Preconception care: a good beginning

Gezondheidsraad
Health Council of the Netherlands

To the Minister of Health, Welfare and Sport

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Dear Minister,

I am pleased to present herewith the advisory report entitled *Preconception care: a good beginning*.

The advisory report summarises the current level of knowledge concerning the various components of preconception health care. This summary was produced in collaboration with the Dutch Cochrane Centre, using an evidence-based approach. Given the broad nature of the topic in question, this advisory report has been reviewed by several standing committees of the Health Council.

On the basis of the scientific insights obtained, the Committee concludes that the provision of preconception advice on diet, lifestyle, diseases, use of medication, working conditions, and genetic factors can be seen as an intrinsic part of effective care. Accordingly, it would be appropriate to offer preconception health care to all prospective parents. The Committee feels that it would make sense to develop a general programme to this end.
I endorse the conclusions of the Committee.

Yours sincerely,
(Signed)
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to:

the Minister of Health, Welfare and Sport

No. 2007/19E, The Hague, September 20, 2007

The Health Council of the Netherlands, established in 1902, is an independent scientific advisory body. Its remit is “to advise the government and Parliament on the current level of knowledge with respect to public health issues...” (Section 22, Health Act).

The Health Council receives most requests for advice from the Ministers of Health, Welfare & Sport, Housing, Spatial Planning & the Environment, Social Affairs & Employment, and Agriculture, Nature & Food Quality. The Council can publish advisory reports on its own initiative. It usually does this in order to ask attention for developments or trends that are thought to be relevant to government policy.

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Executive Summary

Request for advice

Recent years have seen increasing attention focused on preconception care as a means of promoting the health of prospective parents and their children. It was this trend, together with the persistence of relatively high perinatal mortality in the Netherlands, that prompted the Minister of Health, Welfare and Sport to request that the Health Council produce an advisory report on preconception care.

The Minister asked the Council to review the current level of knowledge concerning preconception care. He also wished to know to what extent the available knowledge is already being applied, both in the Netherlands and elsewhere. A further question raised was which specific requirements a programme of preconception care would need to meet. Finally, the Minister asked the Health Council to investigate how one might reach the maximum possible number of parents-to-be, what professional groups and other bodies would need to be involved, and what ethical considerations arise in connection with preconception care.

In collaboration with the Dutch Cochrane Centre, a systematic review has been conducted of the scientific literature, using preconception care as the principal search term. This has generated a limited selection of topics on which sufficient literature with the highest level of evidence is available. In the light of the results, evidence-based recommendations have been made with regard to food, alcohol, tobacco and other recreational drugs, working conditions, illness and

medication. Also discussed are genetic factors and ethical and legal matters. Finally, the Committee that produced this advisory report outlines a programme of preconception care which it advises the Minister to introduce in the Netherlands.

One concept, many forms

The aim of preconception care is, first and foremost, to improve the health of mother and child. Any public health benefits and cost savings are important spin-offs.

Preconception care is defined in this advisory report as the entire raft of measures to promote the health of the mother-to-be and her child. If they are to be effective, these measures should preferably be undertaken prior to conception. Preconception care is therefore multidisciplinary, encompassing lifestyle (including food, drink, tobacco and other recreational drugs), working conditions, illness, medication and genetic factors.

Preconception care has various, complementary forms. Some are aimed at individual parents-to-be, while others may, for example, collectively target all women of child-bearing age.

Individual preconception care can either be of a general or specialist nature. One general measure is the so-called preconception consultation, whereby couples who would like to have a child have a discussion with a GP or midwife. After having identified and assessed the risk factors, he/she gives them a combination of advice that is aimed at changing behaviour (e.g. to stop smoking) and non-directive information aimed at promoting their freedom of choice (e.g. about genetic testing). If necessary, prospective parents can then also be referred for specialist preconception care. This applies to situations where there is an increased risk either of complications during the pregnancy or of an adverse pregnancy outcome.

Examples of collective measures in the field of preconception care are rubella vaccination, iodisation of salt, radiological protection and education campaigns on the use of folic acid.

Food, drink, tobacco and other recreational drugs

A healthy, varied diet is important for everyone, and therefore also for people who wish to have a child. A healthy diet is, to a large extent, also sufficient to meet a woman's needs during early pregnancy. However, certain nutrients are already particularly important before conception. It is, for example, important to

begin taking folic acid supplements (0.4 mg per day) at least four weeks before the planned conception in order to reduce the risk of having a child with a neural tube defect. Furthermore, the level of vitamin D in the body needs to be adequate. Vitamin D supplementation is recommended, especially for women with little exposure to sunlight or who have a very dark skin. Finally, women wishing to become pregnant are advised to refrain from eating liver products in order to avoid an excess of vitamin A.

Parents-to-be are best advised to abstain from of all recreational drugs. Tobacco and alcohol have been shown to have adverse effects both on fertility and on the unborn child. The use of hallucinogenic drugs is also inadvisable.

Working conditions

Exposure to high concentrations of chemical agents is detrimental to the health of all people. This is, however, especially relevant to people who would like to have a child and to pregnant women, because of the possible adverse effects on the unborn child. There are indications that exposure to high concentrations of such compounds as pesticides, solvents and cytostatics is associated with an increased risk of miscarriage and congenital abnormalities. Thusfar no indications have been found suggesting adverse effects of preconception exposure to such physical factors as low dosages of ionising radiation and noise and to other factors such as shift work on pregnancy outcomes. Stress before conception, however, can be harmful. The Occupational Health and Safety Act (*Arbowet*) already includes maximum exposure levels for chemical and physical factors and rules governing shiftwork for pregnant women.

Compliance with the occupational health and safety regulations (protective clothing, extractor systems) should keep exposure to both chemicals and physical factors within safe limits.

Illness and medication

During every preconception consultation it should be investigated whether either of the future parents has – or is at risk of developing – an illness that might affect the pregnancy, or vice versa.

As far as infectious diseases are concerned, rubella (‘German measles’) vaccination status is particularly important. If necessary, booster vaccinations can be given prior to conception. Pre-existing sexually transmissible diseases must be treated prior to conception. In the case of HIV-seropositive individuals, it will be necessary to discuss medication policy.

It is important that women with diabetes should have their blood-sugar levels well under control in advance of conception. Tight glycaemic control has been shown to result in better pregnancy outcomes, in terms of fewer complications and fewer congenital abnormalities. In the case of epilepsy, it is important to switch to monotherapy (if possible) or, if the woman is episode-free, perhaps even to phase out medication completely. This reduces the risk of congenital abnormalities.

As far as the use of other medicines is concerned, it will be necessary to consider (on an individual basis and always under the supervision of a doctor or pharmacist) whether medication may possibly be harmful and, if this is the case, to adjust the dosage or, where possible, phase it out.

Other health related factors with an adverse effect on pregnancy outcomes are obesity, anorexia and a relatively high paternal of maternal age.

Genetic factors

Preconceptional genetic counselling will in the first instance require a proper personal and family history, followed – if necessary – by referral to a clinical genetics centre. The aim of preconception counselling here is to extend the range of options available to individuals with an unfavourable genetic background and to give them more time to consider carrier screening and/or antenatal screening or the consequences of opting for (or against) pregnancy.

The advisory report takes a closer look at carrier screening for cystic fibrosis and haemoglobinopathies, since these genetic disorders are relatively common among various population groups in the Netherlands. It would be advisable to carry out a study to further explore the desirability and efficiency of general carrier screening for these disorders.

Ethical and legal matters

Preconception care can contribute to two values which are especially relevant to (future) parents: firstly, the health and well being of the child and its mother and secondly, the freedom to have children. The broad character of this type of care raises a variety of ethical and legal issues. Some ethical and legal questions are difficult to answer at this stage. One such example is the conflict between the desire to provide people with the best possible information about lifestyle and health and their right “not to know” everything (e.g. about the possible presence of a genetic disorder). Preconception care programmes should therefore be regularly evaluated, taking these possible consequences into account, e.g. in conjunc-

tion with research into the health effects of preconception care. A number of recommendations are made with a view to ensuring the careful delivery of preconception care (e.g. adopting a phased approach to the provision of information and making a clear distinction between advice that is aimed at modifying behaviour in cases where risks can be influenced and non-directive information aimed at increasing reproductive autonomy where they cannot). As far as the legal aspects are concerned, it should be pointed out that the existing statutory framework set out in the WGBO [Medical Treatment Agreement Act], WBO [Population Screening Act] and WMO [Medical Research Involving Human Subjects Act] and in the provisions of the Constitution with regard to self-determination, privacy and public health is also fully applicable to preconception care.

Preconception care programme

Many of the scientific insights discussed in this advisory report are already also being communicated to prospective parents in the form of antenatal education. However, it would be better if most of the information were provided prior to conception, since this would offer greater health benefits.

The Health Council therefore advises the Minister to set up a centrally coordinated programme of preconception care, pointing out that this approach will reach the greatest number of parents-to-be. This strategy will also create the most favourable conditions for monitoring the effectiveness, efficiency and social consequence of this care programme. Furthermore, the various components of the programme (advice and interventions relating to food, drink, tobacco and other recreational drugs, working conditions, illness and the use of medicines and genetic aspects) should not be provided as separate elements but as an integrated healthcare concept.

A sound knowledge infrastructure is also crucially important. The Committee urges that preconception care should be enshrined in medical guidelines. It also believes that the professional groups concerned will require supplementary training and recommends that a proper database should be established and a communications strategy should be developed in order to provide information to the target group.

The organisation of preconception care will necessitate choices as to which professional groups are to deliver the general, individual preconception care. It may be possible to consider this question at regional level. Furthermore, the Committee recommends central governance with regard to monitoring, quality assurance and knowledge infrastructure.

Conclusion

Preconception care offers a simple means of improving the preparedness of women *and men* for pregnancy. This will benefit not only the health of the future child, but certainly also that of the prospective parent(s). It would therefore be advisable to offer this form of programmatic care to anybody in the Netherlands who wishes to have a child.

Chapter 1

Introduction

1.1 Request for advice

Recent years have seen growing attention for preconception care in the Netherlands. For example, it was noted during the Bilderberg Conference on 'Preconception Care for Prospective Parents' in early 2004 that the advice given to parents-to-be was still extremely fragmented and sparse. The Minister of Health, Welfare and Sport expressed the desire to enter into a debate with experts about how people should, ideally, be prepared for pregnancy. In addition, the Dutch Foundation for Preconception Care* was set up on 1 October 2004 to investigate better ways of reaching and advising couples who wish to have children. While preparations were being made to establish the Foundation, the Dutch Genetic Alliance (VSOP) suggested that the Health Council should be asked for advice on the implementation of preconception care, and especially on those aspects that are still scientifically or ethically controversial. This proposal, together with the persistence of relatively high perinatal mortality in the Netherlands, prompted the Minister to request that the Health Council produce an advisory report on preconception care (annex A).

* The Foundation for Preconception Care was established by the VSOP, KNOV [Royal Netherlands Association of Midwives], NACG [Netherlands Association for Community Genetics], NVOG [Dutch Society for Obstetrics and Gynaecology], VKGN [Dutch Society for Clinical Genetics] and GGD-Nederland [the national association of municipal health authorities] and is run by individuals nominated by these organisations.

The care given to the mother and child usually begins when the woman is between 8 and 12 weeks pregnant. It is then that she visits the obstetric caregiver (a midwife, gynaecologist or a general practitioner who is actively involved in obstetrics) for the first time and she and her partner are given information about lifestyle, illness and use of medication. The possibility of genetic disorders in the family is also discussed on this occasion. Prenatal diagnosis is offered in cases where there may be an increased risk of congenital abnormalities and to women over 35. As of 1 January 2007, all pregnant women are being informed about the possibility of prenatal screening for Down's syndrome and neural tube defects or other congenital, structural abnormalities by means of the 'combined test' (a blood test and nuchal translucency measurement) in weeks 9-14 of pregnancy and an ultrasound scan at around week 20, respectively. This prenatal screening, together with the check-ups conducted during pregnancy, comes under the heading of prenatal care.

However, many congenital abnormalities and pregnancy complications emerge either prior to conception or in the first few weeks of a pregnancy. Among the factors at play here are genetic make-up, lifestyle and use of medication. If these factors are addressed in a systematic, integrated manner prior to conception, the individuals concerned can be said to be receiving preconception care.

In his request for advice the Minister expressed the view that more could be done to promote a good pregnancy outcome by giving prospective parents better and earlier advice about risk reduction. He noted, however, that the application of this advice requires support both from the parents and the relevant professional groups.

The Minister requested the Health Council to review the current level of knowledge about efforts to promote the health of mother and child by commencing care prior to pregnancy. He also asked it to investigate the extent to which the available research findings are being applied in present-day practice in the Netherlands and other Western countries, and what criteria preconception care should meet. Finally, the Minister asked the Council how it might be possible to reach the maximum number of prospective parents, which professional groups and agencies should be involved, and what ethical considerations need to be borne in mind when providing preconception care.

1.2 The Committee's working methods

In order to answer the Minister's questions a committee was set up, consisting of experts from the various specialisms associated with preconception care (annex B). The Committee has met on 11 occasions.

In its initial selection of topics the Committee made use of the *US Guide to Clinical Preventive Services* and the *Canadian Guide to Clinical Preventive Health Care*, among other publications.[1,2] Working with the Dutch Cochrane Centre, it then embarked on a systematic search for literature on the effectiveness of the different forms of preconception care, and on risk factors associated with early pregnancy and embryonic and foetal growth. A comprehensive explanation of the systematic, evidence-based approach can be found in annex C.

Where possible, the literature has been systematically analyzed and classified according to the level of evidence.[4] Unfortunately, there is still little literature with the highest level of evidence available in the field of preconception care. There are only a limited number of systematic reviews that are based on several methodologically sound randomised clinical trials. For ethical and practical reasons, it is difficult to conduct randomised, comparative clinical research in a preconception setting. Moreover, preconception care is still a relatively new area and consequently the number of publications on this topic is limited.

As the emphasis in the request for advice was on preconception care as a (new) concept in care, the Committee opted for literature selection at a high aggregation level, with preconception care as the primary search term and using the studies with the highest levels of evidence for this advisory report wherever possible. The disadvantage of the decision to search and select literature in this way is that it might possibly result in literature about individual risk factors and interventions that are also relevant prior to conception or in the first few weeks thereafter being missed. The search for individual risk factors did, however, yield almost encyclopaedic quantities of literature, which – not surprisingly – still turned out to deal mainly with the role of these factors during pregnancy. In autumn 2007 the Clinical Committee of the US Select Panel on Preconception Care hopes to publish a document exploring further risk factors and disorders. The Health Council committee suggests that readers refer to this for additional information about other topics that may be of relevance to preconceptual counselling (e.g. hypertension, cardiovascular disease, auto-immune diseases, eating disorders, socio-economic status and physical limitations).

There was sufficient literature to provide a good overview for the chapters on food, alcohol, tobacco and other recreational drugs, working conditions, illness,

medication and a number of other health-related factors within the specific framework of preconception care. The same cannot be said with regard to the role of genetic factors and genetic counselling in preconception care. However, the Committee considered this topic sufficiently important to warrant the inclusion of a separate chapter in the advisory report. During preparations for the request for advice, it was also decided that this report should include a discussion of carrier screening for cystic fibrosis and haemoglobinopathies, which featured in the Health Council's Work Programme for 2004. This topic also ties in with the comment made by the Minister in the request for advice with regard to the importance of awareness of carrier status for these disorders. The advisory report has been reviewed by the Standing Committees on Genetics, Medicine, and Medical Ethics & Health Law and by the Advisory Council on Health Research (RGO).

1.3 Arrangement of the advisory report

Chapter 2 outlines the background to the emergence of preconception care, followed by a definition of the concept itself and the forms that this care can take. The chapter ends with a summary of initiatives undertaken in the field of preconception care, both in the Netherlands and abroad. Chapters 3-6 consider the effectiveness and efficiency of various groups of risk factors and the interventions that can be undertaken, based on the current level of knowledge. The risk factors and interventions are classified and ranked, starting with those that are mainly exogenous (i.e. controllable in theory) and continuing through to largely endogenous (less controllable or uncontrollable) risk factors. The topics considered are: food, alcohol, tobacco and other recreational drugs (chapter 3); working conditions (chapter 4); illness, medication and other health-related factors (chapter 5); and genetic factors (chapter 6). In chapters 3-6, the Committee formulates detailed recommendations. Chapter 7 contains a discussion of the ethical and legal aspects. Chapter 8 outlines the framework, quality criteria and choices required for a programme of preconception care, together with the key points from the detailed recommendations contained in the earlier chapters. Chapter 9 ends this advisory report by summarising the Health Council's response to the request for advice. When formulating recommendations, it is often necessary to consider other aspects besides the scientific evidence, such as consumer and patient preferences, the availability of special expertise, organisational aspects, social consequences and costs. The recommendations that were ultimately formulated are based on the available scientific evidence, combined with these considerations.

Chapter 2

Preconception care: one concept, many forms

Not every pregnancy leads to the birth of a healthy child without limitations. Congenital abnormalities may occur, newborns may be too light and some die before or shortly after birth. A wide range of initiatives have been developed in order to reduce the risk of adverse pregnancy outcomes, starting with prenatal care for pregnant women and their unborn children. In the meantime we also have what is known as preconception care, which is aimed at ensuring that couples who wish to have children start a pregnancy under the best possible conditions.

This chapter provides background information on the occurrence of adverse pregnancy outcomes such as congenital abnormalities, low birthweight and perinatal mortality. Then the Committee defines the concept of preconception care and presents a paradigm that embraces the various forms of preconception care. The chapter concludes by considering the initiatives that have emerged in the field of preconception care both in the Netherlands and elsewhere.

2.1 Prevalence of adverse pregnancy outcomes

2.1.1 Congenital abnormalities

The TNO report on *Congenital abnormalities in the Netherlands 1996-2004* (published in February 2006) shows that there was no conspicuous increase in the number of children born with abnormalities at the organ-system level in the

period under consideration.[5] The number of neural tube defects fell in the same period from 12.3 per 10,000 children in 1997 to 6.3 per 10,000 children in 2004. According to the researchers, this decrease is probably associated with an increase in the use of folic acid and improved early prenatal diagnosis. A slight fall in the prevalence of neural tube defects from 10.1 in 1996 to 9.7 in 2002 can also be observed at European level.[6] A number of other abnormalities will be closely monitored in the Netherlands over the next few years, however, since it is possible these may, in fact, have increased. The disorders in question are Down's syndrome and abnormal physical characteristics (dysmorphic features) without any identified chromosomal abnormality. Finally, the TNO study reports a significant positive relationship between the occurrence of congenital abnormalities in a child and the following factors: maternal age, parity (the number of children a woman has already had), ethnicity, pre-existing epilepsy or diabetes in the mother, a history of spontaneous abortion, IVF/ICSI treatment and other fertility treatments, and multiple births. For example, the older the mother is, the greater the risk of abnormalities in the child. Another example: mothers who have already had a chronic illness such as diabetes or epilepsy before becoming pregnant are at greater risk of having a child with health problems.

EUROCAT figures also point to a perceptible increase in the prevalence of chromosomal abnormalities at European level: from 32.5 per 10,000 in 1996 to 35.0 per 10,000 in 2002. This increase cannot be attributed to better detection. Increased maternal age may possibly play a role.[6]

The *March of Dimes Global Report on Birth Defects* (2006) names the following as the five most commonly occurring serious congenital abnormalities worldwide: congenital cardiac abnormalities; neural tube defects; the haemoglobinopathies sickle cell anaemia and thalassaemia; Down's syndrome; and glucose-6-phosphate dehydrogenase deficiency.[7] Together, these abnormalities account for a quarter of all congenital abnormalities with a genetic component. The relative incidences are different in the Netherlands, however, with cystic fibrosis being more common here, and haemoglobinopathies and glucose-6-phosphate dehydrogenase deficiency rarer.

Worldwide, the foremost non-genetic causes of congenital abnormalities are: alcohol consumption; iodine deficiency; and German measles or syphilis during pregnancy. The prevalence of congenital abnormalities is substantially higher in countries with low-to-average incomes than in rich countries with an average gross annual income of more than $10,065 per capita.

