocautery, or scissors. If a cyst or a mass is identified in the region of the ovary or the fallopian tube, a decision may be made to remove it. At the end of the procedure, a non-toxic colored dye may be injected into the uterine cavity to determine if the fallopian tubes are open. Depending on the findings, the procedure may take between 1–3 hours to complete.

POSTOPERATIVE CARE

After the procedure has been completed, you will spend a few hours in the recovery room and then be discharged home. Since you may be drowsy following the procedure, it is important that someone is available to transport you home and stay with you. It is not uncommon to have some vaginal spotting and mild lower abdominal cramping following the procedure. You will be prescribed a medication to provide pain relief following the procedure. You should plan on resting the following day after the surgery. There are no restrictions on showering or bathing. You should refrain from intercourse for one week following the procedure. If at any time during the postoperative course you develop any fever, chills, severe abdominal pain, heavy vaginal bleeding, or any other symptoms you should call your physician immediately. If you should have any difficulty in contacting your physician you should proceed to the emergency department of your nearest hospital.

COMPLICATIONS

Serious complications following a laparoscopy are rare. Because sharp instruments are used to insert the instruments, there is the potential to injure vital organs, some of which include the intestines, bladder, ureters, uterus, major blood vessels, and other pelvic organs. Injury could necessitate a hospitalization and the performance of additional surgery. If a significant complication occurs you would be transported by ambulance to a nearby hospital for further treatment. Additional surgery could include a life-saving hysterectomy and/or resection of damaged intestine with a colostomy. Death is a very rare complication following this procedure.

ACKNOWLEDGEMENT OF INFORMED CONSENT

I acknowledge that I have read and understand this written material. I understand the purpose, risks, and benefits of this procedure. I am aware that there may be other risks and complications not discussed that may occur. I also understand that during the course of the procedure, unforeseen conditions may be revealed requiring the performance of additional procedures. I also understand that technical problems with the instrumentation may prevent the completion of the procedure. I acknowledge that no guarantees or promises have been made to me concerning the results of this procedure or any treatment that may be required as a result of this procedure. This procedure has been explained to me in language that I understand. **I have been given the opportunity to ask questions which have been answered to my satisfaction.** I have also considered other options and alternatives**. I consent to the performance of the procedure described above**.

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Signature of Patient Signature of Physician

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Printed Name

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Date

CONSENT FORM FOR A HYSTEROSCOPY

A hysteroscopy is an outpatient surgical procedure that allows visualization of the uterine cavity. This procedure allows the diagnosis and treatment of uterine abnormalities that could be a cause of infertility or abnormal bleeding.

PROCEDURE

During the evening before the procedure it is important that you do not eat or drink anything after midnight. When you arrive at the surgical suite, an anesthesiologist will start an intravenous line. You will then be taken to the operating room and the anesthesia will be administered. You will be placed in the same position as you are for a pelvic exam. A speculum is introduced into the vagina and the cervix is visualized. After the cervical canal is dilated, a small telescope-like instrument, called a hysteroscope, is inserted into the uterine cavity. Distention of the cavity with a solution then allows examination of the uterine cavity. If any abnormalities are identified, such as a polyp, fibroid, uterine septum, or intrauterine adhesions, special instruments can be introduced and an attempt can be made to treat the condition. In some cases following the hysteroscopy, a uterine curettage is performed which involves the placement of a small instrument, called a curette, into the uterine cavity, which allows sampling of endometrial tissue.

POSTOPERATIVE CARE

After the procedure has been completed, you will spend a few hours in the recovery room and then be discharged home. Since you may be drowsy following the procedure, it is important that someone is available to transport you home and be with you. It is not uncommon to have some vaginal bleeding and mild lower abdominal cramping following the procedure. You should plan on resting the following day after the surgery. There are no restrictions on showering or bathing. You should refrain from intercourse and douching for one week following the procedure. If during the postoperative course you develop any fever, chills, severe abdominal pain, heavy vaginal bleeding, or any other abnormal symptoms, call your physician immediately. If you should have any difficulty in contacting your physician you should proceed to the emergency department of the nearest hospital.