2.1.2 *Low birthweight*

Another adverse pregnancy outcome is low birthweight (< 2.5 kg). Children with a low birthweight are at greater risk of perinatal hypoxia, excessively low postnatal blood-sugar level (hypoglycaemia), developmental disorders and death. In a review of worldwide evidence, it is noted that the principal causes of low birthweight in the Western world are smoking, low maternal weight and malnutrition during pregnancy.[8] The UNICEF report *Low Birthweight – Country, Regional and Global Estimates* (2004) identifies Europe as the continent with the lowest incidence of low-birthweight babies (6.4 per cent of all newborns).[9] This percentage was somewhat higher for the Netherlands in 2004 at 7.1 per cent.[3] Worldwide, 15.5 per cent of newborns have low birthweight.[9]

2.1.3 *Perinatal mortality*

The European Peristat study reported in 2003 that the Netherlands had the lowest fall in perinatal mortality figures among the 15 participating EU countries.[10] A systematic review of neonatal mortality (death of live-born infants under 1 year of age) by US Health reveals that the Netherlands has lost its position as the country with the second-lowest neonatal mortality worldwide.[11] Global neonatal mortality fell between 1960 and 2003, as did neonatal mortality in the Netherlands (from 17.9 to 4.8 per 1000 live-born children). However, mortality fell further in countries such as Hong Kong and Singapore than in the Netherlands (to 2.5 or less per 1000).[11]

Although major differences have been identified between the countries in data collection methods, the extent and completeness of the data collection and the definitions of the data items, Buitendijk and Nijhuis ascertained in their discussion of the Peristat results that the comparisons are relatively reliable.[12] They offer various explanations for the relatively high perinatal mortality in the Netherlands at the beginning of the 21st century: high maternal age, more multiple pregnancies (partly on account of the higher maternal age), a large proportion of pregnant women among the immigrant population, relatively little prenatal diagnosis and screening, and a cautious intervention policy in connection with severe premature birth. In particular, the impact of maternal age and a conservative clinical policy on perinatal mortality is confirmed in a regional cohort study conducted in the Zaanstreek region.[13] In a systematic review of the aetiology and prevention of stillbirths, obesity prior to pregnancy and socio-economic factors were cited alongside maternal age as the most prevalent risk factors.[14]

In several of the studies mentioned above, preconception care and counselling are cited as promising preventive interventions in efforts to further reduce the prevalence of congenital abnormalities and stillbirths and to improve the health of pregnant women.[5,7-9,13,14]

2.2 The concept of preconception care

Preconception care extends from some months before conception to the first few weeks thereafter. Some people therefore prefer to call this *periconceptual* care. In order to emphasise the fact that this care should preferably begin before conception the Committee prefers to use the term 'preconception care' in this advisory report.

Various definitions have been formulated for preconception care. De Weerd and Steegers defined it as follows in 2002: "Preconception care encompasses the entire range of measures that can be adopted prior to conception in order to promote the health of the expectant mother and her child".[15] This definition is also adopted in the textbook *Klinische Genetica* [Clinical Genetics].[16] In 2005 the American College of Obstetricians and Gynecologists defined preconception care as: "… *optimizing women's health and knowledge before planning and conceiving a pregnancy (...) to reduce the risk of adverse health effects for the woman, fetus, or neonate*".[17] Other definitions can be found in the literature, such as active preparation for pregnancy with a view to offering the earliest embryonic cells the best possible environment.[18] The following definition of preconception care was included in Pubmed's MeSH Database in 1992: "*An organized and comprehensive program of health care that identifies and reduces a woman's reproductive risks before conception through risk assessment, health promotion, and interventions*".[19]

Partly based on the above definitions, the Committee has formulated the following definition for this advisory report:

Preconception care is the entire range of measures designed to promote the health of the expectant mother and her child, which, in order to be effective, must preferably be adopted prior to conception.

The words "must" and "preferably" in the Committee's definition merit further explanation. "Must" does not mean that people who want to have children are, or ought to be, legally required to take or to accept these measures, but that those who wish to take this action should preferably do so before and/or during the time when they are trying to conceive. The "preferably" is based on the evidence that action during this period is particularly important in order to achieve optimal

results or, for example, maximum freedom of choice if several courses of action are available.

Measures which, in the interests of the mother's and child's health, can or should be taken after the first few weeks of pregnancy fall under the heading of prenatal care. Some measures are beneficial not only prior to conception but also prenatally and, in some cases, even postnatally. An example is smoking cessation. Thus preconception care is an element in the continuum of care for pregnant women, mothers and their children, and is aimed at ensuring that they are in optimal condition on entering prenatal care.

Both prospective parents – i.e. the mother and the father – should be involved in the identification of possible risk factors, since the health, lifestyle and genetic 'baggage' of both partners have a bearing on the pregnancy outcome (i.e. the health of the future child and its mother).

2.3 Paradigm for preconception care

Preconception care can take various forms: general individual preconception care, specialist individual preconception care, and collective measures (Scheme 1). Collective preconceptual measures and certain elements of specialist individual preconception care have existed for some time (although they are only sporadically available and insufficiently organised). In fact, the only entirely new element is general individual preconception care.

Individual preconception care	General individual preconception care	For all couples who want to have a child (e.g. individual advice on stopping smoking, family history)
	Specialist individual preconception care	For: a) couples who want to have a child who are already known to be at great risk for adverse pregnancy outcome[a] or b) couples who are referred from general individual preconception care after risk assessment (e.g. illness in the family, medication, specific working conditions of prospective mother)
Collective measures with implications for preconceptual care		For: a) everyone (e.g. radiological protection) or b) all couples who want to have a child (e.g. nationwide folic acid campaigns)

[a] NB: Specialisms that do not provide any general preconception care (e.g. clinical genetics, internal medicine) need to refer such patients back to general individual preconception care.

Scheme 1 Paradigm for preconception care: the terms used and how they are related.

2.3.1 General individual preconception care

This service (provided by a GP, midwife or child health service worker) is available to all couples who want to have children. It consists of general dietary and lifestyle advice (e.g. on folic acid supplements, smoking cessation and alcohol use) geared towards the future pregnancy. A further element of this general care is risk assessment, since it is not usually known in advance whether would-be parents are at increased risk and if so, what the nature of this risk might be. Further investigations can also be undertaken at the general-care level if required, such as determination of vitamin D status or German measles (rubella) antibody titre. The general care is easy to access and requires a closely integrated, nationwide network of the type already in place for obstetric care, general practitioner care and child health services.

2.3.2 Specialist individual preconception care

Where a couple who want to have a child are known or feared to be at high risk, they are referred to a specialist in the secondary or tertiary healthcare sector. Examples are: consultation of a gynaecologist due to a previous pregnancy complication, consultation of a clinical geneticist for a genetic problem, consultation of a diabetologist due to pre-existing diabetes mellitus in a woman who wants to have a child or consultation of an occupational health physician by individuals whose work is too pressurised or too physically demanding. In these situations, it is crucially important that the various consultations should be coordinated by a single healthcare professional. If the pregnancy and delivery need to be supervised by a gynaecologist owing to serious pathology in the expectant mother or increased risk of an adverse pregnancy outcome, these consultations should preferably also be coordinated by the gynaecologist.

2.3.3 Collective measures

The term “collective measures” is used when actions are aimed at a group of people as a whole and not individually tailored. These measures can, to a certain extent, be communicated in a non-targeted manner (e.g. via the media). Examples of collective measures with an impact on preconception care are: rubella vaccination, iodisation of salt, radiological protection and education campaigns concerning the use of folic acid. Some of these measures apply to all women (and often also to men), regardless of whether or not they wish to have children.

Consequently they will, in many cases, also benefit couples with an unplanned pregnancy. Furthermore, a number of these measures have not primarily been undertaken with a view to providing preconception care (e.g. iodisation of salt), but nevertheless benefit the health of mother and child.

2.3.4 Continuum of care

The previous section tends to suggest that preconception care is a prime example of a continuum of care. Firstly, the care services provided in the 'pre-primary' (child health services), primary (general care from GPs, midwives), secondary and tertiary sectors (gynaecologists, paediatricians, clinical geneticists) are complementary, synergistic and interconnected. Furthermore, preconception care marks the beginning of a 'chain of care' (preconception care → prenatal care → perinatal care → neonatal care and child health services). This continuum of care model will ultimately be crucial to successful implementation when an infrastructure is established for preconception care.

2.3.5 Normative framework

The aim of preconception care is first and foremost to maintain or improve the health of the mother and child. This goal is pursued through a combination of advice that is aimed at changing behaviour (e.g. with regard to lifestyle) and non-directive information designed to promote reproductive autonomy (e.g. with regard to genetic testing). The interests of the individual couple and the child are also of paramount importance to the Committee in terms of health benefits. Any public health benefits and cost savings are important spin-offs.

2.4 A brief history of preconception care

With the development of modern obstetrics and gynaecology at the start of the last century, the emphasis came to be placed on prenatal care, with relatively little attention being paid to health and care prior to conception. Over the past thirty years this situation has gradually begun to change.

In their thesis on *Preconception Counselling in General Practice* (2006), de Jong-Potjer and Elsinga provide an overview (in table form) of preconception care initiatives that have been undertaken over the years at international and national level.[20] This overview demonstrates that modern individual preconception care arose in a secondary healthcare setting. The first article to appear in the literature (published in Britain in 1980) concerned a pre-pregnancy clinic set up

by a consultant obstetrician for women who had experienced problems in earlier pregnancies or attempted pregnancies.[21] Integrated preconception care, i.e. preconception care that considers several aspects (diet *and* medication *and* alcohol, tobacco and other recreational drugs) was originally developed and evaluated for women who had already, prior to their pregnancy, suffered from diabetes mellitus or epilepsy.[22,23] It became clear that preconception care can substantially improve pregnancy outcomes.

The late 1970s and early '80s saw the first large-scale trials to establish the efficacy of preconceptual folic-acid use in preventing neural tube defects such as spina bifida. These studies were notably conducted in Hungary and the United Kingdom.[24,25] Then, in the 1990s, it emerged that folic acid could reduce incidence of spina bifida by two-thirds and women were advised to take folic acid prior to conception.[26]

At the instigation of the VSOP, a nationwide campaign devised by the Institute for Non-Commercial Advertising (SIRE) was launched in the Netherlands in 1984 under the banner *Erfelijkheidsvoorlichting. Zorg dat U de weg weet* [Genetic counselling. Make sure you know the way]. The initiative consisted of a nationwide advertising campaign, a brochure entitled *Wat je van erfelijkheid moet weten voordat je aan kinderen denkt* [What you should know about genetics before you consider having children] and information to all GPs. This campaign met with a big response and has without doubt helped to introduce the concept of preconception care.

The first experiences in the Netherlands were gathered in an out-patient setting in the 1990s, with preconception care being provided by GPs or specialists.[27,28] Here the care was mainly geared towards gynaecological and genetic risk factors. Nowadays there are more forms of preconception care and awareness and demand are increasing rapidly. Preconception consultations are, for example, being offered at several university medical centres (UMCs) from various perspectives (gynaecology, clinical genetics, etc.). Erasmus MC and the Erfocentrum [national genetic resource and information centre] have jointly developed the widely used web application *Zwangerwijzer.nl*. The Dutch Foundation for Preconception Care was set up in 2004 with the remit of promoting easily accessible preconception consultation in the Netherlands. Midwives feel that their profession has a significant role to play in preconceptual counselling. Preconception care is also being advocated outside of healthcare and the patient organisations.[29-35]

In the following two sections we examine several of the initiatives mentioned above in more detail, looking first at the Netherlands and then abroad.

2.5 Dutch initiatives in the field of preconception care

Specialist individual preconception care in the secondary and tertiary sectors is the oldest form of individual preconception care in the Netherlands. Several specialisms have been engaged in these activities for some considerable time, e.g. in the form of clinics held within the gynaecology department at several university medical centres, including Erasmus MC and St. Radboud UMC.[30,35] These initiatives gave rise to the first pilot clinics for integrated general individual preconception care.

A study conducted in Nijmegen from 1996-2000 showed that preconception care in secondary healthcare helped to minimise risk factors in women at increased risk for a less favourable pregnancy outcome. The women from the study had mainly been referred to the preconception clinic by their gynaecologist or GP because of a complicated obstetric history, a chronic illness or a congenital abnormality in a previous child. The preconception care consisted of providing extensive counselling and treating diagnosed metabolic and other abnormalities.[28]

A study was conducted in Leiden from 1999-2005 on preconceptual counselling in general practice.[20] This showed that nearly all couples have one risk factor that requires individual advice in the preconception phase. The benefits of a systematic, integrated approach to preconception care were demonstrated by the fact that knowledge of risk factors and behaviour was better in women who had received preconceptual counselling. In order for preconception care to be successful, the researchers argue that future parents *and* GPs must become more aware of risk factors that need to be tackled prior to pregnancy. In addition, women should be reached in good time and the programme must be feasible and acceptable for the healthcare provider.

Since the 1990s the first steps have also been taken towards actually introducing general individual preconception care. For example, the gynaecology and clinical genetics departments at Maastricht University Hospital have set up a clinic for general individual preconception care.[36] In 2002 Erasmus MC, in collaboration with the Erfocentrum, took the initiative to set up the interactive website *Zwangerwijzer.nl*. This site provides a self-test which enables women and men who want to have children to measure their health risks.[29] The test results can be mailed to a healthcare professional in preparation for a preconception consultation. Through its own site, the Erfocentrum also provides preconception information under the heading *ZwangerStraks* ['pregnant soon'], which also incorporates a link to *Zwangerwijzer.nl*.[37]

The Dutch Foundation for Preconception Care was set up in October 2004 with the aim of promoting easily accessible preconception consultation in the Netherlands. The Foundation was established by six organisations – the VSOP, the Royal Dutch Organisation of Midwives (KNOV), the Netherlands Association for Community Genetics (NACG), the Dutch Society for Obstetrics and Gynaecology (NVOG), the Dutch Society for Clinical Genetics (VKGN) and GGD-Nederland [the national association of municipal health authorities] – and run by six people specially nominated by their respective organisations.[30]

The Amsterdam Municipal Health Authority recently added a further section to its five-part *Groeigids* ['growth handbook']. Section six, entitled *Kinderwens*, provides prospective parents with information on the preconception phase.[38] This organisation's Parent and Child Centres offer would-be parents the opportunity to participate in a preconception clinic.

In addition, two major projects relating to general individual preconception care are now under way in the primary care sector. On 1 October 2006 the KNOV launched a 6-month project whereby more than 20 midwifery practices from all over the Netherlands were offered free preconception clinics. The experience gathered by these practices will be used to launch such preconception clinics at midwifery practices throughout the country and to improve the materials that have been developed. The results of this pilot scheme are expected to be published in late 2007.[32]

A preconception care pilot scheme devised by the Rijnmond Antenatal Centre (a collaborative venture between the Erasmus MC Department of Obstetrics and Gynaecology and STAR Medical Diagnostics Centre in Rotterdam North) has been running in Rotterdam since September 2006.[39] An information campaign refers these Rotterdam couples to the website *Zwangerwijzer* (see above). They then complete a questionnaire, which is mailed to the Rijnmond Antenatal Centre. Here they can also make an appointment for a consultation. The clinics are run by trained midwives and based on predefined medical protocols. Depending on their identified risk factors, couples may be referred to participating subspecialists in the primary, secondary or tertiary sector.

It can be concluded that a range of preconception care options are now available in the Netherlands. As no comparative research has yet taken place, it is unclear whether efficiency varies, and if so, how and to what extent. Furthermore, the internet is awash with 'unofficial' pregnancy sites, which sometimes also provide information on preconception (e.g. www.kindjeopkomst.nl, www.babypret.net). Clearly, the quality of the information on this type of site is not uniformly good.

The fact that there is sufficient support for the introduction of preconception care in the Netherlands is evident from a number of recent statements from various organisations. The Royal Dutch Organisation of Midwives (KNOV) stated in 2005 that many problems that arise during foetal development and pregnancy can be prevented through preconception care.[33]

The Organization for Sickle Cell Anaemia Relief (OSCAR) and the Dutch Genetic Alliance (VSOP) view preconception care as a means of informing future parents at an early stage about hereditary disorders and the courses of action available.[40,41]

Although preconception care initiatives are clearly advancing in the Netherlands, there is still room for improvement. Owing to the wide diversity of schemes, it is difficult to gauge their coverage and scientific quality. Furthermore, it is still not clear to what extent a general concept and a well organised continuum of care can be said to exist.

2.6 Great diversity of preconception care abroad

When looking at the preconception care that is available abroad, one is struck by its great diversity. Any such care that is available is delivered by various professional groups (GPs, nurses, gynaecologists). Furthermore, the particular aspect of preconception care that is most prominent can vary from one country to another (e.g. folic acid campaigns or smoking cessation). Moreover, there is nowhere – with the exception of Hungary – where preconception care is actually integrated into a complete programme. Below we examine the initiatives that have been undertaken in different countries.

Virtually every country advises women to take folic acid and has medical guidelines that include recommendations that women with epilepsy and diabetes mellitus should receive preconceptual information. Furthermore, several countries offer screening for haemoglobinopathies (depending on the prevalence of these disorders in the country concerned or within a particular migrant group) and genetic counselling prior to pregnancy is possible where there are familial genetic disorders. However, these services are not actively offered to couples of child-bearing age and/or couples who want to have children as part of an integrated care concept. They are discrete items.[42]

Experience was gathered in Hungary between 1984 and 1994 with a programme of preconception care which consisted of counselling, medical examination and interventions. The programme proved to be effective in relation to the introduction of periconceptional folic acid supplementation and the reduction of smoking and alcohol consumption. In the group of women who received precon-

ception care, the number of congenital abnormalities was significantly lower than expected: 20.6:1000 newborns instead of 35:1000.[43] In the meantime this has become a nationwide care programme, in which preconception care is provided by specially trained nurses.

In the United Kingdom, a private organisation supports parents-to-be and healthcare professionals with information and training about the preconception phase.[44] In the 1980s there were also two preconception clinics in operation, one of which is still active in the form of a pre-pregnancy advice service, located at the Queen Mother's Hospital in Glasgow.[42,45]

Wallonia has an *Office de la Naissance et de l'Enfance* (ONE), a government agency responsible for protecting and promoting the health of women and children. Owing to the low birth rate and the prevalence of congenital abnormalities (2-3 per cent of all live-born infants), ONE has recently launched a plan designed to determine the feasibility of setting up a programme of preconception care in Wallonia. The intention is to implement this through prenatal care, paediatric and gynaecological clinics and GPs, in collaboration with centres for clinical genetics and counselling.[46,47]

The United States does not have an integrated programme as yet either. In April 2006 the Centers for Disease Control and Prevention (CDC) issued recommendations for the improvement of women's preconceptual health and, together with 35 organisations (insurers, scientific and professional organisations and social organisations, which collectively make up the Select Panel on Preconception Care), they have embarked on an initiative that will establish and implement a broad-based and integrated programme of preconception care.[48] Serious consideration is also being given to financing, monitoring and research. The CDC's role in this initiative is a coordinating and facilitating one. An important difference between the approach adopted by the CDC and that of the Committee that prepared the Dutch advisory report is that the CDC report has been written from a public health perspective, whereas the Health Council committee's report is primarily predicated on health benefits and the options available to individuals who wish to have a child.

In Asia, Hong Kong has the best preconception care facilities, which were set up by the Family Planning Association of Hong Kong (FPAHK) in 1998. This "pre-pregnancy preparation service" (provided in private clinics) integrates medical interventions, counselling and information for couples who want to have children. Every year, between four and five thousand people avail themselves of this service. The programme is self-supporting, with a fee of about US$75 being charged for a consultation and a blood test for HIV (among other diseases). The

low fee is made possible by the fact that the costs of the programme are shared with those of other FPAHK schemes (relating to sexuality and reproduction).[42,47]

Until 2003, couples in China were required to undergo a medical examination before they were allowed to marry. This mandatory scheme included health education and tests for HIV, etc. In 2003 this requirement was dropped, resulting in a drastic fall in the number of couples making use of this service. A study was subsequently conducted to establish whether and how preconception care services could be improved, but although Chinese women are interested in such a service, the initiative is foundering due to obstacles within the healthcare system, a lack of coordination between the government and professional organisations, and a welter of contradictory health information in the media.[42]

In conclusion, it can be stated that preconception care is carried out in a variety of ways abroad and, furthermore, it is attracting growing interest.

Chapter 3

Food, alcohol, tobacco and other recreational drugs

This chapter focuses primarily on nutrients with particular relevance to the health of women who wish to become pregnant. In the course of 2007 and 2008, the Health Council will publish a number of advisory reports on the addition of micronutrients to food. In some cases, these reports will also consider the role of micronutrients in the pre-pregnancy period.

Another type of food-related risk stems from infections caused by eating potentially contaminated food (e.g. unpasteurised milk, cheese made from raw milk, and raw or undercooked meat or fish). See the discussion of illness and medication in chapter 5 to find out more about the consequences of this kind of infection. The same chapter also considers the adverse consequences of being under- or seriously overweight for conception and for the future child.

This chapter also discusses alcohol, tobacco and other recreational drugs that influence the outcome of a pregnancy.

3.1 Food

3.1.1 Food in general

The vital role that a good diet plays in our general health has been beyond dispute for many years. Much research has been conducted with a view to establishing what actually constitutes a healthy diet.[49] The latest insights are described in *Guidelines for a Healthy Diet*, published by the Health Council in December

2006.[50] Among the organisations putting the results of this ongoing research into practice is the Netherlands Nutrition Centre.[51]

Pregnant and breastfeeding women have a different – often greater – need for specific nutrients. Where necessary, this has already been taken into account in the Dutch Nutrition Standards.[52-56] For most nutrition standards, it is not necessary to make specific provision for vegetarians and vegans. The nutrition standards address the need for nutrients and, for most substances, this is not affected by the choice of food, providing we eat a varied diet.

An exception is the nutrition standard for protein. The amino-acid composition of dietary protein is of somewhat inferior quality in the case of vegans and lacto-ovo-vegetarians than for people who also eat meat or fish. Consequently, the protein requirement of lacto-ovo-vegetarians, who eat dairy products and eggs, is generally 1.2 times higher than that of people who eat a mixed diet, and the protein requirement of vegans, who only eat plant-based foods, is 1.3 times higher.[54] Because protein consumption in the Netherlands is almost always considerably higher than the nutrition standard, there is no reason to pay specific attention to this in preconception care.

3.1.2 Vitamins

Folic acid (vitamin B_9)

The link between folic acid deficiency and neural tube defects was first established in 1965.[57] This relationship is now undisputed. A systematic review from the Cochrane Collaboration, based on randomised clinical trials, discovered that periconceptional folic acid supplementation (0.4 mg per day) is very effective in protecting against neural tube defects.[58] Based on this systematic review and recommendations from such bodies as the CDC and the American College of Obstetricians and Gynaecologists, the CDC again establishes in *Recommendations to Improve Preconception Health and Health Care – United States* (April 2006) that taking 0.4 mg folic acid per day (or vitamin supplements containing this amount of folic acid) can reduce the incidence of neural tube defects by two-thirds.[48] Similar findings also emerge from a study conducted in 2004.[59]

Since the identification of the beneficial effect of folic acid on the prevention of neural tube defects in the early 1990s, action has been taken all over the world to increase periconceptional use of folic acid by women who wish to become pregnant. Some 10-15 years later, however, various publications show that too many women are still failing to take folic acid – or else they are not taking it soon enough – and consequently the decrease in neural tube defects has fallen short of

expectations. For example, a systematic review conducted in 2004 and an international retrospective cohort study from 2005 reveal that in many countries in the 21st century less than half of the women attempting pregnancy are taking folic acid. At global level, the recommendations to take folic acid around the time of conception have not led to the anticipated sharp decrease in the birth prevalence of neural tube defects.[60,61] As far as Europe is concerned, the EUROCAT network observes the same trend. Despite a plethora of measures designed to promote folic acid use, the majority of European women are still failing to take folic acid periconceptionally, as a result of which there was only a slight fall in the number of children with neural tube defects throughout Europe in the period 1980-2000.[6,62-64] In the Netherlands, where around 85 per cent of pregnancies are planned, only one in three women are taking the recommended dose of folic acid for at least four weeks prior to conception and eight weeks thereafter.[64,65] Although the fall in the number of neural tube defects in the Netherlands is greater than at European or global level (from 12.3 per 10,000 children in 1997 to 6.3 per 10,000 children in 2004), there could be an even greater reduction in children born with neural tube defects if all women who wish to become pregnant were to start taking folic acid supplements in good time.[5]

One of the reasons cited for this shortfall is the limited effectiveness of media campaigns. The Health Council stated in 2006 that these campaigns can only be effective if they are combined with other targeted activities.[284] De Weerd *et al.* and Elsinga and De Jong showed in 2002 and 2006 that personal preconceptual counselling, including the advice to use folic acid periconceptionally, really does produce results.[20,66]

Food fortification can provide some of the folic acid that women who wish to become pregnant require, but it cannot meet the full requirement, since intake would then become too high in other population groups. Thus the recommendation that women who wish to become pregnant should take supplements still applies even when food is fortified.[67,68] In the year 2000, the Health Council advised against the fortification of foods in the Netherlands owing to the risk of masking a vitamin B12 deficiency. The maximum acceptable intake was then set at 1 mg synthetic folic acid per day.[69] It should, in any case, be noted that an adequate folic acid intake cannot completely prevent children being born with neural tube defects.

This Committee's remit does not allow it to comment on all of the advantages and disadvantages of fortifying food with folic acid. Instead, it refers readers to the forthcoming Health Council advisory report on this topic, which is to be published in late 2007. Nevertheless, the current recommendation is that women

who wish to become pregnant should be "actively and personally" advised to take folic acid supplements during preconception consultations.

Vitamin A

Vitamin A (also known as retinol) is a fat-soluble vitamin and plays an important role in gene expression, embryonic development, growth, vision, reproduction, etc. Sources of vitamin A include crustacea and liver, and it is added to margarine and various dairy products. Western diets contain sufficient vitamin A to prevent deficiency symptoms. However, excessive intake of vitamin A by pregnant women is associated with congenital abnormalities in the unborn child. One systematic review was found (conducted in 1998) concerning the risk of birth defects as a result of excessive vitamin A.[70] No large studies or more recent reviews have been discovered, except for a report published by the erstwhile Dutch Food and Nutrition Council in 1994.[71] The systematic review indicates that there is no known teratogenic threshold for exposure to vitamin A. Teratogenicity has been reported (but not confirmed) in human beings at 10,000 IU/day (corresponding to 3000 µg vitamin A per day). In the interests of safety, however, women wishing to become pregnant are advised to limit their consumption to less than 3000 µg/day. Furthermore, the European Food Safety Agency (EFSA) recommends that women of child-bearing age should consume less than 3000 µg vitamin A per day.[72] Individuals needing to take higher doses for medical reasons (e.g. the treatment of skin disorders with retinoic acid, a highly teratogenic vitamin-A derivative) should only do so under medical supervision. Beta-carotene (the natural form of vitamin A and, from a metabolic perspective, its precursor) displayed no evidence of a teratogenic effect in any of the studies reviewed. In its 1989 report, the former Food and Nutrition Council set the adequate intake (AI) for the consumption of vitamin A during pregnancy at 1000 µg per day.[71] More recently, the US Institute of Medicine (IOM) defined 770 µg per day as the adequate intake for pregnant women and 900 µg for women who are breast-feeding.[73] The Health Council will take a closer look at the fortification of food with vitamin A in an advisory report that is due to be published in 2008.

Nowadays, pregnant women are advised not to eat liver products or crustacea. The Committee recommends that this advice should also be given to women who wish to become pregnant.

Vitamin C and E

No evidence has been found in the scientific literature to warrant specific consideration of the intake and levels of vitamins C and E prior to conception, except as part of a normal, healthy diet. However, because vitamin C and E have received a lot of attention recently on account of their supposed antioxidant effects during pregnancy, mention is nevertheless made here of a number of systematic reviews on this subject.

Rumbold and Crowther investigated whether vitamin C supplementation reduces the risk of complications during pregnancy, such as anaemia in the mother, foetal growth retardation and pre-eclampsia. In a systematic review, they showed that there is, as yet, no solid evidence of such a favourable effect. In fact, it appeared that vitamin C supplementation was actually associated with an increased risk of premature birth (RR 1.38, 95%; CI 1.04 –1.82; three trials; 583 women).[74] A second systematic review concerning the possible preventive effect of vitamin supplementation on oxidative stress indicated that there is insufficient evidence to draw a conclusion about the effects of vitamin E.[75] A systematic review of the effect of antioxidants (including vitamin C and E) on pre-eclampsia showed that antioxidants reduce the risk of this pregnancy complication (RR 0.61, 95%; CI 0.50-0.75; seven trials; 6082 women) and have a positive effect on birthweight. However, this study too revealed an increased risk of premature birth.[74,76] The authors nevertheless urge caution when interpreting the data owing to the generally indifferent quality of the existing studies. A randomised clinical trial conducted in 2006 among 1877 pregnant women who had not previously had a child confirmed the results of the systematic review with regard to the favourable effect of antioxidants on the occurrence of pre-eclampsia.[76,77] No increased risk of premature birth was identified in this study. A second recent randomised, placebo-controlled trial among 2,410 women did not show a favourable effect on the occurrence of pre-eclampsia, and actually pointed to an adverse effect on birthweight.[78] The Committee concludes that supplemental vitamin C and E should not be recommended.

Vitamin D

Vitamin D is required for calcium absorption in the body. Vitamin D requirements can be met by exposing the skin to sunlight and via the diet. However, a pregnant woman requires extra vitamin D in order to satisfy her own calcium needs and those of the child. In 2000 the Health Council recommended that adequate intake of vitamin D for pregnant and breast-feeding women should be set

at 7.5 µg per day if the woman gets outdoors every day, with her head and hands in the sun, and 10 µg per day if this is not the case. These values are 5 µg per day higher than the values for women who are not pregnant or breast-feeding.[53]

A recent Dutch retrospective study has shown that the average serum concentration of vitamin D in non-pregnant women with a non-Western background in The Hague is significant lower than among Western women (15.2 – 26.3 nmol/L versus 52.7 nmol/L, $p < 0.001$, 358 women).[79] Deficiency is considered to occur at concentrations of less than 25 nmol/L. This pattern is also identified in an Amersfoort study among pregnant women of non-Western origin and their newborn children.[80] The same problem arises in the United Kingdom.[81] Many of the women diagnosed with vitamin D deficiency (regardless of whether or not they are pregnant) have such complaints as muscle weakness, fatigue and pain. Vitamin D deficiency in babies is associated with convulsions, rickets and also, possibly, muscle weakness, growth retardation, delayed bone maturation, fractures and abnormal tooth enamel formation.[82,83] In view of the seriousness of the findings, the authors of the Dutch studies advocate that pregnant women with a non-Western background should be screened for vitamin D deficiency.[79,80] The Committee believes that detection of vitamin D deficiency during the first consultation with the obstetric caregiver, which usually takes place between weeks 8 and 12 of pregnancy, may possibly be too late, since the formation of organs, tissues and bones, in which vitamin D plays an important role, begins during the first trimester of pregnancy.

The Committee recommends that particular attention should be paid to vitamin D intake among women of non-Western origin with dark skin or little exposure to sunlight. In the year 2000, the Health Council set adequate intake of vitamin D for individuals with limited exposure to sunlight (i.e. those whose hands and face are exposed to the open air for less than 15 minutes per day) at 5 µg per day for adult males and non-pregnant women. As was stated above, the adequate intake level for pregnant women who are deprived of exposure to sunlight is 10 µg per day.[53] In case of doubt whether an individual's intake is, in fact, adequate, one can determine the vitamin D status and, if necessary, recommend vitamin D supplementation. Further research is required to determine the optimum supplementation level.

3.1.3 *Minerals*

Iodine

Iodine is an essential component of thyroid hormones. Thyroid hormones are especially important during pregnancy for the formation of myelin in the central nervous system. Iodine deficiency during this period can lead to cretinism, which is characterised by swelling of the thyroid gland (resulting in a short, thick neck: the goitre) and mental retardation – possibly in combination with retarded growth, deafness and spasms.[73]

Iodine deficiency mainly occurs in developing countries, but it is also still found in Western countries.[84] Research in the North-East of England has detected iodine deficiency (excretion of iodine in the urine < 0.05 µg iodine/mmol creatine) in 3.5 per cent of pregnant women. In around 40 per cent of the pregnant women in this study, excretion of iodine in the urine bordered on deficiency (0.05-0.10 µg iodine/mmol creatine).[85] The US IOM has defined adequate iodine intake for pregnant women as 220 µg per day and for breast-feeding women as 290 µg per day. Maximum iodine intake for both pregnant and breast-feeding women is 1,100 µg per day.[73] Sources of iodine include sea salt, iodised salt and (since 1999) most bread and the majority of bread substitutes. The forthcoming Health Council advisory report on iodine, in the series on food fortification, will take a closer look at iodine provision in the Netherlands, partly based on data concerning the iodine status of the Dutch population, and at possible policy measures that could be adopted in order to ensure that this is adequate.

Pending this advice (expected in the course of 2008), it would now seem most prudent to make women who want to become pregnant aware of the importance of a varied diet so that they receive sufficient iodine.

Zinc and magnesium

Two systematic reviews of zinc and magnesium supplementation during pregnancy (based on the available studies) failed to identify any added health benefit as a result of supplementation.[86,87] A recent revision of the zinc review showed zinc supplementation to have a modest protective effect against spontaneous abortion. As this was the only effect to be identified and the association with spontaneous abortion may possibly have had more to do with poor (or inferior) nutritional status, the authors did not recommend zinc supplementation but more attention to a good overall diet.[88]

Iron

No systematic reviews were found on iron supplementation during pregnancy. Those trials that were identified indicate that there is no sound basis for introducing iron supplementation for all pregnant women during pregnancy.[89-91] Supplementation based on the diagnosis of anaemia during pregnancy would appear to be sufficient for the time being.

3.2 Tobacco, alcohol and other recreational drugs

3.2.1 Smoking

As long ago as 1973 the US Surgeon General reported that smoking was harmful to mother and child. Smoking was found to be associated with foetal growth retardation, resulting in low birthweight and neonatal mortality.[92] A systematic review of five meta-analyses of observational studies shows that odds ratios for these risks range from 1.58 for placenta previa to 1.77 for ectopic pregnancy.[93] Furthermore, a systematic review conducted in 1997 revealed a clear correlation between passive smoking and 'cot death' (pooled odds ratio 2.08; 95% CI 1.83-2.38; 39 studies).[94] A systematic review from 2002 also showed passive smoking to be associated with reduced birthweight and premature birth.[95] This has also been reported by the Health Council.[96] A systematic review conducted in 2005 clearly showed that smoking adversely affects IVF outcomes.[97]

However, smoking has also been reported to have a protective effect. Pre-eclampsia (development of hypertension together with protein in the urine) was claimed to occur less frequently in babies of mothers who smoked. The authors stated, however, that the biological linkage between smoking and pre-eclampsia is not yet well understood and that they considered the harmful effects of smoking to be more important.[93] It was also pointed out that the observed effect could be attributable to a methodological problem.

The CBO guideline on *Treatment of Tobacco Addiction* states that smoking during pregnancy gives rise to considerable risks for mother and child. Pregnant women who smoke must therefore be urgently and emphatically advised to stop smoking.[98] The 'stop smoking' interventions should preferably amount to more than merely brief supportive advice. In view of the difficulty of stopping smoking, this advice should be given prior to pregnancy and followed up, not least because supportive drug therapy is still possible at this stage. De Weerd *et al.* (2001) showed that a personal approach was significantly more effective than merely general advice to stop smoking.[99] Furthermore, supervision of smoking

cessation prior to conception was found to be cost-effective.[100] A Cochrane systematic review summarised 64 studies of various interventions aimed at smoking cessation in pregnant women. Intervention resulted in a significant decrease in smoking (RR 0.94; 95% CI 0.93-0.95). Smoking cessation resulted in fewer children with a low birthweight (RR 0.81; 95% CI 0.70-0.94) and fewer premature births (RR 0.84; 95% CI 0.72-0.98).[101]

The Committee recommends that both women who wish to become pregnant and their partners should be advised "urgently and personally" to stop smoking prior to conception and, if necessary, that cessation should be supervised.

3.2.2 *Alcohol*

In early 2005 the Health Council published an evidence-based advisory report on the risks of alcohol consumption in relation to conception, pregnancy and breastfeeding.[102] This shows that consumption of alcohol prior to pregnancy is associated with reduced fertility in the woman. Consumption prior to conception and in early pregnancy by the woman, but also by the man, was associated with an increased risk of spontaneous abortion and foetal death. The Committee concluded that it was not possible to establish a threshold for alcohol consumption by the man and/or the woman before conception below which an adverse effect on fertility and pregnancy can be categorically ruled out. Alcohol consumption during pregnancy affects the breathing movements and psychomotor development of the child and increases the risk of spontaneous abortion, premature birth, low birthweight, foetal alcohol syndrome and foetal death. Some abnormalities might even occur in connection with low alcohol intake, and there is a clear dose-effect relationship. The Health Council has pointed out that it would be necessary to abstain from alcohol altogether in order to rule out any risk.[102]

Several studies have been performed with a view to establishing the effect of education on the alcohol consumption of heavy drinkers. General public information campaigns were found to have little impact on women who consume more than 5-6 glasses per day during pregnancy.[103] In the United States, it was found that alcohol intake among this group of women could only be reduced through intensive educational programmes and supervision.[104,105] Education is more effective in moderate drinkers. It has been known for some time that the percentage of women who drink during and prior to pregnancy decreases in periods when there is a great deal of publicity about the effects of alcohol on the foetus.[106,107] Finally, personal counselling has been found to be more effective if it is given to both prospective parents rather than to the mother only.[102,108]

As in the earlier Health Council advisory report, the Committee recommends that women who wish to become pregnant and their partners should be "urgently and personally" advised against consuming alcohol.[102]

3.2.3 *Other recreational drugs*

The effects of using recreational drugs other than alcohol and tobacco on conception, pregnancy and the foetus depend greatly on the type of substance that is used. Sufficient data have been collected on the use of cannabis, cocaine, opiates and amphetamines to conclude that these recreational drugs have adverse effects. To start with, there is a relevant adverse impact on fertility prior to conception.[109-111] More serious for the health of the child, however, are the consequences of drug use during pregnancy, which include increased risk of death, low birthweight, postnatal withdrawal symptoms and subsequent developmental and concentration disturbances.[112-116] Less is known about the effects on the unborn child of other substances such as LSD and hallucinogenic mushrooms. Nevertheless, drug use is frequently associated with serious psychosocial problems and addiction.

The Committee believes that enough is known to urgently advise women and men who want to have children against using any hallucinogenic drugs.

3.3 Conclusions and recommendations with regard to food, alcohol, tobacco and other recreational drugs

3.3.1 *Conclusions and recommendations with regard to food*

A healthy, varied diet is important to everybody, and therefore also for those who wish to have a child.

Folic acid and iodine are the only nutrients discussed above for which it has been shown that an appropriate level ought to be achieved and maintained prior to conception. The Committee feels that this may also be advisable in the case of vitamin D. As far as vitamin A is concerned, the maximum intake should be considered prior to conception. The conclusions that have been reached with regard to the effects of these nutrients are summarised below:

Nutrients	Level of evidence
An intake of 0.4 mg folic acid per day, starting at least four weeks before the desired conception and continuing for eight weeks thereafter, reduces the incidence of neural tube defects by two-thirds. A1[48,58]	Level 1
Folic acid supplementation also assists in preventing other congenital abnormalities apart from neural tube defects. B[59]	Level 3
The recommendations regarding folic acid supplementation are still inadequately heeded and followed up. B[60,61]	Level 2
Vitamin A may possibly give rise to birth defects at dosages above 3000 µg per day. B[70,71]	Level 2
Vitamin D deficiency occurs in more than half of the non-Western women in the Netherlands. B[79,80]	Level 2
Vitamin D deficiency in the third trimester of pregnancy is (among other things) associated with convulsions and rickets in newborns. B[82,83]	Level 2

Based on the above conclusions, the Committee recommends that women who wish to become pregnant should be advised to start taking folic acid supplements at least four weeks before the desired conception and continue for eight weeks thereafter, and that women with a non-Western background should likewise take vitamin D supplements if they are dark-skinned or have little exposure to sunlight. Furthermore, it is inadvisable to eat liver products owing to the hazards associated with excessive vitamin A intake.

Finally, pending the Health Council advisory report, such women must be alerted to the important role that a healthy diet plays in ensuring adequate iodine intake.

As far as iron is concerned, it is sufficient to monitor haemoglobin levels during pregnancy. There is no evidence that magnesium and zinc supplementation is necessary before or during pregnancy. Specific preconceptual advice is not necessary in these cases.

Nor does specific consideration need to be given to the other vitamins and minerals during preconceptual counselling, since – as far as we know – levels of these substances in the mother's body do not need to be any different before conception or during the first few weeks thereafter than at any other time. For these nutrients, it is sufficient to give advice about a normal, healthy and varied diet

(see the Health Council's *Guidelines for a Healthy Diet*). A diet history can help to determine whether future parents do actually eat healthily.

3.3.2 *Conclusions and recommendations concerning alcohol, tobacco and other recreational drugs*

Tobacco, alcohol and other recreational drugs	Level of evidence
Smoking (active or passive) is associated with low birthweight and "cot death" A1[93,94]	Level 1
In order to be effective, advice to stop smoking should be personally supervised A1[98,101]	Level 1
Preconceptual counselling on smoking cessation is cost-effective B[100]	Level 3
Alcohol consumption prior to conception adversely affects the fertility of women *and* men A1[102]	Level 1
Alcohol consumption during pregnancy is associated with foetal alcohol syndrome, spontaneous abortion and foetal death A1[102]	Level 1
Education about alcohol consumption is most effective in moderate drinkers and when given both to the man and the woman. B[105,108]	Level 2
Use of cannabis and hard drugs prior to conception is associated with reduced fertility in men *and* women B[109-111]	Level 2
Drug use during pregnancy is associated with increased perinatal mortality, low birthweight, developmental disorders B[112-116]	Level 2

Based on the above conclusions, the Committee believes that preconception care should include urgent advice to stop smoking and using drugs before conceiving a child. Furthermore, in order to be sure of excluding all of the undesirable effects of alcohol, it is necessary to abstain from alcohol altogether prior to conception.

Chapter 4

Working conditions

This chapter considers working conditions that can adversely affect the course and outcome of pregnancy. For many of these factors, the critical period is periconceptional – i.e. both before conception and in the first few weeks of pregnancy, when many women are still unaware that they are pregnant.