COMPLICATIONS

Serious complications following a hysteroscopy are rare. One complication from this procedure is perforation of the wall of the uterus. If this occurs, the procedure is stopped and a decision may be made to examine the injury site by a laparoscopy. In most instances, the bleeding at the perforation site is minimal, and the perforation heals without problems. Perforation can result in injury to adjacent organs including the intestines, bladder, ureters, uterus, and blood vessels. Injury to these organs could result in a hospitalization and additional surgery to repair the injury. Additional surgery could include a life-saving hysterectomy and/or resection of damaged intestine with a colostomy. Another complication following a hysteroscopy is fluid overload. Fluids are used to distend the uterine cavity to allow the procedure to be performed. Some fluid is absorbed into the blood vessels. The amount of fluid absorbed is followed carefully to avoid fluid overload. Fluid overload can compromise the function of the heart and lungs. In rare cases fluid overload can cause brain injury. Death is a very rare complication following a hysteroscopy.

ACKNOWLEDGEMENT OF INFORMED CONSENT

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Signature of Patient Signature of Physician

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Printed Name

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Date

CONSENT FOR METHOTREXATE TREATMENT

INTRODUCTION

When a normal pregnancy is established the fertilized egg or the embryo implants in the uterine cavity. However, sometimes the embryo implants outside of the uterine cavity. This situation is referred to as an ectopic pregnancy and cannot lead to a normal pregnancy. The vast majority of ectopic pregnancies (>95%) occur in the fallopian tube but an ectopic pregnancy can also implant in the cervix, ovary, or abdominal cavity. The major concern with an ectopic pregnancy is that it can rupture through the fallopian tube and result in internal bleeding.

In the past, the diagnosis of tubal pregnancy was made when the pregnancy was more advanced and surgical removal of the tube was usually necessary. With the development of vaginal ultrasound and a sensitive pregnancy test, the diagnosis of an ectopic pregnancy can be made earlier. When the diagnosis is made at an earlier stage, there is a greater likelihood that the ectopic pregnancy can be removed surgically and the fallopian tube can be conserved.

Methotrexate administration is available as an alternative to surgery. This medication stops rapidly dividing cells from multiplying (pregnancy tissue grows in this fashion). Methotrexate is a chemotherapy drug, which has been used to treat women with molar pregnancies. Molar pregnancies are non-viable intrauterine pregnancies that are made up of very aggressive placental tissue that can grow into the wall of the uterus. Several studies have demonstrated that properly selected patients with ectopic pregnancies can be successfully treated with methotrexate.

INDICATIONS FOR METHOTREXATE

Methotrexate treatment has several applications in the treatment of ectopic pregnancy, which are discussed below.