Working conditions that are associated with one or more adverse pregnancy outcomes – such as spontaneous abortion, premature birth, low birthweight and congenital abnormalities – include chemical factors, physical factors and general factors. Examples of chemical factors are organic solvents and pesticides. Physical factors include heat, cold, ionising radiation, noise and vibration. General factors are physical/psychological stress and shift work. In this chapter we examine all of these factors, after a brief discussion of the Occupational Health and Safety Act (*Arbowet*). Another possible work-related factor with adverse pregnancy outcomes is infections, which are discussed in chapter 5. Most of the literature about the impact of working conditions on pregnancy outcomes deals with the second and third trimester of pregnancy. As far as the Netherlands is concerned, this body of knowledge is summarised in the *Signaleringsrapport Beroepsziekten 2006* [horizon-scanning report on occupational diseases], published by the Netherlands Centre for Occupational Diseases (NCVB).[117] In addition, a guideline on *Pregnancy and Work* is due to be issued by the Dutch Association for Occupational and Industrial Medicine (NVAB) in autumn 2007. Less is known about the impact that working conditions during the periconceptional period (i.e. prior to conception and in the first few weeks thereafter) have

on the subsequent pregnancy outcome. The available literature on this topic mainly concentrates on the first few weeks of pregnancy. Where possible, the Committee endeavours to make a distinction in this chapter between effects prior to conception and effects during early pregnancy.

When formulating its recommendations in this chapter, the Committee has worked on the premise that measures aimed at preventing adverse health effects due to working conditions in the first few weeks of pregnancy usually come too late if one waits until the pregnancy has been established. If steps need to be taken in early pregnancy, it is therefore usually advisable, for safety's sake, to act prior to conception.

4.1 Occupational Health and Safety Act

Under the Dutch Occupational Health and Safety Act (*Arbowet*), employers are required to ensure that their employees work under good conditions, so that, ideally speaking, they will not suffer any appreciable harm during their working lives (approximately 40 years) as a result of their work.[118] This is even more important in the case of women who are, or want to become, pregnant. In order to obtain advice on this subject, most employers are registered with an occupational health and safety service (*Arbodienst*), whose experts can give them the necessary advice.

4.1.1 Protection of employees

The occupational hygiene strategy provides a framework within which one can adopt control measures of the type described in the Occupational Health and Safety Act. This strategy consists of the following elements:

1 Preferably, one should eliminate or reduce the source of the problem (i.e. replace a hazardous substance with a less hazardous one, or use closed systems).
2 If this is not possible, or does not reduce the risk sufficiently, general technical safeguards should be considered (e.g. venting).
3 The next step consists of collective, usually organisational and/or procedural measures (e.g. placing personnel in a sealed room from which the process can be monitored or providing advice on lifting).
4 If this is not successful, personal protective equipment is used (e.g. protective gloves or respiratory protection).

By adopting this strategy, the employer ensures that the employees are effectively informed about the work they are to perform and the associated risks, and also about the measures that are aimed at preventing or limiting these risks. A good source of information is the risk identification and assessment (RIA) system something which every company, in theory, possesses providing it is up to date. If the information from the RIA is out of date, unclear or incomplete, assistance can be sought from an occupational health and safety specialist, who can instigate a study.

As far as chemical agents are concerned, the RIA will indicate whether the company uses substances that feature on the lists of carcinogenic, mutagenic and reprotoxic substances.[119-121]

4.1.2 *Protection of parents-to-be*

The Dutch Occupational Health and Safety Decree (*Arbobesluit*) and the Occupational Health and Safety Regulation (*Arboregeling*), which implement the general provisions of the Occupational Health and Safety Act, state that the following strategy can be adopted when supporting couples who want to have children or pregnant women who have been exposed to chemical agents at work:

1 There must be no exposure to substances with a direct genotoxic mechanism of action around the time of conception, during pregnancy or during breastfeeding. These include all mutagens and a significant proportion of carcinogenic substances. This is because it is not possible to determine a safe exposure level for these compounds.

2 It may be possible to determine a safe exposure level for substances which have been identified as potentially harmful to the unborn child or infant but which definitely do not have a genotoxic mechanism of action. However, this requires a high level of expertise which not every occupational health and safety officer can automatically be presumed to possess. If, however, it proves impossible to establish a safe exposure level then the precautionary principle will apply: i.e. avoid all exposure.

3 If the reprotoxic effect has been taken into account when setting the statutory limit value for the substance in question then women may work with this substance during pregnancy and breastfeeding providing it can be shown that the statutory limit value is not exceeded. It should be borne in mind here that the statutory limit value may be out of date. An occupational health and safety specialist should, in any case, carefully consult the Health Council advisory reports about the substances in question.

4 If insufficient data are available about the possible reprotoxic properties of a substance and/or if there is uncertainty about the safety of the actual exposure level (and absorption through the skin is considered possible) then the precautionary principle should be applied. In other words, the advice must be: avoid exposure.

4.1.3 Rule-making and compliance

As far as occupational exposure limit values are concerned, it was mainly the government that defined limit values up until 1 January 2007. Now, however, industry is itself, in the first instance, responsible for setting limit values – although it should be noted that all limit values must be set at a medically safe level. It makes no difference whether the limit value is set by industry or by the government. The government will still define the limit values for a certain group of substances. This category comprises a total of 170 substances, which are listed in Appendix XIII of the *Arboregeling*.

The *Arbobesluit* and the *Arboregeling* also provide guidelines and limit values or process standards (if it is not possible to set a specific limit value) for exposure to physical factors.[122]

Although risk reduction would also be adequately managed for couples wishing to have a child if there were proper compliance with the legislation and regulations, compliance is frequently found to be lacking in practice. Admittedly, working conditions usually receive sufficient attention in larger organisations, but in the small and medium-sized enterprises and in the case of small independent businesses, occupational health and safety efforts have in recent years mainly been aimed at reducing absence through illness (with considerable success) and not primarily at ensuring good working conditions around the time of conception. Renewed attention needs to be paid to working conditions, especially in relation to pregnancy. It might be possible for the Dutch Health and Safety Inspectorate to conduct more frequent checks into whether pregnancy is taken into consideration in a company's occupational health and safety policy, especially in the RIA.

4.2 Chemical factors

4.2.1 Organic solvents

It has long been known that exposure to organic solvents (such as toluene, xylene, trichloroethylene) during the first trimester of a pregnancy can harm

women and their unborn children. A meta-analysis performed in 1998 on case-control and cohort studies in which women had been exposed to solvents during the first trimester of pregnancy produced an odds ratio of 1.64 (95% CI 1.16-2.30) for congenital abnormalities (five studies; 7036 patients) and an odds ratio of 1.25 (95% CI 0.99-1.58) for spontaneous abortion (five studies; n=2899 patients).[123]

A case-control study conducted among 200 children revealed an increased risk of abnormalities when the mother had been exposed to solvents during pregnancy. Further analysis revealed an increased risk of abnormalities in connection with exposure to organic chlorinated aliphatic solvents (e.g. tetrachloroethylene: OR 4.40 (95% CI 1.41-16.15)).[124]

Looking at the period prior to conception, a meta-analysis from 2005 revealed an association between exposure to organic solvents and the birth of a child with a neural tube defect, but no increased risk of spontaneous abortion.[125] As the exact relationship between exposure and effect is not yet known, the authors advise for the time being that not only women but also men who want to have a child should minimise their exposure to organic solvents from at least three months before the desired conception date. The authors adopt this time-frame because it is the time that spermatozoa take to mature. A Dutch study from 2006 also showed a relationship between exposure to solvents and congenital abnormalities in offspring, with painters appearing to have a higher risk for congenital abnormalities in their offspring than carpenters.[126]

Research performed by the Solvent Team at the Academic Medical Centre (AMC) in Amsterdam shows that solvent exposure in connection with hobbies or when painting one's own house generally only amounts to a fraction of average occupational exposure*.

One problem with all of the studies that have been mentioned is the great variation in solvents, exposure levels and effects, which makes it difficult to draw firm conclusions, other than the conclusion that there appears to be a relationship between preconceptual exposure to high concentrations of organic solvents and adverse pregnancy outcomes. A further Health Council publication about these substances a draft advisory report entitled *Occupational exposure to organic solvents: effects on human reproduction* is to be released at around the same time as this report on preconception care. This will take a closer look at various groups of solvents and their effects on human health, including the health of would-be parents.

* Personal communication from Dr. T. Brand

Pending this second report, the definitive version of which is expected to be published in early 2008, the Committee recommends that parents-to-be should be asked at the preconception consultation whether they work with organic solvents and that, if necessary, the risks of such exposure should be discussed with them. In theory, the risks will be minimised by applying the limit values, which are based on health-based recommended exposure limits stipulated in the *Arbobesluit*, and thus complying with the Occupational Health and Safety Act.

Couples can also be asked about any hobbies that might involve exposure to organic solvents at the first preconception consultation.

4.2.2 Anaesthetic gases

A meta-analysis conducted in 1997 revealed that women who were occupationally exposed to anaesthetic gases during the early part of their pregnancy were at increased risk for spontaneous abortion (OR 1.9; 95% CI 1.72-2.09).[127]

An association was discovered as long ago as 1994 between occupational exposure to nitrous oxide ('laughing gas') during early pregnancy and increased risk of having child with a low birthweight.[128] No literature was found with regard to exposure of men and possible adverse pregnancy outcomes.

The Committee recommends that the occupational exposure to anaesthetic gases of women who wish to become pregnant should be discussed at a preconception consultation. In theory, the risks are minimised by applying the health-based exposure limits and therefore complying with the Occupational Health and Safety Act. The Committee also draws readers' attention to the previous advisory reports published by the Health Council on this subject.[129-134]

4.2.3 Chemotherapeutic agents

Medical doctors, nurses, pharmacists and pharmacy assistants may be exposed to chemotherapeutic agents during their work. Many of these anti-cancer drugs serve to inhibit cell division. Others induce programmed cell death, inhibit certain enzymes or hamper the formation of blood vessels. Researchers have investigated the extent to which female workers were harmed by preconceptual occupational exposure to these substances.

Saurel-Cubizolles and Job-Spira (1993) studied the relationship between ectopic pregnancy and exposure to antineoplastic drugs in two groups of female employees (namely operating theatre personnel, with very little exposure to cytostatics, and nurses from other departments, with a higher exposure) in hospitals in Paris.[135] Using logistical regression analysis, they found that women who had

been exposed to antineoplastic drugs had a higher risk of ectopic pregnancy than nurses who had not experienced such exposure (OR 10.0; 95% CI 2.1-56.2).

Valanis *et al.* (1999) conducted a case-control study on the effects of antineoplastic drugs on self-reported spontaneous abortion and stillbirths in nursing and pharmacy staff. A total of 7,094 pregnancies in 2,976 women were examined.[136] After correction for confounders, maternal occupational exposure to antineoplastic drugs during pregnancy was found to be associated with an increased risk of spontaneous abortion (OR 1.5; 95% CI 1.2-1.8).

There is clear evidence that pregnant women who are exposed to antineoplastic drugs during their work have a greater risk for spontaneous abortion or stillbirth. The Committee recommends that women should preferably avoid exposure to antineoplastic drugs prior to conception (from the moment that the woman wishes to become pregnant), since it is too late to intervene once pregnancy has been established.

4.2.4 *Pesticides*

Several European case-control studies have shown that women who were exposed to pesticides during the first three months of their pregnancy were at increased risk for having a child with congenital abnormalities, such as a cleft palate or abnormalities of the central nervous system.[137-139] Furthermore, two case control studies have shown that preconceptual exposure of the father also led to an increased risk of congenital abnormalities and foetal death.[110,141]

The Committee believes that men who want to have children should minimise their exposure to pesticides well in advance of the desired conception date (at least three months, this being the time that sperm take to mature). It also recommends that women who want to have children should preferably avoid exposure to pesticides prior to conception (from the moment that the woman wishes to become pregnant), since the Committee feels that it is too late to intervene once pregnancy has been established.

4.2.5 *Metals*

There is little recent literature available on the effects of exposure to metals during pregnancy on its outcome. A number of metals and salts are nevertheless included on the Ministry of Social Affairs and Employment's *Non-Limitative List of Reprotoxic Substances*, with lead and methyl mercury compounds being the most harmful to the unborn child. Other substances also listed as harmful (albeit somewhat less so) are: cadmium salts, chromium VI and several of its

compounds, metallic mercury and nickel salts. Finally, cadmium is listed as potentially harmful to the unborn child.[121,145]

Exposure of prospective fathers (and mothers) to the fumes produced when welding stainless steel appears to be harmful due to the carcinogenic hexavalent chromium that is released. The literature about this potential hazard is still inconclusive, however. Various explanations have been advanced, such as the possibility that the registries may be incomplete and the differences between study populations.[142-144]

The Committee recommends avoidance of exposure to metals featured on the above-mentioned non-limitative list of reprotoxic substances prior to conception. In the interests of safety, occupational exposure (of men and women) to welding fumes should also preferably be avoided prior to conception (from the moment that the woman wishes to become pregnant), since it is too late to intervene once pregnancy has been established. Compliance with the Occupational Health and Safety Act will, generally speaking, reduce the risks to a minimum.

4.3 Physical and general factors

4.3.1 Radiation, noise, temperature, vibration

Physical factors that may possibly affect the course and the outcome of a pregnancy are radiation, noise, temperature and vibration. Little or no literature has been found about the impact on pregnancy outcomes of limited (preconceptual) exposure to physical factors. This is not to say, however, that there are no adverse effects. For example, it is known that high doses of ionising radiation are harmful throughout pregnancy. This has not been demonstrated in the case of low doses, but it may well be that these effects only emerge with the passage of time. In view of the methodological shortcomings of those studies that are available in this area, well-designed research into the relationship between physical working conditions prior to conception and pregnancy outcomes is needed in future in order to clarify the situation. As exposure to radiation, noise, temperature and vibration during pregnancy has, in fact, been found to have an impact on pregnancy outcome in a number of studies, it is important to adopt a precautionary approach.[146-149] Various regulations are therefore laid down in the Occupational Health and Safety Decree with this in mind.[150] During her pregnancy, a pregnant worker must not:

- be exposed to more than 1 mSv of radiation in addition to the background radiation that is always present;
- be exposed to noise in excess of 80dB for any more than eight hours per day;

- be exposed to vibration with an acceleration in excess of 0.25 m/s^2 for eight hours.

Men are subject to the normal occupational health and safety standards.

4.3.2 *Stress*

Evidence has been found in the literature to suggest that pregnant women who experience a high level of psychological stress are at increased risk of spontaneous abortion (OR 2.27, 95% CI 0.97-5.27).[151]

Oths *et al.* (2001) found that babies whose mothers had experienced a great deal of stress in the first trimester of pregnancy weighed an average of 190 grams less at birth than those whose mothers had not experienced this stress.[152] Effects of this kind on birthweight were also evident from the initial results of the Amsterdam Born Children and their Development (ABCD) study. The combination of high job demands, low decision latitude and a long working week (32 or more hours per week) during the first trimester of pregnancy was found to correlate with a reduction of around 150 grams in the child's birthweight.[153]

4.3.3 *Shift work, night work and physically demanding work*

Pregnant women who perform shift or night work or do work that is physically demanding in some other way are at increased risk of premature birth (RR 1.25).[146,154,155] There is no known, obvious threshold to identify the moment in the pregnancy at which the adverse effects of shift or night work make themselves felt. The Croteau study indicates that the adverse effect can be substantially mitigated by adapting the working conditions before week 24 of pregnancy.[155] In the Netherlands, a pregnant woman must stop working between the hours of 11 pm and 7 am from week 20 of her pregnancy. The adverse pregnancy outcomes of physically demanding work can be prevented by reducing the physical demands made on pregnant women during the second and third trimester of pregnancy.[154]

The literature search failed to find any evidence of these factors having adverse effects prior to conception or in early pregnancy.

4.4 Conclusions and recommendations concerning working conditions

4.4.1 Conclusions and recommendations: chemical factors

Chemical factors	Level of evidence
Occupational exposure of women *and* men to high concentrations of organic solvents prior to conception and of women in early pregnancy leads to an increased risk of spontaneous abortion or congenital abnormalities in the child. B[123-126]	Level 2
Occupational exposure to anaesthetic gases during early pregnancy increases the risk of spontaneous abortion. B[127]	Level 2
There is clear evidence that women who have been occupationally exposed to antineoplastic drugs in early pregnancy are at increased risk of spontaneous abortion or stillbirth. B[135,136]	Level 2
Women who have been occupationally exposed to pesticides in early pregnancy are at increased risk of having a child with abnormalities of the nervous system or a cleft lip or palate. B[137-139]	Level 2
Exposure of the father to pesticides around the time of conception increases the risk of foetal death as a result of congenital abnormalities. B[141]	Level 3
Lead, methyl mercury compounds, cadmium salts, chromium VI and some of its compounds, metallic mercury and nickel salts are harmful to the unborn child. Cadmium may be harmful to the unborn child. A[121,145]	Level 1
Exposure of future parents to stainless-steel welding fumes around the time of conception appears to increase the risk of spontaneous abortion. B[142-144]	Level 2

In theory, compliance with occupational hygiene regulations reduces the risks of exposure to chemical factors sufficiently. However, the Committee recommends that occupational exposure to chemicals should be discussed in a preconceptual consultation.

4.4.2 *Conclusions and recommendations with regard to physical and general factors*

Stress	Level of evidence
Work stress in the first trimester of pregnancy is associated with an increased risk of spontaneous abortion and lower birthweight. B[152,153] C[151]	Level 2

No evidence has been found to justify preconceptual measures with regard to radiation, noise, temperature and vibration over and above the existing occupational safety rules . Pending the results of further research, the Committee therefore recommends that the standards laid down in the Occupational Health and Safety Decree should be observed during early pregnancy and that these should be applied as soon as the pregnancy is established. For men, the existing occupational health and safety standards can be applied for the time being.

Based on the evidence it has gathered, the Committee concludes that there is no need at this stage to advise against shift work and night work prior to conception. For the time being it is sufficient to comply with the standards that have been laid down for pregnant women in the Occupational Health and Safety Decree and the Occupational Health and Safety Regulation. The Committee does recommend, however, that exposure to stress should be limited even before conception.

Chapter 5

Illness, medication and other health-related factors

This chapter discusses those illnesses and medicines for which specific advice is given for prospective parents in the scientific literature*. This may either be due to possible adverse effects of pregnancy on the illness or, conversely, the potential impact of the illness on the health of the future mother and/or her child.

It was already stated in chapter 1 that, for the purposes of this advisory report, we searched for literature that offered the highest level of evidence, with "preconception care" as the limiting search term. Consequently, not all disorders that merit consideration in preconception consultations have been included in this chapter. Most importantly, a pre-existing illness (chronic or otherwise) must always be discussed in a primary-care preconception consultation and, if necessary, the patient should be referred to secondary care. As preconception care is developed, research will shed further light on which disorders merit attention prior to conception and which ones can be monitored equally well or better in prenatal care.

* A precise explanation is given in chapter 1 and annex C.

5.1 Illness

5.1.1 Infectious diseases

The systematic literature search that was performed for this advisory report yielded little literature about infectious diseases during the preconception phase. As far as food- and pet-related infectious diseases are concerned, we therefore used the information from the Netherlands Nutrition Centre. For diseases that feature in the National Vaccination Programme (RVP), we used the RVP website, which is hosted by the National Institute of Public Health and the Environment (RIVM), and the Health Council advisory report on *The Future of the National Vaccination Programme*.[156,157]

Transmission via food or animals

Pregnant women are made aware of the hazards posed by infectious diseases that can be transmitted via food or pets during their first visit to the midwife and through a wide variety of leaflets and websites. The Netherlands Nutrition Centre website names several micro-organisms that can occur in contaminated food, such as Salmonella, Campylobacter and Listeria. Perishable, potentially contaminated foods should, in any case, be refrigerated and consumed as soon as possible. Eggs and meat must be cooked thoroughly (there is, for example, a greater risk of undercooking meat when barbecuing). Chicken is particularly notorious in this respect. Milk should be pasteurised or sterilised (i.e. boiled).[51] Two parasites merit special consideration as far as contact with pets is concerned: *Echinococcus multicularis* and *Toxoplasma gondii*. In view of the seriousness of the associated illnesses, care should be exercised when eating wild fruit, mushrooms and fallen fruit (apples, pears, plums) or raw meat, and when cleaning out cat litter trays and gardening.

The Committee recommends that this information should be given to couples at a preconception consultation and discussed, so as to avoid the possibility of infections in early pregnancy.

Sexually transmissible diseases (STDs)

If the prospective mother and/or father are known to have an STD, it is important that steps are taken prior to conception to prevent the child from becoming infected and to avoid complications in the expectant mother.[37,158]

HIV, chlamydia, gonorrhoea, herpes genitalis, syphilis and hepatitis B can be transmitted to the child during delivery if the mother is infected. HIV, syphilis and hepatitis B can also be transmitted during pregnancy. Consequently tests are currently always conducted for syphilis and hepatitis B during pregnancy. If these STDs are detected in good time, it is possible to prevent the baby contracting the disease. This can be done either with medication or by taking the appropriate action during and immediately after the birth (caesarean, vaccination of the newborn). Diagnostic testing for the presence of these conditions prior to pregnancy is clearly preferable, since the illness can then be treated and cured or consideration can be given to the implications of the illness for a pregnancy and vice versa.

It is worth pointing out that transmission of HIV from mother to child can take place not only during pregnancy or childbirth, but also postnatally via the breast milk. In its guideline on antiretroviral treatment, the Dutch Association of Physicians in AIDS (NVAB) states that since 1 January 2004 all pregnant women in the Netherlands have been required to undergo an HIV test in order to prevent vertical HIV transmission.[159] Here too, however, it is better to know whether a woman is HIV-positive before she becomes pregnant. Without intervention the incidence of HIV transmission from mother to child ranges from 15-40 per cent. By administering antiretroviral therapy, possibly combined with an elective caesarean section, avoidance of invasive procedures during pregnancy and delivery, and refraining from breast-feeding, it is nowadays possible to reduce maternal transmission of HIV to less than 1-2 per cent. Partly through the success of current antiretroviral therapy, an increasing number of HIV-infected women are consciously choosing to become pregnant, or at least no longer avoiding pregnancy. Readers are referred to the above-mentioned guideline for detailed information about policy regarding HIV-positive pregnant women.

The Committee believes that couples who want to have children but are suspected to be at increased risk of an STD (especially HIV) should be fully informed about possible diagnostic tests and about the advantages of being tested prior to pregnancy. They should also preferably be informed prior to conception about treatment and about the potential consequences for the future child.

Infectious diseases and the National Vaccination Programme

Immunisations against significant infectious diseases that pose a threat to pregnant women and/or unborn children are included in the National Vaccination Programme (RVP). The Health Council's advisory report on *The Future of the National Vaccination Programme*, published in early 2007, indicates the infec-

tious diseases for which specific vaccinations could be available prior to conception.[156]

The first such disease to be considered is rubella ('German measles'), which is hazardous for the unborn child and can lead to congenital rubella syndrome (blindness, deafness and immune disorders). Children are currently vaccinated against rubella, together with measles and mumps, at 1 and 9 years of age.[157] The advisory report states that the possibility of incorporating rubella vaccination in the preconception care programme could be considered.

At present, pregnant women are often given a blood test during their first visit to the midwife in order to measure their rubella antibody titre. During the rubella epidemic in 2004-2005 there were no recorded cases of the disease in women who had previously been vaccinated or in their newborn children. This further reinforces the belief that vaccination (or infection) gives rise to extremely long-term (and perhaps even life-long) protection. A woman's vaccination status could be examined during preconception care and then, if she has been vaccinated under the RVP, she can be assumed to be adequately protected against rubella. If this is not the case then the antibody titre can be tested. If the titre is low or non-existent then the woman can be vaccinated (or revaccinated) prior to conception.

In theory, the same applies for measles, which is mainly hazardous to very young children. If it is uncertain whether a woman who wishes to have a child has been vaccinated against measles under the RVP, or whether she has had the disease, the antibody titre can be determined. If necessary, she can then be vaccinated before she becomes pregnant.

Since around 1980, a worldwide increase has been observed in the number of cases of whooping cough owing to declining levels of immunity among older children and adults. Given the seriousness of the disease – especially for very young children –the preconception consultation could be used as an opportunity to determine which adults and children around the future child might need to be vaccinated (or revaccinated) in order to protect the newborn against whooping cough infection. This particularly concerns those who will be in daily contact with the baby.

Pending further advice from the Health Council Committee on the National Vaccination Programme, the Committee recommends that the vaccination status of future parents (and possibly other family members) should be discussed during the preconception consultation, especially as far as rubella, measles and whooping cough are concerned. Based on the findings, antibody titres can be determined and, if necessary, (re)vaccinations can be performed.

5.1.2 *Chronic illness*

Epilepsy

An epileptic seizure or attack is a reaction to an abnormal electrical discharge in the brain. Someone who suffers repeated attacks of this kind is said to have epilepsy. Approximately 1 in 50 adults experience a seizure at some time, but 1:1500 suffer recurrent attacks. As seizures can damage the brain and muscles, they are treated with anti-epileptic drugs. However, these compounds are frequently teratogenic. Women with epilepsy may (depending on the type) be at increased risk of having a child with epilepsy.

In a meta-analysis of ten studies conducted in 2004, it was not conclusively demonstrated that epilepsy *per se* is associated with a higher risk of congenital abnormalities (OR 1.92; 95% CI 0.92-4.00), but this does not mean that maternal epilepsy does not represent a risk to the unborn child.[160] A maternal seizure can cause problems in the child's blood circulation and oxygen supply. Furthermore, there is an increased risk of a seizure during childbirth. A recent observational cohort study involving 2,000 pregnant women with epilepsy from the EURAP epilepsy pregnancy registry reported increased seizure frequency in 17 per cent of the pregnant women and a decrease in 16 per cent. No change was observed in the other 67 per cent. Ninety-three per cent of these women were actually seizure-free throughout their pregnancy.[161]

Although 90 per cent of pregnant women with epilepsy give birth to a healthy child, the use of anti-epileptic drugs (AEDs) is associated with an increased risk of an adverse pregnancy outcome. In the introduction to a 2004 Cochrane review of the most widely prescribed and used anti-epileptic drugs (examining the literature between 1966 and 2003), it was stated that exposure of the unborn child to AEDs increases the risk of stillbirth, perinatal and neonatal mortality and mild and severe physical congenital abnormalities.[162] Although estimates of the precise risk vary, AED use appears to result in a two- to threefold increase in the risk of congenital abnormalities compared with women who do not use these drugs. It was not possible to undertake a comparison of different anti-epileptic drugs in this review since the majority of studies on individual substances were of limited quality. Polytherapy is more often associated with an adverse outcome than monotherapy. Monotherapy with the lowest-possible effective dose is therefore preferable to polytherapy.

Guidelines and preconceptual recommendations have for many years advised that women with epilepsy who are seizure-free should be allowed to

taper down their medication under the supervision of their neurologist – or, if complete withdrawal is not possible, the medication should be reduced to a single drug in the lowest dosage that can still effectively control the illness.[22,163,164] It has not been shown that newer anti-epileptic drugs are clinically superior and more cost-effective than older compounds.[165] Larger, sufficiently powerful studies that also examine specific congenital abnormalities are needed in order to determine precisely which drug(s) is (are) the least teratogenic.

In its epilepsy guideline, the Dutch Neurology Society (NVvN) states that education about epilepsy and pregnancy should include information about the risks for the mother's epilepsy, the teratogenic risks of the medication and the possibilities of reducing these by adjusting the medication and preconceptual supplementation with folic acid.[166]

In line with current practice, the Committee recommends that expectant mothers with epilepsy should, if possible, be switched to monotherapy during the preconception phase or, if the patient is seizure-free, that the medication should be tapered down under the supervision of a neurologist. The woman in question should continue to be managed by the specialist (or by a gynaecologist and a neurologist). Where there is a possibility that the woman or the man may have a hereditary form of epilepsy, referral to a clinical geneticist for investigation and counselling may be considered .

Diabetes mellitus

In this section we discuss only pre-existing diabetes. Treatment of gestational diabetes falls under prenatal care. During a second pregnancy, an earlier episode of gestational diabetes should, however, be discussed in the preconception phase.

The children of diabetic women are at increased risk of diabetes and congenital abnormalities. The malformations occur before the eighth week after conception.[167,168] Consequently, preconception care with close monitoring of blood sugar (glycaemic control) around the time of conception is generally recommended in order to minimise the number of congenital abnormalities in this group of children.[23,48] In fact, tight glycaemic control is important throughout the pregnancy, wherever possible, in order to prevent complications in the mother (destabilisation of the disease, deterioration of vascular abnormalities and parturitional trauma) or in the newborn child (excessively low blood sugar, high bodyweight (macrosomia), respiratory problems and birth trauma).

A meta-analysis of studies on preconception care in diabetic women (published between 1970 and 2000) showed that the pooled prevalence of serious congenital abnormalities in children of women who had received preconception

care was significantly lower than when no preconception care was received (2.1 % versus 6.5%; relative risk 0.36 95%; CI 0.22-0.59).[23] This was reflected in the significantly lower first-trimester glycosylated haemoglobin levels (used to measure the blood-sugar level over a longer period) of the women who received preconception care (pooled absolute average difference 2.3%; 95%CI 2.1-2.4), although the authors did identify heterogeneity between the various studies.

The American Diabetes Association (ADA) stated in 2004 that the care given to all diabetic women ought to include education about the risks of congenital abnormalities in the event of unplanned pregnancies and insufficient glycaemic control.[169] All women should also be advised to take long-term contraceptive measures until sufficient control is achieved and the patient actually wishes to conceive. This means that preconception care should be actively offered to these women instead of waiting until the woman herself indicates that she wishes to become pregnant.

The Dutch Society for Obstetrics and Gynaecology (NVOG) and the Dutch Diabetes Federation (NFD) also indicate in their respective guidelines on diabetes and pregnancy that care for diabetic women who want to have children begins prior to conception.[170,171] The NDF also states explicitly that risks during pregnancy must be actively discussed with *all* diabetic women of child-bearing age.

Two cost-effectiveness studies have independently shown that, although preconception care increases the costs per delivery for pregnant women with diabetes, those costs are amply recouped due to the cost savings achieved as a result of the reduced number of complications during pregnancy and childbirth.[172,173] Savings are likewise achieved through the lower incidence of congenital abnormalities and fewer complications in the newborn child.

The Committee recommends that preconception care should be discussed with diabetic women in good time and personally (and, if necessary, without needing to be requested). Tight glycaemic control must be achieved prior to conception.

Other chronic disorders

There are other chronic disorders apart from epilepsy and diabetes mellitus that can potentially have far-reaching effects on a pregnancy and vice versa and entail risks for the future child. Examples are hypertension, thyroid disorders and cardiovascular disease in the mother. For a detailed discussion of these conditions, readers are referred to the forthcoming report on *Best Practices in Preconception Care* from the Clinical Committee of the US Select Panel on Preconception Care, which is due to be published in autumn 2007. When the literature search was

specifically limited to the search term "preconception care", epilepsy and diabetes mellitus were found to be the best researched conditions. As far as other chronic disorders are concerned, little or no literature was found that was of relevance to preconception care. The Committee has therefore confined its attention to these two disorders.

In actual fact, any chronic disorder can complicate a pregnancy (and vice versa). These aspects will need to be discussed in the personal preconceptual history. What is needed is a multidisciplinary care plan in which the gynaecologist who will supervise the pregnancy coordinates the treatment and support.

5.1.3 Obstetric/gynaecological history

A woman's obstetric/gynaecological history can influence her fertility and the course of a future pregnancy and delivery. Known risk factors for less favourable pregnancy outcomes are: abnormal outcomes of earlier pregnancies (repeated spontaneous abortion, premature or stillbirth, caesarean section, low birthweight or congenital abnormalities in previous children); pregnancy-associated disorders (gestational diabetes, blood-group antagonism, pre-eclampsia, HELLP syndrome); a history of gynaecological problems (malformations of the uterus or cervix, previous gynaecological operations, DES use by the mother or grandmother).[174]

A woman with a complicated medical history (gynaecological or otherwise) who wishes to have a child should be referred to a gynaecologist. He/she can then still discuss the problems with the future parents prior to conception and monitor the pregnancy. Women with this kind of history who have already experienced a pregnancy are usually monitored by a gynaecologist from the outset during a subsequent pregnancy. In some cases (especially in connection with repeated spontaneous abortion, stillbirth or prolonged infertility) referral to a clinical geneticist may also be appropriate.

Malformations of the uterus or cervix and other anatomical abnormalities (e.g. narrow pelvis) may possibly complicate a pregnancy, and vice versa. So too can past illnesses and operations.

Women with a problematic medical history who have already undergone pregnancies are usually monitored by a gynaecologist from the outset during a subsequent pregnancy. The Committee recommends that this support should be brought forward to the moment at which a further pregnancy is contemplated (i.e. preconceptual counselling).

5.2 Medication

5.2.1 Medication and pregnancy

Much is published about adverse health effects of medication (over-the-counter and prescription-only) for mother and child. When planning a pregnancy, it is therefore also important to consider any medication and, if necessary, to adjust this in consultation with the attending physician. Information about medication can serve as a warning, but it can also be reassuring in the case of drugs that can safely be used during pregnancy.[175]

In the case of many substances, however, little or nothing is known about what consequences they may have if used periconceptionally or during pregnancy. This is partly because pregnant women are excluded from the clinical trials that are required in order to obtain marketing authorisation for a given drug. There may be harmful effects on the child. Furthermore, pregnancy also causes physiological changes in the mother which may alter the way in which drugs are absorbed and eliminated.[176] Consequently it may be difficult to achieve optimal drug concentrations during pregnancy. In some cases (e.g. when using anti-epileptic drugs), it is then necessary to determine the plasma level.[177]

Many medicines have not been investigated sufficiently to draw definitive conclusions with regard to risk. There is a limited group of substances that have been proven to adversely affect foetal development, while incidental data have been published about the harmful effects of many other substances. A few well-known examples of drugs that have led to serious congenital abnormalities in the past are thalidomide (Softenon), diethylstilboestrol (DES) and isotretinoin (a vitamin A derivative). It was the Softenon affair that led to the establishment of the Dutch Medicines Evaluation Board (CBG) in 1963. In the case of DES, the effects were noticeable for several generations. It is partly because of experiences with these highly teratogenic drugs that medication use in the period prior to and during pregnancy is now subject to closer scrutiny and more animal toxicology studies take place before a product is allowed on to the market.[178,179] In the majority of cases, however, the data that are needed in order to accurately estimate the risks a drug may pose during pregnancy are simply not available.

There are various reasons for the lack of information about the risks of medication. Firstly, much of the published research is methodologically flawed. Some publications give the total number of identified congenital abnormalities but do not include any data about specific abnormalities. Other researchers have

grouped several substances together (e.g. serotonin reuptake inhibitors), thus neglecting to explore the possibility that particular substances may present relatively high risks. Furthermore, the prevalence of congenital abnormalities in a group of exposed pregnant women is often compared with the prevalence in the general population, whereas the average age and health of these women differs from that in the population as a whole. Secondly, studies often only involve a limited number of exposed pregnant women and consequently lack sufficient power to identify less common congenital abnormalities.

Generally speaking, a woman who is or would like to become pregnant should preferably take as little medication as possible owing to the risk of harming the unborn child. This also applies in the case of over-the-counter drugs, herbal remedies and homoeopathic medicines. She should therefore always consult a doctor or pharmacist to establish whether the preparations in question can be used. A study performed in Groningen showed that 80 per cent of pregnant women were prescribed at least one medicine during pregnancy.[180] 1.7 per cent of the drugs that were prescribed for chronic disorders and 2.3 per cent of the drugs for temporary use were classified as harmful to the pregnancy. Thus even more restraint needs to be exercised, especially when prescribing medication to women of child-bearing age for temporary use.

It is sometimes impossible to discontinue medication completely prior to pregnancy. In this case it will be necessary to assess what medication is to be used for a particular individual during pregnancy and how it is to be administered. Doctors, midwives and pharmacists can consult the Teratology Information Service (based at the RIVM) on these matters. The Committee also refers readers to *Geneesmiddelen, Zwangerschap en Borstvoeding* [Medication, Pregnancy and Breast-feeding] (RIVM/Stichting Health Base), the fourth edition of which was published in early 2007. This book includes a chapter entitled ‘Medication and the desire to have a child’. In each chapter, medicines are classified by therapeutic category and an indication of risk is provided. This reference work also has an alphabetical index of all of the drugs that are discussed. It includes virtually every medicinal product on the market in the Netherlands and/or Belgium, listed both by brand name and by active compound.[181]

It is extremely important that women of child-bearing age should be made aware of the risks of medication prior to pregnancy. Meijer *et al.* showed that information from pharmacists about folic acid was not only valued by the target group but also perfectly feasible.[182]

Below we consider two classes of drugs whose use in the preconception phase definitely ought to be discussed in view of the explosive increase in their use, not least by women of child-bearing age.

5.2.2 *Antidepressants*

A substantial proportion of women of child-bearing age suffer from depression. A recent meta-analysis of prospective comparative studies on antidepressants showed that the use of modern antidepressants (introduced after 1980) did not lead to more congenital abnormalities than in the babies of women who did not take antidepressants.[183] However, this review encompassed a wide range of substances and all congenital abnormalities were considered collectively. The individual studies lacked the power to examine individual drugs and specific congenital abnormalities. More recent studies do identify increased risks, such as cardiac abnormalities following exposure to paroxetine in the first trimester of pregnancy and lower birthweight and respiratory difficulties after exposure to SSRIs during pregnancy.[184,185] Severe withdrawal symptoms and pulmonary hypertension have also been observed in newborns whose mothers had taken antidepressants during pregnancy.[186,187] In those situations where these drugs do need to be taken before and during pregnancy, the advantages and disadvantages of this treatment should be discussed in full with the women concerned.

Where possible, the Committee believes that the use of antidepressants ought, in the interests of safety, to be adjusted prior to conception. If the patient is free of symptoms, discontinuation may be considered. This can take several months.

5.2.3 *ACE inhibitors*

Another class of drug that has come to the fore since the 1990s are the ACE inhibitors, which are used in the treatment of hypertension. The range of indications for these compounds has broadened over the years and the number of younger patients treated with them has risen. In a recent cohort study, the use of ACE inhibitors in the first trimester of pregnancy was shown to be associated with an increased risk of congenital malformations of the cardiovascular system (RR 3.72; 95% CI 1.89-7.30) and of the nervous system (RR 4.39; 95% CI 1.37-14.02).[188] Although the use of ACE inhibitors by pregnant women in the Netherlands is currently very low, De Leeuw warns that ACE inhibitors should not be considered for treating hypertension in women who wish to have children or are already pregnant.[189,190] The Committee believes that women who use ACE inhibitors should preferably be switched to a different drug as soon as they wish to become pregnant.

The Committee recommends that women should be made aware of the general risks posed by medication (including OTC compounds) during preconception consultations. Wherever possible, the use of medication should be reduced. In those situations where medication is necessary before and during pregnancy, the GP or pharmacist and the relevant specialist should discuss the effects of the treatment in full with the women concerned.

It is important, however, to ensure that those people who genuinely need medication are still prescribed these drugs and that they continue to take them. It is likewise necessary to prevent women from stopping taking their medication without consulting their doctor.

5.3 Other health-related factors

5.3.1 Maternal and paternal age

The risk of chromosomal abnormalities increases with the age of the parents (see also chapter 6) and, partly because of this, so too does the risk of reduced fertility and congenital abnormalities in the children.[191]

In particular, research shows that the risk of numerical chromosomal abnormalities (aneuploidy) is to a great extent determined by the woman's 'reproductive age'. Research into oocyte donations has shown that the cause of aneuploidy lies in the age of the oocytes.[192] Among women under 25 years of age, aneuploidy was detected in 2 per cent of pregnancies, whereas this figure rose to more than 25 per cent among women over 40.

Women in the Netherlands tend to have their first child at a relatively late age (the average age in 2006 was 29.4 years).[193] Spain is the only country in the European Union where the average age at which women have their first child is higher.[194] As far as late motherhood (childbirth at 40-44 years of age) is concerned, the Netherlands occupies a mid-ranking position in the European Union. In 2003 there were 7.1 births per 1000 women aged 40-44 years in the Netherlands. Late motherhood is most common in Ireland, with 14.5 births per 1000 women between the ages of 40 and 44, and rarest in eastern Europe, with 3 births per 1000 women in this age range.[195] The chances of becoming pregnant fall sharply with increasing age.[196] The reduced chance of conceiving leads to a greater need for assisted reproduction, with all of the attendant adverse consequences such as multiple and premature births.

Paternal age can also have adverse implications for the future child. Irrespective of the mother's age, higher paternal age (>40 years) is associated with an

increased risk of spontaneous abortion, *de novo* dominant genetic disorders, autism and schizophrenia.[197-200]

From a medical standpoint, the optimum age to have children is between 25 and 30 years. Prospective parents ought to be encouraged during individual pre-conception consultations not to wait too long. Since people who have attended such consultations tend to discuss the issues with family members or friends, the latter might also stand to gain from advice of this kind. There are also often opportunities to encourage conception at a relatively young age in the case of young people with a chronic illness, since they are generally under the regular supervision of a doctor. This topic also deserves more attention from society at large. In its recent horizon-scanning report *Uitstel van ouderschap: medisch of maatschappelijk problem?* [Postponing parenthood: medical or social problem?], the Council for Public Health and Health Care (RVZ) highlights widespread ignorance about the medical risks of late pregnancies, even in well-educated circles. The RVZ therefore recommends that steps be taken to ensure that people are adequately informed about these risks. It also states that women, in particular, are nowadays receiving mixed messages in that they being are encouraged both to go out to work more and to have children at a younger age. The government can create a favourable environment and hope that this will result in different choices being made, and that people will come to feel that they can allow themselves to have children earlier from the point of view of education, work and income, career and stress.[201]

The Committee endorses the recommendations advanced by the RVZ.

5.3.2 *Weight before and during pregnancy*

Overweight and obesity can cause problems during pregnancy and childbirth. The standard measure of overweight and obesity is the body mass index (BMI: weight in kilograms divided by height in metres squared). People are considered overweight if they have a BMI of between 25 and 30, and obese if their BMI is 30 or above.