1. **Persistent ectopic pregnancy following conservative surgery** – If the diagnosis is made early, an ectopic pregnancy can be removed from the fallopian tube by a surgical procedure called laparoscopy. This procedure is performed under general anesthesia and involves the placement of a telescope-like instrument and other instruments through small incisions in the abdomen. A small incision is made in the tube over the ectopic pregnancy and the pregnancy tissue is removed. However, not all of the tissue can be removed and some remains in the tube. In the majority of cases, the remaining pregnancy tissue goes away on its own but in other cases the tissue can remain in the tube and continue to grow. Following conservative surgery periodic blood samples are taken to follow the level of the pregnancy hormone, human chorionic gonadotropin (hCG). As long as the hCG level decreases no intervention is necessary. However, if the hCG levels plateau or increase, additional treatment is indicated. Treatment options include repeat laparoscopy with possible removal of the fallopian tube or medical treatment with methotrexate.
2. **An ectopic pregnancy in a location that is not amenable to conservative surgery** – If the ectopic pregnancy is located in the cervix, the ovary, or in the portion of the tube that is located in the uterine wall, surgical removal may be difficult and potentially complicated. Treatment with methotrexate is another alternative.
3. **A woman who is a poor operative risk** – Medical treatment can be considered for the woman who is at greater risk for surgical or anesthetic complications.
4. **A presumed ectopic pregnancy** – Some women who achieve pregnancy have slowly rising levels of pregnancy hormone. In this situation, there is no chance for a viable pregnancy. This occurrence can be the result of a failed intrauterine pregnancy or an ectopic pregnancy. Another presentation of an ectopic pregnancy is when an ultrasound exam fails to document an intrauterine pregnancy at 6 weeks of pregnancy and/or when the hCG titer has reached 2000 mIU/ml. In these situations there are several alternatives:
   (a) ***Performance of a D&C*** – This procedure involves placing an instrument into the uterine cavity to remove the pregnancy tissue. This surgery is performed under anesthesia. A pathologist can examine the tissue and if pregnancy tissue is identified, the presence of a failed intrauterine pregnancy is confirmed and no further treatment is indicated. Alternatively, if the pathologist fails to identify pregnancy tissue, then this raises further suspicion of an ectopic pregnancy. If this occurs, there are two options – medical treatment with methotrexate or surgical treatment by laparoscopy.
   (b) ***Methotrexate treatment*** – The other option is to <u>not</u> undergo a D&C and be treated with methotrexate initially. A single intramuscular injection will be administered and you will be asked to return for weekly blood work to have the pregnancy hormone level assessed. If the level decreases, then simple observation is indicated. Alternatively, if the level increases or plateaus a second injection of methotrexate or surgery may be indicated.

5. **Confirmed ectopic pregnancy** – If an ultrasound exam confirms the presence of a gestational sac (evidence of an early pregnancy) outside of the uterine cavity then the diagnosis of an ectopic pregnancy is established. In this situation there are two options:
   (a) ***Laparoscopy*** – This is an outpatient surgical procedure that is performed under general anesthesia. The procedure involves the placement of a telescopic instrument through a small incision into the abdominal cavity, allowing visualization of the pelvic organs. When the ectopic pregnancy is localized in the tube then a small incision is made in the tube to remove the pregnancy tissue. During the postoperative period pregnancy hormone levels will be followed until they are negative. If at the time of the laparoscopy there is significant damage to the tube then partial or complete removal of the tube may be indicated. At the time of surgery the other tube will be examined to determine its condition.
   (b) ***Methotrexate treatment*** – This treatment is reviewed below.

METHOTREXATE TREATMENT

If you elect to proceed with methotrexate treatment, the first step is to obtain routine blood work. If it is determined that you are a candidate for this treatment, the methotrexate will be administered by an intramuscular injection. Side-effects may occur but usually don't appear until 2–7 days after administration. Side-effects include nausea, vomiting, abdominal pain, and loss of appetite. Sores or ulcers of the mouth, tongue, vagina, and bowel occur rarely, are usually mild, and resolve over a short period of time. Rarely, methotrexate can lower the white blood cell and platelet counts. Other very uncommon side-effects include hair loss, skin rash, dizziness, and liver dysfunction. Because of the potential liver toxicity it is important that you do not consume any alcohol while taking this medication.

A pregnancy blood level (hCG) will be determined at weekly intervals. If the level is dropping then the pregnancy hormone level will be followed periodically until it reaches zero. It can take up to 4–5 weeks or sometimes longer after the injection of methotrexate before the pregnancy hormone level reaches zero. If the pregnancy hormone level plateaus or increases, then either another injection can be administered or surgery can be performed.

It is important to remember that even though you have received methotrexate, tubal rupture can still occur and emergency surgery may be required. Therefore, you should contact your doctor immediately if you develop abdominal pain. If you should have any difficulty in contacting your physician you should proceed to the emergency department of the nearest hospital.

Even though your tubal pregnancy totally resolves on methotrexate treatment, scarring may occur in your tube as a result of the tubal pregnancy as it can follow surgical treatment. This could predispose you to a tubal pregnancy in the future and/or subsequent infertility. Your chances of conceiving after medical therapy with methotrexate are the same as after surgery. There is no increased risk of congenital anomalies in babies born to women who have taken methotrexate in the past.

It is important that during and up to 2 weeks after receiving methotrexate you should not drink any alcohol or take aspirin or aspirin-like compounds (Advil®, Motrin®, etc.), folic acid, or vitamins containing folic acid. You should also avoid excess exposure to the sun or the use of sunlamps for 4 weeks following methotrexate therapy because your skin may be more sensitive to sunlight than usual and you can burn excessively. You should also avoid intercourse until resolution.

ACKNOWLEDGEMENT OF INFORMED CONSENT

I acknowledge that I have read and understand this written material. I understand the purpose, risks, and benefits of this treatment. I am aware that there may be other risks and complications not discussed that may occur. I also understand that during the course of the treatment, unforeseen conditions may be revealed requiring the performance of additional procedures. I acknowledge that no guarantees or promises have been made to me concerning the results of this treatment or any subsequent treatment that may be required. This treatment has been explained to me in language that I understand. **I have been given the opportunity to ask questions which have been answered to my satisfaction.** I have also considered other options and alternatives**. I consent to the treatment with methotrexate.**

_____ _____

Signature of Patient Signature of Physician

_____

Printed Name

_____

Date of Birth

_____

Date

Office fee Ticket

Name:		**DOB**	**Clinician**	**Site:**	
Service Date:	**Primary Insurance:**			**Referral #**	
Reason:	**Initials:**		**Is there a co-pay? Y / N**	**Amount-**	
Outstanding balance:	**Global: Y / N**		**How was it paid?**		
	Initials:		**Any change in address/insurance? Y / N**	**Initials**	