In 2000 a systematic review was published of 20 studies into complications during pregnancy and childbirth in overweight or obese women.[202] This review reveals the principal problems to be gestational diabetes and hypertension in the mother and congenital abnormalities in the child. The risk of diabetes is 1.8 to 6.5 times greater in overweight women than in those of normal weight, and 1.4 to 20 greater in the case of obesity. The risk of hypertension is increased by 2.2 to 21.4 times in women who are obese and the risk of pre-eclampsia by a factor of 1.2 to 9.7. A systematic review conducted in 2003 similarly showed a correlation

between overweight and the risk of pre-eclampsia, which doubled with every 5-7 kg/m^2 increase in BMI.[203] Neural tube defects are 1.5 to 3.0 more common in children of obese mothers.[202] Mortality among newborns rose by a factor 1.1 to 2.5 in overweight women and by a factor of 2.5 to 3.4 in the case of obesity.[202] In 2004 these risks were confirmed in a prospective multi-centre trial involving more than 16,000 female patients.[204] The American College of Obstetricians and Gynecologists (ACOG) has issued the following advice on preconception care with regard to obesity: "Obstetricians should provide preconception counselling and education about the possible complications and should encourage obese patients to undertake a weight reduction program before attempting pregnancy".[205] The ACOG also points out that the children of obese mothers are probably at increased risk of becoming overweight.

Anorexia (BMI < 20) also gives rise to problems. It is, for example, associated with increased risk both of spontaneous abortion and cardiovascular disease in mothers and of diabetes in the child at a later age.[206,207]

The Committee believes that women must endeavour to reach a normal BMI (between 20 and 25) prior to conception – if necessary under the guidance of their GP and dietician.

5.3.3 Physical exercise

A recent systematic review established that regular, moderately strenuous physical exercise during pregnancy appeared to improve or maintain the physical condition of the women, who were otherwise healthy.[208] This would mean that women who wish to become pregnant can simply continue to exercise and engage in sports. The sports mentioned in the review are swimming, cycling and floor exercises. However, since the methodological quality of the 11 studies examined (involving 472 women) was only moderate, it was not possible to draw any definitive conclusions regarding positive or negative effects on the health of the mother or child. The authors recommend that larger studies be conducted in order to permit confident recommendations with regard to the effects of physical exercise.

Partly in the light of its earlier conclusion about physically demanding work, the Committee is convinced that there is no need to discourage regular, moderately strenuous physical exercise in the preconception phase.

5.4 Conclusions regarding illness, medication and other health-related factors

Illness	Level of evidence
It would be preferable if the information about food-related infectious diseases that is currently given to pregnant women during their first visit to the midwife were to be given in the preconception phase. C[51], D: the Committee	Level 3
Diabetes mellitus in expectant mothers is associated with an increased risk of congenital abnormalities in the child. B[167,168]	Level 2
Active preconceptual counselling in women with diabetes mellitus improves pregnancy outcomes. A[23,169]	Level 1
Preconception care for women with diabetes mellitus is cost-effective. B[172,173]	Level 2
Medication	
The risks of medication in pregnancy are not always apparent. B[177,179,181]	Level 2
The use of anti-epileptic drugs by expectant mothers is associated with an increased risk of congenital abnormalities. A1[162]	Level 1
Modern anti-epileptic drugs are no safer or more cost-effective than the classic drugs. A1[165]	Level 1
The use of antidepressants during pregnancy is associated with an increased risk of adverse pregnancy outcomes, including congenital abnormalities and withdrawal symptoms in the newborn child. B[184-187]	Level 2
The use of ACE inhibitors during the first trimester of pregnancy is associated with an increased risk of congenital abnormalities in the child. B[188]	Level 3
Health-related factors	
Older mothers and fathers are at greater risk of having a child with congenital abnormalities. B[192,197-200]	Level 2
Overweight and obesity in pregnant women are associated with an increased risk of adverse pregnancy outcomes (e.g. pre-eclampsia and congenital abnormalities in the child). A[203-205]	Level 1

Anorexia in prospective mothers is associated with an increased risk of spontaneous abortion and, in addition, an increased risk of cardiovascular disease in the child at a later age. B[206,207]	Level 2
Regular, moderately strenuous physical exercise during pregnancy does not appear to have any adverse implications with regard to its course and outcome. C[208]	Level 3

The conclusion to be drawn from this chapter is that chronic disorders, medication and over- or underweight can adversely affect the pregnancy and the unborn child, and vice versa. The Committee therefore believes that medication (occasional *and* chronic), present and/or past illnesses, and existing anorexia or overweight must always be carefully discussed in a preconception consultation. It also feels that consideration must be given to the age of the future parents.

Chapter 6

Genetic factors

This chapter provides a brief summary of the different types of genetic abnormalities that can occur, the risk factors that influence them, and the possibilities for risk assessment and intervention. A literature search using "preconception care" as the search term yielded little or no specific literature about genetic factors. However, the Committee considered them to be so important that it has nevertheless devoted a chapter of the advisory report to this topic. This chapter is based on literature that has been furnished by the Committee, and also on its experience in this area. In preparing the request for advice it was also decided to consider carrier screening for cystic fibrosis and haemoglobinopathies, a topic featured in the Work Programme at the time. The topic of carrier screening will be addressed in this chapter.

6.1 Genetic abnormalities

Genetic abnormalities are the result of changes that have occurred in the genetic material either recently (just before or after conception) or in a previous generation. These abnormalities can lead to physical and/or mental limitations in the child.

6.1.1 *Abnormalities in the number of chromosomes*

Abnormalities in the number of chromosomes frequently lead to spontaneous abortion. However, infants born with some numerical chromosomal abnormalities are viable. The principal risk factor for these anomalies is maternal age (see also 5.3.1).

The best known example of a numerical chromosomal abnormality is trisomy 21 or Down's syndrome, whereby body cells contain three copies of chromosome 21 instead of two. The risk of giving birth to a child with Down's syndrome depends on maternal age: at 25 years it is 1 in 1250; at 36 years, 1 in 250 and at 40 years, 1 in 100.[16] More than 200 children are diagnosed with this condition in the Netherlands every year.

The only viable, non-sex-linked trisomies apart from Down's syndrome are trisomy 18 (Edwards' syndrome) and trisomy 13 (Patau's syndrome), although affected children usually die within 12 months.[16]

Numerical abnormalities can also affect the sex chromosomes, leading to such conditions as Klinefelter's syndrome (XXY) and Turner's syndrome (X0). If they survive delivery, children with these disorders have a normal life expectancy. However, they have a greater risk of physical abnormalities. For example, their growth is retarded and they experience fertility problems later in life.

6.1.2 *Chromosome structure abnormalities*

There are several structural chromosome abnormalities. A deletion is said to occur when part of a chromosome is missing, whereas the term duplication is applied when a certain part of a chromosome appears twice. Inversion occurs when a piece of chromosomal material breaks in two and becomes reattached to the chromosome in reverse orientation, and translocations occur when two chromosomes break and the pieces exchange places.

The individual concerned will not necessarily be aware of inversions and translocations as the overall genetic information is still intact. Problems may occur in offspring, however, since the foetus may then receive either too much or too little chromosomal material. This can give rise to repeated spontaneous abortions, congenital abnormalities and/or mental limitations.

6.1.3 *DNA abnormalities (gene mutations)*

Gene mutations occur when a change has occurred in an individual gene or a limited number of genes. If a single base pair in an individual gene has mutated, there is said to be a point mutation. The mutation can also extend over several base pairs. In some cases, gene mutations are inherited, or alternatively a new mutation can occur. Gene mutations can result in various types of hereditary disorder.

Autosomal dominant disorders

These disorders require only one mutated allele for the disease to manifest itself, in which case carriers of the mutation become clinically ill. A well-known example is Huntington's disease, an extremely serious disorder which usually manifests itself in middle age in the form of akinesia and progressive dementia. In families with an autosomal dominant illness, the condition in question will often occur in several generations. However, it is also possible that only one individual will have the disorder (as a result of a new mutation, for example). There is a 1:2 chance that individuals with an autosomal dominant illness will transmit that condition to their offspring.

Autosomal recessive disorders

People with autosomal recessive disorders require two mutated alleles in order to become clinically ill. Thus carriers of one mutated allele are themselves healthy. Well-known examples are cystic fibrosis (CF), phenylketonuria (PKU) and the various haemoglobinopathies. A child born to two healthy carriers of an autosomal recessive mutation has a 25 per cent risk of having two affected alleles and thus actually developing the disease. In families with an autosomal recessive disease, the condition is usually confined to one or more family members.

X-linked disorders

These disorders mainly manifest themselves in males, since they only have one X chromosome. Examples are Duchenne dystrophy, a condition associated with progressive muscle weakness, abnormalities of the myocardium and haemophilia.

6.1.4 *Multifactorial disorders*

Disorders can be associated with mutations in a single gene. With many disorders, however, it is a combination of several hereditary and environmental factors that determines whether an individual becomes clinically ill. These are known as multifactorial or complex disorders, examples being diabetes, various cardiovascular diseases, cancer and several congenital abnormalities. Lifestyle (food, exercise, use of alcohol, tobacco and other recreational drugs) and working conditions can be influential environmental factors. The conditions that the foetus experiences *in utero* can also have a major bearing on the occurrence of congenital abnormalities and whether or not individuals develop disorders later in life.[209]

6.2 Risk factors

This section outlines the risk factors that can be detected without undertaking a more detailed investigation of the prospective parents. This applies both to the factors that govern the occurrence of new mutations (possibly resulting in an adverse pregnancy outcome) and the risk factors associated with disorders that are based on pre-existing, inherited mutations that have been in the family or ethnic group for some time.

6.2.1 *Risk factors for numerical chromosomal abnormalities and new mutations*

The chances of having a child with a numerical chromosomal abnormality increase with maternal age. Advanced paternal age is associated with a higher risk of a child with a new gene mutation.[197,198] This has been demonstrated in particular by comparing the ages of fathers of children with an autosomal dominant illness that has not previously occurred in the family with the ages of fathers among the population as a whole.

New mutations can also be caused by ionising radiation and by particular chemicals and drugs, such as cytostatic agents. As it is not possible to predict whether a gene will be affected by a new mutation (and if so, which gene), it is likewise impossible to say which disorder will occur.

6.2.2 *Risk factors for inherited mutations*

There are three known risk factors for the development of disorders based on inherited mutations: firstly, the presence of such an illness in one of the prospective parents, in his or her family, or in a previous child; secondly, a couple's ethnic background; and thirdly, consanguinity (e.g. as a result of cousins marrying).

Disorders in the father or mother, the family or a previous child

Once mutations have arisen, they can be passed down for many generations. In the case of hereditary disorders, there may be one or more affected individuals within a family. This may be one or both prospective parents, family members, or one or more previous children. A couple who want to start a family may be at increased risk of having an affected child, even if both partners are themselves healthy. Determining the extent of the risk requires knowledge of the genetics of the illness in question.

Ethnic background

Other factors that can be important apart from the family background are ethnic origin and sometimes even the place of origin. Some disorders are more prevalent in specific groups or in a particular location. For example, cystic fibrosis (CF) is more prevalent among people from Europe, the Mediterranean region and the Middle East. Sickle cell anaemia and thalassaemia are more commonly encountered in people who themselves (or whose ancestors) originate from areas where malaria occurs or formerly occurred. Owing to their slightly abnormal blood profile, carriers of these disorders are less susceptible to the malaria parasite, but they do not themselves necessarily fully develop the disease in question (i.e. sickle cell anaemia or thalassaemia). Tay-Sachs disease and several other rare disorders are mainly encountered in people with an Ashkenazi Jewish background. Certain rare hereditary disorders are also relatively prevalent in certain parts of the Netherlands. For example, Batten-Spielmeyer-Vogt disease, a degenerative neurological illness, is relatively common in West-Brabant and Zeeland and the Ijsselmeer region has more benign recurrent intrahepatic cholestasis (BRIC) – an obstruction of the bile ducts in the liver – than other parts of the country.

Consanguinity

Consanguinity is commonly encountered all over the world.[210,211] In Turkey, for example, between 20 and 25 per cent of marriages are estimated to be consanguineous.[212] A marriage between relatives is frequently considered to make the relationship more stable and to be socio-economically beneficial.[211,213] The risk of an autosomal recessive hereditary illness increases by 2 to 3 per cent in a relationship between cousins.[214] Children from this type of relationship are 4.4 per cent more likely to die before the age of 11 than when parents are not related.[214,215] In some cases it is possible to predict what specific disorders a child will be at increased risk for based on the family history or the parents' region of origin. It is then sometimes possible to undertake carrier screening for these disorders. If the parents are blood relatives but there is no knowledge of a specific illness then, generally speaking, genetic testing will not be possible.

6.3 Scope for risk assessment and intervention

6.3.1 Personal and family history

When people are or wish to become pregnant, it is important to consider the medical histories of the future parents and their families. The importance of family history-taking has been established during research conducted in Germany among women who presented for prenatal diagnosis either on account of their age or because they had an abnormal result in the triple test.[216] In more than ten per cent of these women, the tests revealed a relevant and significant illness in the family. A family with a history of a particular genetically determined illness may be at increased risk for this condition. In the case of autosomal dominant diseases, there is a 1:2 risk that a child will inherit and develop this disorder if one of the parents is affected. For autosomal recessive hereditary diseases, too, the risk is considerable (25 per cent for each child) if both parents are carriers. When taking the personal and family history, consideration should also be given to consanguinity.

Taking a personal and family history is an art in itself. It is not sufficient merely to ask whether there are any genetic abnormalities in the family. Nor, conversely, is it feasible to ask specifically about each of the many thousands of hereditary disorders. Lists are available (at the clinical genetics centres and in the literature) that contain a limited number of questions with which it is possible to detect most potential risk situations.[217] Furthermore, Zwangerwijzer.nl uses a questionnaire to investigate whether any such disorders occur in the families of

prospective parents (and if so, which ones). Two ongoing preconception-care pilot projects are already using the Zwangerwijzer.nl questionnaire.[32,39] At present, the family history is usually considered during the first visit to the obstetric caregiver. If there are any pre-existing disorders, he/she can then determine whether there is an increased risk and whether prenatal diagnosis is an option.

However, it is also logical to take a family history prior to pregnancy so that, in the event of disorders in the personal or family history, the future parents can be referred in good time to a clinical geneticist, and, if necessary, they can undergo carrier screening and/or consider, from the outset, what implications and options they will have in the event of pregnancy. The detection of mutations for a disorder can be very time-consuming. If prenatal diagnosis (chorionic villus sampling) is to be worthwhile, the mutation(s) must be known. Pre-implantation genetic diagnosis (PGD) can be an alternative to prenatal diagnosis – though even then it is only possible to detect known mutations.[32,39,218,219]

The Committee believes that consideration needs to be given in the course of preconception care to the possibility of a personal and family history of hereditary disorders, as well as to ethnic origin and possible consanguinity. If the history suggests that the individual(s) concerned could be at increased risk, she/they should be fully informed about referral to a clinical geneticist. If there is definitely found to be an increased risk of having an affected child, good information about the possible reproductive options should be available.

6.3.2 *Preconceptual screening*

Two screening programmes are currently available for the detection of hereditary disorders. Prenatal screening was introduced on 1 January 2007. Here all pregnant women are informed about the possibility of prenatal screening for neural tube defects and Down's syndrome. Under the neonatal screening programme, which also commenced on 1 January 2007, blood samples are obtained from newborn children during the first few days by heel prick and tested for 17 mostly hereditary, rare, but serious congenital abnormalities.

In both of the above programmes, screening is conducted at a point when the pregnancy has already been established or the child is already born. Prenatal screening cannot be brought forward to a time prior to conception, since it is not possible to determine the risk of Down's syndrome or neural tube defects with sufficient accuracy prior to pregnancy, even if certain risk factors are known (maternal age or folic acid deficiency). In theory, it would be possible to offer all prospective parents preconceptual screening for the majority of disorders for

which neonatal screening is performed, either because the mutations associated with the majority of disorders are known or because carrier status can be detected in some other way. This would give those couples who are both carriers (and whose children therefore each have a 1:4 chance of having the disorder in question) the opportunity to prepare themselves for the possible birth of an affected child, or else to reach their reproductive decisions in the light of this knowledge. However, certain fundamental questions arise in the case of disorders that are readily treatable: What is then gained by knowing that a person is a carrier? – see also chapter 7). Practical questions also arise if the illness is exceptionally rare: Is it feasible to screen all people who want to have a child – without evidence of carrier status from the personal or family history – for a large number of disorders when the risk of the person being a carrier is exceptionally small and the carrier neither is, nor will become, clinically ill?.

These limitations do not apply in the case of two groups of disorders for which neonatal screening can be (or is already being) performed. Both cystic fibrosis and haemoglobinopathies (sickle cell anaemia and the thalassaemias) are only to a limited extent treatable. The average life expectancy of people with cystic fibrosis is still around 30 years and the blood transfusions required by thalassaemia sufferers have serious side effects due to iron overload. Both disorders are relatively common, albeit in different population groups. Below are separate considerations of carrier screening for each of these disorders and in couples with an Ashkenazi Jewish background.

Cystic fibrosis

The principal feature of cystic fibrosis (CF) is the occurrence of chronic pulmonary disorders, but the pancreas is also usually involved. In babies, meconium ileus is a symptom that can be indicative of CF.[220-222] The lung infections frequently occur in the first few months of life, but average life expectancy has to around 30 years as a result of improved and intensive treatments. Men with CF are frequently infertile since the passage of sperm is impeded. In female patients, pregnancy may bring additional health risks (due to impaired lung function, for example). CF is an autosomal recessive illness. The mutations lie in the gene that encodes the so-called cystic fibrosis transmembrane conductance regulator (CFTR). Over a thousand different mutations have been described.[223] The disease is relatively common among the white population compared with other hereditary disorders. The birth prevalence among the indigenous population of the Netherlands is approximately 1:3600 and consequently around 1 in 30 people within this group is a mutation carrier.[224] In the Turkish population it is estimated

that 1 in 50 people are CF carriers. Prevalence among black Africans and Asians is estimated to be lower (1 in 60 and 1 in 90, respectively). Carrier screening is possible and usually involves testing people for the commonest mutations. If one of the more frequent mutations is identified in one parent and not in the other, the latter can undergo a more detailed test for rare mutations.

A study conducted in the Netherlands offered 38,000 would-be parents aged between 20 and 35 years the possibility of carrier screening for CF.[225,226] Some of them were able to go to their GP for pre-test counselling and to give a mouth swab while others received this service from the municipal health authority (GGD). This had to take place within a specified timeframe (at the GP) or on a specified date (at the GGD). Although this limitation made it difficult for many couples to participate, the majority of participating and non-participating couples felt that people should be given the opportunity to undergo the test (89 and 69 per cent, respectively). If they were to be given the option again, all identified carriers (18 in total) and 95 per cent of the other participants would again choose to take part in the screening. Furthermore, 88 per cent of the participants would advise other couples to undergo the test.

Following on from the above-mentioned experiment, a study was then conducted of the opportunities for, and barriers to, implementation. In this study too, the majority of couples who wanted to have a child were found to be positively disposed towards CF screening.[227] A clear majority of those questioned considered it desirable that couples who want to have a child should be informed about the disease and about the possibility of receiving genetic counselling. A smaller proportion of the target group take part in this counselling: 10 per cent in the case of group sessions and 25 per cent if a personal consultation with the GP is offered. 89 per cent of the participants were in favour of this form of preconception care being routinely offered. Among the non-participants, 69 per cent held this view. The timeframe available for the screening was relatively short, which may explain why many people cited the fact that they currently had no time to spare as their reason for not participating.

The majority of GPs and GGD personnel were found to be willing to assist in a screening programme.[228] The study has resulted in a detailed implementation plan, which was presented to the Netherlands Organisation for Health Research and Development (ZonMw) in 2003. At the heart of the proposal was a plan to stage a large-scale pilot project to see whether the favourable response to carrier screening that had been identified in the study would also hold true in practice. The project never got under way, however, as there were plans at the time to produce a Health Council advisory report on carrier screening. In fact, carrier screening has been included in this report, since it fits well into this context.

The primary aim of carrier screening is to offer people information about risks that will enable them to make informed choices about having children and about the support (medical and otherwise) that is available. However, the research into the costs and consequences of carrier screening also showed that this type of screening can yield savings on medical care.[229]

In its advisory report on *Neonatal Screening* the Health Council has stated that CF cannot be included in the neonatal screening programme until a better screening technique is available owing the large number of follow-up investigations that are required in connection with the current test.[230] This problem does not arise in the case of preconceptual carrier screening, since carrier screening involves a direct mutation test and follow-up testing is not required. After all, CF carriers are not clinically ill and it is therefore not necessary to confirm the illness.

A key question is whether neonatal screening for CF and preconceptual carrier screening for CF are to be regarded as mutually exclusive alternatives. They differ from each other in terms of their objectives and effects (secondary prevention for patients versus informed choice for carrier couples). Thus they should perhaps be regarded as complementary techniques rather than as alternatives between which the government or care providers must choose in advance. The still limited life expectancy of children who are identified as having CF by means of neonatal screening is a good reason for supporting the provision of carrier screening. Another reason may be that it is not possible to identify all affected children by means of neonatal screening.