OFFICE VISITS			DIAGNOSIS		DIAGNOSIS	
New (referred)	**PE or Time**		**INFERTILITY**		**GYNECOLOGY**	
LEVEL 1	(15)	99241	Anovulation	628.0	Pain	
LEVEL 2	(30)	99242	Cervical	628.4	Abdominal	789.67
LEVEL 3	(40)	99243	Male factor	628.8	Dysmenorrhea	625.3
* LEVEL 4	(60)	99244	Tubal factor	628.2	Dyspareunia	625.0
LEVEL 5	(80)	99245	Uterine factor	628.3	Pelvic	625.9
New (not referred)	**PE or Time**		Unexplained	628.9	PCO	256.4
LEVEL 2	(20)	99202	Other, specified origin	628.8	Premenstrual symptom	625.4
LEVEL 3	(30)	99203			Polyp Ð endometrial	621.0
LEVEL 4	(45)	99204	**ENDOCRINE**		Ð cervical	622.7
* LEVEL 5	(60)	99205	Amenorrhea	626.0	Vaginitis	616.10
Repeat office visit	**Time**		Hirsutism	704.1	**PREGNANCY**	
LEVEL 1	(5)	99211	Hyperprolactinemia	253.1	Supervision	V23.0
LEVEL 2	(10)	99212	Other ovarian dysfunction	256.8	Twin pregnancy	651.00
LEVEL 3	(15)	99213	PCO	256.4	Triplet pregnancy	651.10
* LEVEL 4	(25)	99214	Premature ovarian failure	256.31	Miscarriage: SAB	634.90
LEVEL 5	(40)	99215	**GYNECOLOGY**		Threatened	640.03
Prenatal visit	(15)	99213	Adenomyosis	617.0	Missed	632
	(25)	99214	Adhesions Ð tubal/pelvic	614.6	Habitual AB	629.9
			Annual gyn exam	V72.31	Ectopic pregnancy (tubal	633.10
Post-op visit		99024	Asherman syndrome	21.5	Ectopic pregnancy (presumed)	633.90
Annual GYN Exam			Bleeding		**OTHER DIAGNOSES**	
18-39YRS	NEW PATIENT	99385	Menorrhagia	626.2	Egg donor	V99.9
	ESTABLISHED	99395	Abnormal uterine bleeding	626.6	Genetic counseling	V26.3
40-64YRS	NEW PATIENT	99386	Unspecified	626.9	Gestational carrier	V99.9
	ESTABLISHED	99396	Cervical polyp	622.7	TDI Ð single Ð female	V26.8
			Cervical stenosis	622.4	Other specified procreative mgt	V26.8
CANCELLATION		CAN	Cervical dysplasia	622.10	Previous tubal ligation	V26.51
NO SHOW		NO SHOW	Chronic anovulation	626.1	Previous vasectomy	V26.52
			Dysmenorrhea	625.3	**Ultrasound procedures**	**Diagnosis**
Hospital Care Services			Dyspareunia	625.0	Follicle Ð initial complete 76830	628.9
Initial inpatient visit	(50)	99222	Dysuria	788.1	Follicle-F/U 76857	628.9
Repeat inpatient visit	(25)	99232	Endometrial hyperplasia	621.30	Prenatal (initial) 76817	V23.0
Discharge day	(30)	99238	Endometrial polyp	621.0	Prenatal (follow-up)	
Emergency room visit			Endometriosis:		Bleeding 76815	640.03
Level 3 (Pt discharged)		99283	of ovary	617.1	? Miscarriage 76815	632
Level 4 (Pt admitted)		99284	of fallopian tube	617.2	Twin 76815	651.00
			of pelvic peritoneum	617.3	Triplet 76815	651.10
OFFICE PROCEDURES			Herpes genitalia	054.10	Age > 34 years 76817	659.53
Cervical dilation		57800	Leiomyoma	218.9	R/O ectopic 76817	633.90
Cervical polyp removal		57500	Menopause	627.2	Other 76815	V23.0
Endometrial Bx		58100	Menstrual irregularity	626.4	Gyn US 76830	
HSG		58340	Mittleschmirtz	625.2	**Please circle any special situations:**	
Injections	IM	90772	Mullerian anomaly			
	IV	90784	Didelphys	752.2	A consultation takes place on the	–25
IUI treatment	Natural-IUI	58322	Mullerian agenesis	752.49	day of the procedure	
	CC-IUI	58322	Sept/bico/unic:	752.3		
	FSH-IUI	58322	Ovarian cyst		A decision is made to do	–57
Sonohysterogram		58340/76831	Luteal	620.1	major surgery in 1Ð2 days	
Other Services			Follicular	620.0		
Urine pregnancy test **DX V72.4**		81025	Endometrioma	617.1	A procedure is started but can	–53
Urine analysis		81000	Unspecified	620.2	not be completed	
Specimen handling		99000	Ovarian hyperstimulation	256.9/789.67		
Wet smears		87205	Ovarian torsion	620.5	Unrelated service during surgical	–24
Paracervical block		64435	PID Ð chronic	614.9	global	

Coding Tip Sheet

New patient

1. **Definition – a patient who has not seen you or another physician in your group for the last 3 years**

2. **New patient (*referred*) (CPT codes 99241–99245)**
   – an outside physician has asked that you see a patient in consultation

   - Document all necessary information including medical, social, and family history information along with review of systems
   - Complete physical exam (8 systems) performed
     - Yes – PE done, bill for 99244 or 99245 (if complicated)
     - No – document time in chart and use time as the driving factor to determine the level of coding
   - Write letter to referring physician 'I have recently seen Mary Smith in consultation…'

3. **New patient (*not* referred) (CPT codes 99202–99205)**
   – patient is self-referred or referred by a friend

   - Document all necessary information including medical, social, and family history information along with review of systems.
   - Complete physical exam
     - Yes – bill for 99205
     - No – document time in chart and use time as the driving factor to determine the level of coding

Repeat office visits
– all other visits (other than new patients)

1. No physical exam performed (follow-up, prenatal visits)
   - Use time spent with the patient to be the driving factor of the level of coding and document time spent in chart –

     'A total of ____minutes was spent face to face with the patient and >50% of the time was spent in counseling'.

2. Physical exam (5–7 systems) performed (i.e., OHSS, ectopic pregnancy, pain)
   - Use code 99215

3. At the time of an office visit if a procedure is performed (i.e., endometrial biopsy, sono-hysterogram) – attach modifier (–25) to the office visit code

Surgical coding

1. On fee ticket circle all procedures that were performed and link with diagnostic codes
2. Use modifiers for any of the following:
   (–22) – the surgery is more difficult that usual
   (–22) – an open laparoscopy is performed
   (–50) – a bilateral procedure is done
   (–53) – the procedure is started but cannot be completed
3. Document everything you did in the operative report

Understanding Your Insurance Benefits

We know that insurance and financial matters can be complicated. This document is designed to outline important insurance and financial information that you need to know while receiving services at our center.

- Please contact your insurance company as it is your responsibility to obtain your infertility benefits. Your insurance company customer service representative will help you to understand your plan**, what it covers and what it does not.**
- Your insurance company may require referrals from your primary care physician for your visits. It is your responsibility to obtain these referrals. If you are not able to obtain a referral from your primary care physician you will be charged for that visit.
- If your insurance plan imposes a dollar limit on your treatment, you are responsible for keeping track of the money paid by your insurance. Once you have met this dollar maximum, you will be responsible for the cost of services that are provided to you.
- Please notify us **immediately** of any changes to your insurance. If your coverage terminates while you are undergoing treatment, you will be financially responsible for charges incurred during your lapse in coverage. Due to the pre-authorization requirements of the insurance companies, if you change insurance plans while undergoing a treatment cycle, your cycle may be delayed or cancelled and you may be responsible for the cost of that treatment cycle. If you proceed with any treatment that has not been approved by your insurance company, you will be responsible for those charges.
- Many patients choose to freeze sperm and/or embryos at our facility. This may or may not be a covered benefit under your plan. Please check with your insurance company to determine if these services are a covered benefit for you.
- There are annual storage charges for frozen embryos as well as frozen sperm that are not covered by insurance. Your financial counselor can provide you with our current prices for these services if they apply to you.
- We require 24 hours' notice if you are canceling your appointment. If you do not cancel your appointment with 24 hours' notice or if you do not appear for your appointment you may be responsible for a cancellation fee of up to the full cost of the visit.

MY SIGNATURE BELOW INDICATES THAT I HAVE READ AND UNDERSTAND THE INFORMATION PROVIDED IN THIS DOCUMENT.

Please bring this document with you to your appointment and give to your financial counselor.

_____ _____

(Print Name) (Date)

_____

(Signature)

21.

Quick reference

Basic Infertility Evaluation
➢ CD 3-FSH, estradiol ➢ Hysterosalpingogram ➢ Semen analysis ➢ Preconceptional blood work • TSH • CBC • Blood type & screen • RPR • Antibody screens for: – Rubella – Varicella – Hepatitis – HIV • Genetic screening (if indicated) ➢ Laparoscopy (optional)

Interpretation of cycle day 3 hormone levels

FSH Level* (mIu/ml)	Estradiol Level (pg/ml)	Ovarian* Reserve
>10	<70	↓
>10	>70	↓
2–10	>70	↓
2–10	<70	normal

* Cut-off value may depend on assay method.