No fundamental objections came to light when preconceptual screening for CF was examined for compatibility with the Health Council's criteria for genetic screening and with the international criteria.[20,231-234] Carrier screening for CF does not, as yet, require a permit under the Population Screening Act (WBO). The Health Council did, however, propose in the late 1990s that the WBO should perhaps be amended to impose a permit requirement for carrier screening.[235]

Where carrier screening for CF is available abroad, this usually takes place prenatally. Offering this service prior to conception gives the participating couples more freedom of choice by providing a wider range of options. In the event of a positive (i.e. unfavourable) test result, prospective parents can choose whether or not they actually still wish to become pregnant, consider adoption or artificial insemination, or discuss pre-implantation genetic diagnosis. It is too late for any of these options once the pregnancy has been established. The Netherlands has a high percentage of planned pregnancies and some people are reluctant to decide on an abortion following a prenatal diagnosis.[65,236] Bearing these points in mind, preconceptual carrier screening would appear to be a better

option than offering prenatal screening. Carrier screening will nevertheless still need to be available during pregnancy for those who have not undergone a test prior to conception and still wish to do so.

Haemoglobinopathies

Abnormalities in the genes that code for the protein chains of haemoglobin, the most important protein in the red blood cells, can result in disorders characterised by severe anaemia and damage to various organs.[237-240] Qualitative abnormalities are found in people with sickle cell disease, whereby abnormal haemoglobin molecules give rise to abnormal sickle-shaped red blood cells. Quantitative abnormalities are characteristic of thalassaemias, whereby there are too few red blood cells owing to the fact that synthesis of the haemoglobin molecule becomes difficult or impossible and the red blood cells are therefore broken down too quickly. Haemoglobinopathies are autosomal recessive disorders, whereby patients inherit a mutation from both parents. The birth prevalence of sickle cell disease and thalassaemia has risen considerably in the Netherlands as a result of immigration from regions where malaria has long been endemic. At least 10 per cent of the Dutch population originates or has ancestors from such areas (i.e. first to third generation). One in every 106 inhabitants of the Netherlands (more than 150,000 in total) is a carrier of a mutation and 800 people suffer from sickle cell disease or thalassaemia major.[241] The majority of these carriers and patients originate from the Dutch Antilles and Aruba, Surinam, Indonesia, Ghana and the Cape Verde Islands. The total birth prevalence of children with haemoglobinopathy in the Netherlands is estimated at 60 patients per year, around 80 per cent of whom suffer from sickle cell disease and 20 per cent from thalassaemias.[242]

Since 1 January 2007 newborns in the Netherlands have been screened for sickle cell disease by heel prick, as a result of which ß-thalassaemia is also detected. There is, however, still no carrier screening programme, whereas many such schemes are available abroad (e.g. in the UK, Sardinia and Cyprus). The number of children born with this disease has fallen dramatically in these countries. The information provided there usually has a directive character. In Cyprus, for example, which formerly had a very high birth prevalence of thalassaemia, carrier screening was required by the Church before couples could be married.

Carrier screening programmes for haemoglobinopathies often exist alongside neonatal screening for this group of disorders.[243,244]

Neonatal screening is, in the first instance, aimed at secondary prevention, i.e. the detection of a pre-existing illness. The symptoms of this condition are

then treated as quickly and effectively as possible, thus preventing complications. If an illness is, in fact, identified, this means that the parents are carriers. In the case of haemoglobinopathies, the child may also be found to be carrying the disease, which means that at least one of the parents is also a carrier.

From that point onwards, this knowledge can be taken into consideration when deciding whether or not to have another child. In the Netherlands, carrier status of a thalassaemia mutation can sometimes also come to light when investigating the cause of anaemia.[16]

Preconceptual screening can provide this knowledge sooner and to more future parents, who will then have more time to consider the possibilities and limitations of a decision to have a child. In the Netherlands, immigrants from areas where haemoglobinopathies occur were asked whether they would like to be informed about carrier status, and whether, if their foetus were to be affected, they would opt for a selective termination.[241] This study among risk groups showed that the majority of people questioned were in favour of preconceptual carrier screening and a large proportion of them would also consider selective termination as a possible option in connection with prenatal screening. Education and carrier screening could lead to a sharp decrease in patient numbers.[15,245]

Combined screening for CF and haemoglobinopathies

As in the case of cystic fibrosis, preconceptual and neonatal screening for haemoglobinopathies can exist in parallel and complement one another. A choice can then be made between screening all willing couples or screening risk groups only.

Lakeman *et al.* showed that prospective parents are usually quite capable of indicating in a questionnaire what form of screening (CF and/or haemoglobinopathies) would be most relevant to them.[246] This ZonMw-financed study, which will offer a combined screening programme of this kind to migrant and indigenous inhabitants of Amsterdam, should reveal how they respond to this offer and whether such a study design is feasible. The results are expected to be published in 2008.

The Committee sees little or no difference between the basic conditions required for preconceptual carrier screening for haemoglobinopathies and those applying to preconceptual carrier screening for CF.[230,233]

Whereas education about such risk factors as smoking and alcohol consumption is usually provided in the form of urgent, directive advice, genetic counselling is generally non-directive. Genetic counselling is provided, which examines the potential risks and looks at the ways in which these risks might be managed.

Recipients of this counselling are thus enabled to make their own informed choice, which is why this procedure is described as counselling rather than advice in clinical genetics circles (see also chapter 7).

In the multicultural context, it is claimed to be insufficient to offer people with a non-Western background carrier screening for cystic fibrosis alone. Although CF is less common among this section of the population, it should in many cases be possible to screen them for haemoglobinopathies in view of their country of origin.

Couples of Ashkenazi Jewish background

In Israel and among Ashkenazi Jewish communities abroad (e.g. in the US and Canada) carrier screening is offered for around ten disorders that are far more common in this ethnic group than in the rest of the population. The oldest and best known example is Tay-Sachs disease, an untreatable neurodegenerative disorder which leads to death at an early age. It is also fairly common for couples of Ashkenazi Jewish background who want to have a child to present for screening at clinical genetics centres in the Netherlands. This screening is then performed, subject to the applicable due care criteria. This is a very limited group compared with the above-mentioned groups with an increased risk of CF or haemoglobinopathies.

6.4 Conclusions and recommendations concerning genetic factors

The presence of possibly hereditary disorders in future parents, in a previous child, or in their families is an important consideration when preparing for a pregnancy. Proper information and, if necessary, genetic counselling are essential in order to enable couples who want to have children to make timely and well-informed choices. A good personal and family history is an essential prerequisite for preconception care.

The Committee believes that there are sufficient grounds for considering the introduction of carrier screening for CF and haemoglobinopathies: the seriousness of CF and haemoglobinopathies, their relatively high prevalence, the anticipated added value as an additional service on top of neonatal screening and prenatal and pre-implantation genetic diagnosis, and the extensive body of international scientific literature concerning carrier screening. However, the research performed hitherto does not provide a sufficient platform for nationwide implementation. The Committee therefore recommends that the feasibility and effectiveness of preconceptual screening for these disorders should be investigated in

a large pilot study, combined with other elements of preconception care. Within this pilot scheme, one could then undertake a comparison of several different variants (e.g. with or without distinction by origin).

At present, the Committee believes that only CF and haemoglobinopathies lend themselves to broad-based preconceptual carrier screening. Other disorders do not meet the prerequisites for a programme of this type (e.g. because there is no effective screening technique available, the disorder is rare or not particularly serious, there is a lack of international experience, or because there are other obstacles to carrier screening). It is therefore simply not appropriate to screen for all screenable genetic disorders at this point in time.

The Committee is aware of the demands that preconceptual screening places on healthcare professionals in the field of preconception care. This requires training and support.

Chapter 7

Ethical and legal aspects

Preconception care can make an important contribution to two issues that are particularly relevant to future parents: firstly the health and welfare of the child and mother, and secondly the reproductive autonomy of people who wish to have children. The broad-based nature of the care that is offered raises a variety of ethical and legal questions. Much has already been published in the ethical and legal literature about a number of different elements of preconception care (e.g. health promotion and genetic screening).[233,247-249] This chapter consists of separate considerations of the ethical and legal aspects of preconception care.

7.1 Ethical aspects

7.1.1 Context

The unusual thing about preconception care as an integral care concept is the fact that it combines several different types of intervention, each of which can be said to have its own normative framework.

1 Health education is primarily aimed at promoting healthy behaviour and avoiding risk. The aim is to convince people to make certain healthy choices if they are not already inclined to do so from the outset. The health education that is imparted during preconception care has an even stronger normative element than is the case in 'ordinary' health promotion, since it is not only

the health of the parents themselves that is at stake, but also that of a future child.

2 Where an individual is already 'under treatment' from a doctor – a woman with epilepsy, for example – preconception care will be subject to the 'traditional' medical-ethical framework of the healthcare provider/patient relationship. Healthcare providers have a professional duty to advise their patients of any potential risks that illness or use of medication might pose for the outcome of a future pregnancy.

3 Other risk factors fall outside the framework of the doctor/patient relationship and are difficult or impossible for individuals themselves to control (e.g. risks associated with working conditions). If risks of this kind are identified, steps should be taken to protect health in and around the workplace. Responsibility for taking this action rests primarily with the employer.

4 Although it is not possible to influence a person's genetic make-up, one can extend the range of options available to future parents by giving them information about potential genetic risks and opportunities for further referral. If it is discovered that there is a genetic risk of an adverse pregnancy outcome, the individuals concerned can consider the various options in good time: i.e. acceptance of the risk, pre-implantation or prenatal diagnosis, donor insemination (DI), adoption, or the decision not to have children. Although these choices can enhance people's reproductive autonomy, it must be noted that the knowledge that one is carrying a hereditary disease can be extremely distressing (even though the carrier does not become clinically ill).The task of actually enhancing the reproductive autonomy of individuals or couples therefore represents a major challenge.[250,251]

The same autonomy has an important bearing on the manner in which screening is offered. Since several of the above options are controversial for many people, clinical geneticists argue that screening or genetic testing ought to be offered in a non-directive manner.[250,252] Those seeking advice may be confronted with major dilemmas when genetic testing or screening reveals a clear genetic risk of a hereditary disease. Counselling about the possible choices that can be made following a positive test result will need to take place at specialist clinical genetics centres. The ethical questions that arise during the subsequent care of affected individuals fall outside the remit of this advisory report, since a great deal has already been said and published on this subject.[233,253,254]

Generally speaking, preconception care can offer health benefits for mother and child and enables future parents to make informed choices with regard to their

wish to have a child. On the other hand, this is regarded by many as a strictly private matter. Is this an area where government and the health service should (or must) intervene? An important reason why the government ought to do this is that our knowledge about major risks for mother and child is constantly increasing – as the foregoing chapters have shown. Active preconception care would appear to be the only way to make that knowledge readily available to everyone. It is unfair that only a select group should have access to knowledge about risks relating to conception and pregnancy. By actively providing preconception care, we can prevent major disparities in access to preventive care. However, such an intervention should go no further than is strictly necessary and desirable for the users of this service. Preconception care will therefore need to be of a voluntary nature. In the sections that follow we discuss a number of reservations that have been raised about this care. In the light of these reservations, those seeking advice must be given a high degree of control over the topics that come up for discussion in preconception care.

7.1.2 Knowledge brings responsibility

Preconception care will provide couples who want to have children with more knowledge about risk factors and about steps they can take in order to avoid risks. However, that knowledge also brings responsibility, and this raises ethical questions. It is important here to draw a distinction between those risk factors that the individuals concerned can control and those they cannot.

Controllable risk factors

The more aware future parents are of the effects that their behaviour (e.g. diet, smoking, alcohol and drug use) has on the health of a future child, the more receptive they will be to advice about that behaviour. Preconception care aims to increase knowledge about risks and can therefore influence moral attitudes among the general public about those lifestyles that are ‘responsible’ for prospective parents and those that are not. Such attitudes are associated with perception, criticism and feelings of guilt. People may ask themselves subsequently whether they have dealt with the information and care appropriately. This same question may also be posed by others in their social circle – especially if a child is born with an abnormality. This can be painful, stigmatising and also – above all – unjust, since a congenital abnormality can rarely simply be ascribed to choices that were made by the parents. While it may well be possible to reduce

the risk of an adverse pregnancy outcome by following preconceptual advice with regard to lifestyle, this risk cannot be eliminated.

However, this does not alter the fact that if someone makes choices that unquestionably have an adverse effect on the health of a future child (e.g. using hard drugs), and thus knowingly accepts a risk, this may well be irresponsible. The principle that parents must, wherever possible, avoid harm to their own children is a widely held truism. For example, a woman who wishes to become pregnant may find her feelings of guilt about smoking distressing, but they are nonetheless justified. This normative element may also be manifested in the way information is provided. In the case of risk factors that are clearly controllable (especially if they are lifestyle-related), this will not necessarily be neutrally informative, but may be aimed at changing behaviour.[255,256]

Non-controllable risk factors

It is wrong for society at large to form moral judgments about what is responsible or irresponsible in relation to every issue on which information is provided – let alone every test or screening service. Although use of medication is, to some extent, controllable, it is frequently not possible to eliminate this risk factor for congenital abnormalities in the future child – as in the case of women with a chronic illness. Thus use of medication is a less controllable risk factor. The same applies to working conditions. Well thought-out preconception care prevents future parents from feeling that they are themselves responsible (or being perceived as responsible by society at large) for risks that are largely beyond their control. Consequently it ought to be possible to assign responsibility for risks in the workplace directly to the employer. Future parents must be able to address reproductive questions to the occupational health physician, who may then alert the employer to his responsibilities.

Nor is it possible to control one's genetic make-up or one's susceptibility to a particular disease. Choices that parents make in relation to genetic diagnosis and screening in the context of preconception care are highly personal and are frequently associated with painful moral dilemmas.[257] Genetic testing may put them in a situation where they have to consider a series of controversial choices: donor insemination (DI); in vitro fertilisation (IVF) and pre-implantation genetic diagnosis (PGD); prenatal diagnosis and possible termination of pregnancy; or abandoning the idea of conception and pregnancy altogether. The scenario must be avoided in which a decision not to make use of a service such as preconceptual carrier screening is regarded as irresponsible. Information about the possibilities of carrier screening will therefore be an entirely different proposition to educa-

tion about lifestyle factors. This would not need to be an advisory discussion that is aimed at persuading those seeking advice to make specific choices. What the information about the available options must do is to help them to make a decision that *they themselves* believe to be good and prudent.

In conclusion, if preconception care is successful, the public will become more knowledgeable about risk factors surrounding pregnancy and about possible means of avoiding risks. And if people are informed about avoidable risks, they can also be asked to account for their choices. We must prevent judgments of this kind being made about responsibility where they are not warranted. Firstly, it is important that healthcare providers should make a clear distinction between information about controllable and non-controllable risks, and that they should recognise the fact that communication aimed at health promotion can have a directive character that is inappropriate for other interventions.

7.1.3 *Information does not only foster autonomy and welfare*

Respect for the autonomy of future parents places demands on the content of care and the manner in which it is delivered. The information that is provided must be correct and relevant. Furthermore, one should consider advising healthcare providers to take account of the 'level of evidence' that exists for different risk factors and the associated advice. This will, however, increase the complexity of the information. And as the issues that are raised become more complex – e.g. when it is pointed out that complications can even occur in connection with the best care – so some people will come to feel that this information is hindering (rather than supporting) their decision. This certainly applies when genetic risk factors are discussed, and when the advantages and disadvantages of screening are considered. Decision-making then becomes particularly arduous and there can be no question of optimal freedom of choice. Healthcare providers will therefore need to be well trained in delivering information and individually tailored options.

A further possible adverse effect of preconception care is that as prospective parents become better informed about risks, they may also become more concerned about the outcome of the pregnancy. On the other hand, they may also find it reassuring that they have done everything within their power to help bring about a favourable outcome. Research into the psychological impact of preconception care on mothers reveals only limited anxiety with regard to the course and outcome of pregnancy.[20,258]

Also important is the fact that the provision of information about risk factors can prevent or dispel anxiety (for example where medication is being used that is

known not to be detrimental to the health of mother and child). There is, however, a difference between providing information to people who are aware that they may be subject to specific increased risks, and informing individuals who were not previously aware of any risk. Whereas in the former case it may be possible to dispel uncertainties and anxiety, in the latter case information will serve to compound any anxiety. Simply summarising all of the potential risks will tip the balance between reassurance and anxiety too far in the direction of the latter. Clearly, good health education requires a high level of communication skills on the part of healthcare providers. Furthermore, it would appear to be necessary to restrict the information and care to those aspects that are genuinely important and easily explainable. In 2003 the Health Council concluded that little was known about the level of public awareness on the subject of genetics. There was already evidence of regular misunderstandings among GPs and centres for clinical genetics. In this age of rapid advances in the field of genetic diagnosis, this raises the question as to whether a better basic awareness of genetics ought to be promoted among the public at large. In 2003 the Health Council believed that the key to achieving an elementary level of public awareness lay in general information and, above all, education.[259]

7.1.4 Medicalisation

Medicine is sometimes criticised for 'interfering' with aspects of daily life on the grounds that this is leading to ‘medicalisation’. This certainly applies in the case of reproduction. Something that is, in theory, a natural process is increasingly becoming controlled by ultrasound scans, blood tests and other medical interventions. Preconception care is a further step in the medicalisation of conception and pregnancy, taking its place alongside the existing prenatal care services. It alerts future parents to risks, disease, and opportunities for medical control. But should we regard this medicalisation as a problem?

Medicalisation is an umbrella term which encompasses a whole range of considerations and problems (such as limitations of autonomy, anxiety and impact on moral judgments).[260] In an ethical analysis it is preferable simply to identify these as potential problems and to avoid an umbrella term which has strongly negative connotations. In 2004 De Wert argued in his gynaecology textbook that the charge of medicalisation cannot be construed as a hard ethical argument against population-wide preconception care.[256] Preconception care can also influence people's perceptions of the physical and health implications of having a child. Ideally, the avoidance of disease and the promotion of health will not be uppermost in the minds of prospective parents. Preconception care does, how-

ever, mean putting risks and disease on the agenda at a very early stage (preferably when a couple first considers having children). Although women feel a great need for information and advice, it is also possible that those seeking advice may wish to avoid adopting a medical perspective when making their initial reproductive choices.[258] Health professionals are bound by their duty of care to provide clients with the best possible information so that they are able to make all of the relevant fully informed choices. But do couples actually want to have all of these choices? Preconceptual advice and care are best delivered by adopting a phased approach that is tailored to the needs of the parents-to-be. When giving individually tailored advice, one should explain to prospective parents that certain elements of the preconception care consultation are of a general nature (for example a discussion of generally acknowledged lifestyle risks and a review of relevant disorders and use of medication). However, certain other, more specific, topics can also be considered – but only if parents actually wish to know more about them. This especially applies to the possibility of genetic diagnosis, various reproductive options and carrier screening for hereditary disorders. In the first instance, parents can be provided with limited information about the possibility of undergoing these tests, but this is only followed up with more specific information if parents indicate that they would value this. This phased approach to information provision and to the range of choices that parents are offered within the preconception care package also underlines the fact that it is not, in any way, irresponsible to forgo particular options or additional information (7.1.2).

A possible danger of this phased approach to preconception care is the fact that the care provider does not become involved if the client, due to a lack of knowledge and understanding, shows no interest in the services on offer. This can mean that some very real risks are ignored. The information about risks and ways of avoiding them must therefore from the outset be broader than the generally acknowledged health risks. Of course, the degree of emphasis may vary according to the topic and will depend on how much support there is for a particular intervention.

7.1.5 *Confidentiality and relevance of information to third parties*

Preconception care could be detrimental to clients if information about risk factors finds its way into the hands of third parties. This would, for example, apply if healthcare insurers were to get hold of genetic data, or if mortgage lenders were to obtain information about illness. Healthcare providers are bound by a duty of confidentiality and must not pass this information on. In some cases, people seeking advice may well themselves have to hand over the information that

they are given (e.g. about genetic risks) if it is requested by an insurer. The greater the role that genetic information comes to play in risk assessment by insurers and other parties, the greater will be the need to inform those seeking advice – in advance – about these implications of genetic testing.

If genetic data concerning clients may be of importance to their family members, the clinical geneticist will point this out to the clients. The principle of autonomy dictates that they are not obliged to inform their family. However, the doctor may decide subject to certain strict conditions (e.g. in the case of major risks, if acceptable options are available whereby it is possible to prevent great distress, or if all other avenues have been exhausted) that the interests of family members demand that the duty of secrecy be set aside.[255]

7.2 Legal aspects

This section follows on from the foregoing ethical discussion by examining preconception care from a legal perspective. Owing to the broad-based nature of preconception care, general precepts – i.e. legal principles and constitutional rights – and specific rules of law both have a role to play from a legal standpoint. As preconception care is a component of overall healthcare, it follows that the rules of law that apply to healthcare as a whole will also apply to medical procedures that are undertaken in the preconception care setting.