Clomiphene citrate challenge test
1. Cycle day 3 – FSH + estradiol levels 2. Clomiphene citrate 100 mg cycle days 5–9 3. Cycle day 10 – FSH level *Interpretation: If any of the FSH levels are >10 mIU/ml or the estradiol is >70 pg/ml the test is considered abnormal and confirms reduced ovarian reserve.*

Genetic testing based on ancestral backgrounds

Ancestral Group	Disease	Screening Test
Caucasian, Native American	Cystic fibrosis	DNA testing
French Canadian, Cajun	Tay-Sachs	Assessment of hexosaminadase enzyme activity or DNA testing
Jewish	Canavan disease Cystic fibrosis Familial Dysautonomia Tay-Sachs	DNA testing DNA testing DNA testing Assessment of hexosaminadase enzyme activity or DNA testing
African, Asian, Cambodia, Caribbean, Central America, India, Indonesia, Laos, Malaysia, Mediterranean, Middle Eastern, Pakistan, Thailand, Turkey, Vietnam	Hemoglobinopathies	CBC, Hgb electrophoresis

American Diabetes Association (ADA) threshold glucose values

Time	Normal	Borderline	Diabetes mellitus
Fasting	<100 mg/dl	100–125 mg/dl	≥126 mg/dl
2-Hour	<140 mg/dl	140–199 mg/dl	≥200 mg/dl

For screening purposes it is recommended to do a fasting blood glucose initially. If the fasting blood glucose is abnormal then a 2-hour glucose tolerance test should be performed. For this test a fasting level is measured, the patient drinks 75 g of glucose and blood is drawn again 2 hours later for a glucose determination

Internet Resources for Reproductive Toxins

Pregnancy and Environmental Hotline
http://www.thegenesisfund.org/hotline.htm

TOXLINE
http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?TOXLINE

United States Food and Drug Administration
http://www.fda.gov/cder/

Physicians Desk Reference
www.pdr.net

Reprotox
www.reprotox.org

TERIS & Shepard's Catalog of Teratogenic Agents
http://depts.washington.edu/~terisweb/

Recurrent Miscarriage Workup

1. Rule out environmental exposures and lifestyle issues
2. Assessment of ovarian function
   - Menstrual history
   - Cycle 3 – FSH, estradiol, TSH
3. Examination of uterine cavity by one of the following:
   - Hysterosalpingogram
   - Sonohysterogram
   - Hysteroscopy
4. Autoimmune workup
   - Anticardiolipin antibodies
   - Lupus anticoagulant
   - Thrombophilia workup
5. Chromosomal
   - Karyotypes on both partners

Chromosomal abnormalities in liveborn infants and maternal age*

Maternal Age	Risk for Down's Syndrome	Total Risk for Chromosomal Anomalies†
20	1/1667	1/526
21	1/1667	1/526
22	1/1429	1/500
23	1/1429	1/500
24	1/1250	1/476
25	1/1250	1/476
26	1/1176	1/476
27	1/1111	1/455
28	1/1053	1/435
29	1/1000	1/417
30	1/952	1/385
31	1/909	1/385
32	1/769	1/322
33	1/602	1/286
34	1/485	1/238
35	1/378	1/192
36	1/289	1/156
37	1/224	1/127
38	1/173	1/102
39	1/136	1/83
40	1/106	1/66
41	1/82	1/53
42	1/63	1/42
43	1/49	1/33
44	1/38	1/26
45	1/30	1/21
46	1/23	1/16
47	1/18	1/13
48	1/14	1/10
49	1/11	1/8

*The data presented above were modified from Hook DB, Cross PK, Schreinemachers DM. Chromosomal abnormality rates at amniocentesis and in live-born infants. J Am Med Assoc 1983; 249:2034–8, and Hook EB. Rates of chromosomal abnormalities at different maternal ages. Obstet Gynecol 1981; 58: 282–5

†The other chromosomal anomalies that are increased with maternal age in addition to 47,+21 (Down's syndrome) are 47,+18; and 47,+13; 47,XYY (Klinefelter's syndrome); 47,XYY and 47,XXX. The incidence of 47,XXX for women between the ages of 20 and 32 years is not available

Medication	Indications	Dosage	Comments
Progesterone	1. Recurrent miscarriages 2. IVF/egg donation treatment 3. Surgical removal of corpus luteum during first trimester	**Vaginal** – Crinone® 90 mg q.d. – suppositories 100 mg b.i.d. – Prometrium® 200 mg b.i.d. **Oral** – Prometrium 100 mg t.i.d. **Intramuscular** – Progesterone-in-oil available in 10-cc bottles (50 mg/cc); administer 50 mg q.d. (1 cc) by IM injection	1. Natural progesterone medications are not associated with an increased risk of birth defects 2. Progesterone can delay the onset of a menstrual period even if the patient is not pregnant 3. Progesterone should be discontinued by 10 weeks of pregnancy
Clomiphene citrate	1. Anovulation 2. Unexplained infertility 3. For intrauterine insemination treatment 4. See Chapter 7 for more detailed description	50–150 mg cycle days 3–7	1. Common side-effects: hot flushes, visual symptoms, emotional irritability 2. Multiple pregnancy rate – 10% 9% twins 1% triplets 3. Most pregnancies are achieved after 3–4 months of treatment
Metformin	1. Chronic anovulation/ polycystic ovarian disease 2. See Chapter 6 for detailed description	1. Metformin is available in 500 mg tablets 2. 500 mg q.d. × 1 week; then 500 mg b.i.d. × 1 week; then 500 mg t.i.d.	1. Check renal and liver studies; fasting glucose 2. Side-effects: gastrointestinal upset including diarrhea 3. See patient every 4–6 weeks. Check pregnancy test if indicated 4. Discontinue metformin with the establishment of pregnancy
Dopaminergic agents Parlodel® Dostinex®	1. Hyperprolactinemia 2. See Chapter 6 for a detailed description	1. Parlodel – 1.25 mg q.h.s. for 1 week then increase to 2.5 mg q.h.s. 2. Dostinex – 0.5 mg twice a week	1. Repeat prolactin level in 2–3 weeks and adjust dose accordingly 2. Side-effects: gastrointestinal upset, fatigue, dizziness and nasal stuffiness
Dexamethasone	1. Adrenal hyperandrogenism– need to R/O Cushing's disease and adrenal tumor 2. Used in combination with clomiphene citrate 3. See Chapter 6 for a detailed description	0.5 mg q.h.s.	1. Check AM cortisol level in 1 month if <3 µg/dl then the dose should be decreased to 0.25 mg. q.h.s. 2. Discontinue when pregnancy is achieved

Live birth rates (per cycle initiated) by age group for various IVF procedures.

	Live birth rates by age group (%)				
Treatment	*<35*	*35–37*	*38–40*	*41–42*	*Multiple pregnancy rate*
IVF (± ICSI)*	37.3	30.2	20.2	11.0	34.2%†
Frozen embryo transfer‡	29.4	28.4	22.6	16.5	
Egg donation‡			50.8		

*Live-birth rates per cycle initiated
†Multiple pregnancy rate includes: twins – 31.0% and triplets and more – 3.2%
‡Live birth rates per embryo transfer

Index

The BOSTON IVF

Handbook of Infertility

A practical guide for practitioners who care for infertile couples

Second Edition

Edited by
Steven R Bayer MD
Michael M Alper MD
Alan S Penzias MD
Boston IVF and Harvard Medical School, Boston, MA, USA

Affiliated with Harvard Medical School, Boston IVF is one of the leading outpatient fertility and in-vitro fertilization centers in the world. *The Boston IVF Handbook of Infertility* is based on the gold-standard procedures and protocols that have been developed at Boston IVF. The book provides a coherent and structured approach to treating the infertile couple that can be of benefit to the gynaecologist, reproductive endocrinologist and reproductive endocrine nurse. Both clinical and laboratory techniques are included, along with a chapter on preconception care. New chapters for this revised and enlarged edition include sections on preimplantation genetic diagnosis, third party reproduction, ethics and quality management tools to effectively operate an infertility practice. Forms and documents that can be used in clinical practice including consent forms, male and female history forms and a fee ticket that can help with billing for infertility services are presented.

Contents:

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ISBN 0-415-39432-5
9 780415 394321