7.2.1 General legal framework

The general legal framework relating to preconception care is defined both by general legal precepts – including the principles of self-determination and equality – and by important basic rights which have been enshrined in legislation. A distinction can be made between individual and collective basic rights. Individual basic rights set out to prevent the citizen's rights from being violated by government and society. Examples are the right to protection of personal privacy (Art. 10 of the Dutch Constitution [*Grondwet*]) and the right to inviolability of one's person (Art. 11 of the Constitution). Collective basic rights, on the other hand, impose a positive obligation on the government. Thus it follows from Art. 22, para. 1 of the Constitution that the government must take steps to promote public health. The emphasis below is on individual basic rights.

To avoid a possible conflict between the ‘care’ and the ‘interference’ aspects of preconception care, it is always necessary in this context to draw attention to the – unwritten – basic right to procreate. This is the right to decide, without any outside interference, whether or not to have children. This right is a corollary of

the right to respect for one's private life, as laid down in Article 8 of the European Convention for the Protection of Human Rights.[261] In view of the fact that preconception care is usually offered unsolicited – and, in addition, may be associated with a certain amount of social pressure – it is quite feasible that the right to procreate may be compromised as a result.

7.2.2 *Specific legal framework*

When examining the specific legal framework relating to preconception care it is important to make a distinction between collective and individual preconception care.

Collective preconception care

Collective preconception care involves undertaking measures that are aimed at a certain group of people that is addressed as a single body. The focus is on health education that can be accomplished by such means as education campaigns, internet sites and articles/advertisements in magazines and newspapers. In other words, general information about preconception care which is aimed at any member of the general public who wants to have a child – and, in addition, concrete measures such as vaccinations administered as part of the National Vaccination Programme and the iodisation of salt. Although these measures have been undertaken in the interests of general public health, they have a particular significance for people who want to have children and for pregnant women. The activities undertaken in this context (e.g. a campaign to highlight the danger of alcohol consumption immediately prior to pregnancy or iodisation of salt) can be seen as a corollary of the government's above-mentioned 'positive constitutional obligation' to take steps to promote public health.

Individual preconception care

General individual preconception care consists of giving individually tailored assistance to couples who want to have children. Couples can obtain this care from a GP, a midwife or a community child health doctor. They do so either: 1) in response to collective information; 2) in response to a specific invitation from a GP or municipal health authority (GGD) to all women of child-bearing age; or 3) entirely on their own initiative.

Specialist individual preconception care consists of assistance to couples who want to have children and who are known or feared to be at high risk of an

adverse pregnancy outcome. This type of assistance is provided by the secondary (e.g. a gynaecologist) and tertiary (e.g. a clinical geneticist) sectors.

Individual (general and specialist) preconception care is subject to the current general rules of law concerning medical procedures, notably the so-called 'Medical Treatment Agreement Act' (WGBO). This Act lays down the general rights of patients and sets out to create a legal framework for effective cooperation between patient and doctor.[261] The WGBO enshrines the above-mentioned right to self-determination. It applies in cases where a care provider performs "*handelingen op het gebied van de geneeskunst*" ['actions in the field of medicine'] either within or outside the context of a treatment agreement. These actions are understood to mean "all procedures – including examinations and the provision of advice – directly affecting a person and intended to cure a disease, prevent its onset, assess a person's state of health or render obstetric assistance" (Article 7:446, para. 1 and para. 2a of the Dutch Civil Code (BW)). 'Medical actions' also include other actions that are performed by a doctor acting in that capacity (Article 7:446, para. 2b of the BW). In particular, this extension of meaning relates to the actions that a doctor performs on a healthy person (providing these actions do not fall under Article 7:446, para. 2a of the BW). The Explanatory Memorandum to this section of the Act emphasises that this also includes information about prevention of pregnancy.[262]

It follows from the above that if a couple who want to have a child register with a care provider for preconception care and the care provider delivers this care then the provisions of the WGBO will apply. This is also the case if the advice relates only to diet and lifestyle. Advice of this kind that is provided within the context of general individual preconception care is covered by the phrase 'actions in the field of medicine'.

Patient rights as enshrined in the WGBO – such as the right to information, the right 'not to know', the requirement of consent and the right to privacy – will be considered below, especially during the discussion of individual (general and specialist) preconception care. We shall also comment on the legal aspects of collective preconception care that fall outside the statutory framework of the WGBO (but only where these are relevant). Several other laws besides the WGBO are also of relevance. Below we shall comment on those provisions of the Personal Data Protection Act (WBP), the Population Screening Act (WBO) and the Medical Research Involving Human Subjects Act (WMO) that are of relevance in this context.

7.2.3 *The specific nature of preconception care*

When discussing the specific nature of preconception care, people often point out that it is policy-led. Preconception care is provided unsolicited (e.g. by means of education campaigns and/or through targeted invitations to women of child-bearing age). The initiative lies with the doctor or care provider and not with the patient, and hence this form of care differs from the care that is routinely provided. There is a striking similarity here to the service offered in connection with population screening, since there too the initiative emanates not from the client but from the care provider. As in the case of population screening, the delivery of preconception care must therefore be accompanied by the necessary safeguards. Stringent standards of safety, effectiveness and efficiency must be met.[263] Preconception care must serve the interests of the recipients and can only be acceptable if the balance of advantages and disadvantages for them tips clearly in favour of the advantages. It must promote the health of mother and child and extend the range of options available to the recipients.

The delivery of preconception care cannot always be regarded as unsolicited. For example, specialist individual preconception care is often provided in response to a specific request. It often involves couples who have ended up under the care of a specialist because of their particular medical history (i.e. couples who are known to be at high risk of an adverse pregnancy outcome). Clients might include women with earlier pregnancy complications, those who are already receiving treatment owing to diabetes or couples with particular genetic issues.

7.2.4 *The right to information and the requirement of consent*

The care provider's duty to provide information, as enshrined in the WGBO, is twofold: it consists both of a general duty to inform the client and a duty that is aimed at obtaining informed consent for a specific intervention or treatment. It follows from the general duty to provide information that the client needs to know what conclusions the care provider has been able to draw about his state of health and future health prospects.[264] Generally speaking, the individuals concerned – i.e. couples wishing to have children – must be informed clearly and, if they so wish, in writing (Article 7:448, para. 1 of the BW). “Clearly” does not only mean that the care provider must express himself in terms that are readily understandable; he must also be mindful of whether those involved have understood the information.[265]

The aim of preconception care is, in part, to increase knowledge about risk factors and the options available in order to avoid risks. In fulfilling his duty to provide information, the care provider must be guided by what the individuals concerned "should reasonably know" (Article 7:448, para. 2 of the BW).[265] As a general rule of thumb, he should provide whatever information concerning facts and possibilities a reasonable person may be expected to consider, in the stated circumstances, before making a decision or may require for his future behaviour.[261] Although the provision of information is governed by the criterion of reasonableness, it is important not to lose sight of the individual situation of the person concerned. This will have a crucial bearing on the provision of further information.[266] There is, for example, a difference between information that is provided to couples wishing to have children who are themselves aware that they have to contend with specific high risks and information for couples who have no advance knowledge of this.

In the former case, the care provider can focus attention on the specific risks and – depending on what the couple already know – tailor the information he provides accordingly. In this case, information provision can be properly targeted – as opposed to the situation of a couple for whom possible risks still need to be assessed. Here the care provider will need to be mindful of not providing too much information at once, with the result that the couple in question could become unnecessarily anxious or unable to make the right decisions owing to 'information overload'. Clearly, the same could, to a certain extent, be said of the couple with known risks, since they may still be unaware of certain risks at the time they request a preconception consultation. In this case, the care provider must beware of providing too much information at once about newly identified risks.

General individual preconception care

General individual preconception care is, in the first instance, focused on general dietary and lifestyle advice. In addition, this general preconception care relates to risk assessment in the workplace, illness and medication, and genetic make-up or susceptibility to a particular disease. The aim of providing general preconceptual information is to increase awareness of possible reproductive risks. As was noted in the discussion of the ethical aspects, dietary and lifestyle advice can have a directive character. This type of information does not need to be neutrally informative, since it is aimed at changing behaviour. The situation is different in the case of less controllable risk factors, such as use of medication and working conditions, and in the case of non-controllable, genetic risk factors. For example,

information about the possibility of preconceptual carrier screening should be non-directive and it is also necessary to adopt a phased approach.

From a legal standpoint, it is important not to compromise the clients' right to self-determination (as enshrined in the WGBO) through the manner in which information is provided (i.e. directive or non-directive). When dealing with a topic such as preconceptual carrier screening, the information provided will therefore have to meet higher quality standards.[265]

Preconceptual carrier screening requires explicit informed consent, both for participation in the study and for any subsequent stage in the screening programme. As screening of this kind is unsolicited, there can be no presumption of tacit consent.[265] The requirement of consent is laid down in Article 7:450, para. 1 of the BW. In principle, consent cannot extend any further than the information itself.[261]

The information provided must be sufficient and understandable, such that recipients are enabled to make a carefully considered choice. When providing information in complex situations, it is important not to impart it all in one go but instead to concentrate on gradually acquainting clients with the salient facts.[261] Prior to screening, the care provider will need to clearly explain precisely what is involved. This will certainly entail providing information about the nature and aim of preconceptual carrier screening, its consequences and risks, and about the anticipated advantages and disadvantages of participation (Article 7:448, para. 2 of the BW).[262,266] This also includes providing information about the possible implications for blood relatives.[261] The client(s) must, in any event, be clear as to what implications the outcome may have for the reproductive decisions that need to be made. It is important here that the care provider should indicate that the outcome of the screening may be psychologically stressful for those involved. The care provider will need to give those involved sufficient time to digest the information that has been provided. It is advisable to supply written information and to discuss the possibilities more fully in a follow-up appointment.

If the screening reveals that both partners are carriers then more detailed information will need to be provided after the test about the options that are available.

Specialist individual preconception care

What was stated above about general individual preconception care also applies in the case of specialist individual preconception care, though with specialist care it is even more important that the information provided should be tailored to each

specific case. Both the content of the information and the way in which it is provided will be governed largely by the circumstances.[262] It is possible that those individuals who receive specialist care – in view of their history – will be better informed than those who receive general individual preconception care. However, the complexity of the cases in the specialist care arena may mean that the information provided will need to be of a higher standard.

7.2.5 The right not to know

Collective preconception care

The collective measures that are undertaken in connection with preconception care may raise the question as to how every individual's right to shape his/her own life (under Art. 10 of the Constitution, protection of personal privacy) is to be accommodated. It may be that couples who want to have children will wish not to be fully informed (or else not informed at all) about the possibilities afforded by preconception care or about the action to be taken if one wishes to have children. In many cases, however, the general information that is provided in the preconception care setting – e.g. about smoking, alcohol consumption or folic acid – will need to have a directive character, since it is not only the health and well-being of the mother that is at stake, but also that of the unborn child.

General individual preconception care

As far as the 'contract' between doctor and patient is concerned, the general rule of thumb is that a care provider has a duty to inform, even if not requested to do so. The client, however, is under no obligation to receive information. If the client is informed against his will then his right to self-determination will be infringed and his right to protection of personal privacy will be violated.[261] The right not to be informed is enshrined in Article 7:449 of the BW. There must, however, be a request from the client not to be informed. If no such request is received then the care provider has a theoretical obligation to inform the individual concerned.[265]

But how is the right not to know to be interpreted in the context of general individual preconception care? How 'phased' must the provision of information be in order to ensure that the individuals concerned have the opportunity to make it known if they do not wish to receive any further information? The fact that a couple who want to have a child consult a care provider for preconception care indicates that they attach importance to initial information provision. It is then

reasonable to provide general advice about food and lifestyle. Furthermore, the care provider would be able to indicate, broadly speaking, what potential risks may be identified (e.g. working conditions, use of medication, family history and carrier screening) in order to enable the individuals concerned to indicate which issues they do wish to be informed about and which they do not.

The right not to know has special relevance in connection with genetic testing and is important at various stages.[261] First and foremost, if those concerned indicate from the outset that they do not wish to receive any further information about the possibility of preconceptual carrier screening, the care provider must not provide them with further information unintentionally. Furthermore, he must make it clear to them that preconceptual carrier screening is an option that they can also decline, and also that parents-to-be can assert the right not to be notified of the outcome even after the screening has taken place. It is important that the parties involved should reach the clearest possible agreements about whether or not information is to be provided and about how preconceptual carrier screening is to be approached.[261] In the event that the right not to know is nevertheless asserted after the screening has been performed, it is important to establish whether exceptions may be made to this right. This is possible if not providing information would disadvantage the person concerned or others. In this context situations may arise whereby a care provider may feel compelled – owing to a conflict of duties – to disregard the wish of those concerned not to be informed.[261]

Specialist individual preconception care

Specialist individual preconception care is usually given in response to a specific need and is subject to the terms of the customary legal framework governing the care provider-client relationship. Also fully applicable in this context is the right not to know.

7.2.6 Privacy

The right to privacy is enshrined in various treaties on human rights, and also in Article 10 (protection of personal privacy) of the Dutch Constitution. It has already been stated above that collective measures relating to preconception care can give rise to conflicts with the right to privacy. Couples who wish to have children may feel that the unsolicited provision of such information restricts their freedom of choice. Furthermore, data concerning risk factors must not simply be allowed to fall into the hands of third parties (e.g. healthcare insurers, employers

or mortgage lenders), since this may be disadvantageous to the individuals concerned.

The provision of individual preconception care (general or specialist) is subject to the medical profession's duty of confidentiality and the rules concerning the protection of personal data, which are, in turn, governed by a statutory framework consisting of the WGBO and the Personal Data Protection Act (WBP). The provisions of these two laws are complementary.[267]

The WBP can be regarded as a general privacy law. In the context of preconception care, the use of personal medical data is governed by the general principles of the WBP. For example, personal data may only be processed if they are relevant and correct, and processing must be conducted properly and carefully. Data of this kind may only be collected for legitimate purposes and identifiable personal data must not be retained for longer than is necessary in order to fulfil the purposes for which they were collected (Sections 6–11 of the WBP).

The provisions of the WGBO are sector-specific. The provisions relating to the use of personal data are: the duty to keep patient records, the duty to retain records, the right to demand the destruction of data, the right of access to documents and the rules governing the exchange of data (Article 7:454-458 of the BW).

Use of personal medical data

The medical record. A care provider is obliged to include the data collected about his patients during preconception care in the relevant medical record (Article 7:454, para. 1 of the BW). This might include data concerning the health of the future parents, any disorders that they or their family experience, the course of any previous pregnancies, any other risk factors (e.g. living and working conditions) and the outcomes of any examinations such as carrier screening that are performed in the course of preconception care. Generally speaking, data in the medical record will be retained for a maximum of 15 years or for as long after the expiry of this period as is reasonable in order to provide the proper standard of care (Article 7:454, para. 3 of the BW). In 2004 the Health Council pressed for a considerably longer retention period in order to prevent the loss of data that might later prove useful for patient care or for research purposes.[268] The advisory report refers to new findings concerning the association between certain disorders and therapeutic procedures performed around the time of birth and the occurrence of health problems later in life. It may therefore prove to be extremely important that certain data from the perinatal period have been retained with a view to preventing, diagnosing or treating subsequent problems.

The well-known ‘winter of hunger’ study (started in the 1990s with obstetric records collected some 50 years earlier) does not only underline the importance of retaining perinatal data for longer. It also illustrates the fact that it is not always possible to predict which data from the records may, at a later perhaps even much later date, prove important for patient care or research purposes.[269-273] The current retention period of 15 years is a provisional measure. Under an interim ruling, it is still prohibited to destroy any medical records until 1 April 2010 (15 years after the Act came into force). In response to the Health Council's advisory report, the Minister has let it be known that a decision will be made before that date about whether the retention period is to be extended.[274]

A patient can request that the medical data about his or her treatment that have been retained by the care provider be destroyed. This does not apply, however, if it is reasonably likely that retention of this data could be of considerable relevance to someone other than the patient (Article 7:455, paragraphs 1 and 2 of the BW). That other person may be a member of the patient's family who has a considerable personal interest in the retention of this data in connection with a hereditary illness.[262]

Confidentiality. A care provider (general or specialist) who provides individual preconception care is obliged to keep data concerning his patients confidential. The patient's consent is required in order to provide information about the patient and in order to grant access to or a copy of the patient records. This consent is not required if a care provider is legally obliged to provide information or if the information is provided to people who are directly involved in the treatment of the patient. Preconception care usually involves several care providers/institutions and it may be necessary to exchange information at various levels. The information to be provided must be confined to those data that are necessary for the treatment (Article 7:457, para. 2 of the BW).[262] Furthermore, the WBP expressly provides that information may only be exchanged with other care providers/institutions on the condition that this exchange is necessary to the proper treatment of the individual concerned and that these other parties have been bound to a duty of confidentiality (Section 21, subsection 2 of the WBP).

Use of personal medical data concerning hereditary characteristics

The data collected about hereditary disorders during preconception care can be of importance to relatives. It may therefore be appropriate to keep them after the expiry of the statutory 15-year retention period for medical records. This period may be extended at the instigation either of the care provider or the patient.[262,275,276]

A patient has the right to inspect data that have been collected in the course of preconception care.

The WBP contains a specific provision concerning personal medical data relating to hereditary characteristics that is collected in the course of preconception care. In theory, such data may only be processed in relation to the individual to whom it pertains, unless a) there is an "overriding medical need" (This may apply if this hereditary data may be of interest to third parties. Depending on the specific circumstances, it should be possible to contact these third parties.) or b) this data needs to be processed for research or statistical purposes (Section 21, subsection 4 of the WBP).[267] The use of personal medical data for research or statistical purposes will be considered below.

Use of personal medical data for research or statistical purposes

The WGBO contains a specific provision concerning the supply of personal medical data to third parties for research or statistical purposes. According to Article 7:458 of the BW, such information may be supplied without consent from the individual concerned under certain conditions. One such condition is if it cannot reasonably be deemed possible to ask for consent and the research incorporates safeguards to ensure that the personal privacy of the individual concerned will not be disproportionately compromised (Article 7:458, para. 1a of the BW). The same applies in cases where it would be unreasonable to request consent – in view of the nature and the aim of the research – and the care provider has taken steps to ensure that the data is provided in such a form that it cannot reasonably be traced back to the individual concerned (Article 7:458, para. 1b of the BW). Furthermore, the research must be in the public interest and incapable of being performed without the data question, and the individual concerned must not have expressly objected to its provision (Article 7:458, paragraphs 1 and 2 of the BW). The WBP contains similar provisions.

Use of body tissues

Article 7:467 of the BW is relevant if preconception care involves the collection of body tissues – as in the case of blood testing. Such substances may be used for medical-statistical or other medical research purposes, providing that they and the resultant data cannot be traced back to the donor and also providing the individual concerned has raised no objection and the research is performed with due care.

7.2.7 *Preconceptual carrier screening and the law*

As has already been indicated earlier, the Committee recommends that the feasibility and effectiveness of preconceptual carrier screening for CF and haemoglobinopathies should be investigated in a large-scale population screening trial. This type of screening is not subject to obligatory licensing under the Population Screening Act (WBO). When prenatal screening is performed for these disorders and the test result is positive, it is only possible to choose between allowing the pregnancy to continue to term and terminating it. By contrast, preconceptual carrier screening for CF and haemoglobinopathies is not classified as "population screening for serious disorders that cannot be treated or prevented" (Section 2, subsection 1 of the WBO).[235,277] In the event of a positive result, it is therefore still possible to choose between various preventive measures prior to conception. Thus it is not the WBO that should be used as an assessment framework but the Medical Research Involving Human Subjects Act (WMO).

Proposals for this type of study must be formulated in a research protocol (Section 2, subsection 1 of the WMO). Before the population screening trial can be commenced, the research protocol must first be approved by a medical ethics review committee (METC) that has been accredited by the Central Committee on Medical Research Involving Human Subjects (CCMO). Among other things, this approval requires "a reasonable likelihood" that the study will lead to new medical insights and that the interests to be served will be commensurate with the burdens and the risk for the subject (Section 3 WMO).

Section 6, subsection 1(a) of the WMO states that research must not be performed without written informed consent. According to Section 6, subsection 3 of the same Act, before consent is requested the individual concerned must be informed in writing about the aim and the nature of the research, and also about the risks and burdens that participation will entail. Furthermore, it is important that the information is provided in such a way that it is reasonably certain that the individual concerned will have understood the contents. The WMO also states that the individual concerned must be given time for reflection, so that he or she can reach a carefully considered decision based on the information provided (Section 6, subsection 4 WMO).

7.3 Conclusions regarding ethical and legal aspects

7.3.1 Conclusions regarding ethical aspects

Preconception care can offer health benefits for mother and child and increase the reproductive autonomy of future parents. However, effective delivery of preconception care will also require that a number of potential problems are taken into account. A broad range of preconception care will probably influence people's attitudes (partly unintentionally) to the responsibility of future parents for the health of their child. The situation must be avoided in which choices relating to the actual desire to have children in terms of non-controllable factors (e.g. the decision to forgo genetic screening) are also perceived by the general public to be 'irresponsible'. It is crucial that parents-to-be are free to decide whether or not they wish to take advantage of preconception care (and all the various possibilities that this entails) – especially as far as the non-controllable factors are concerned. This is less important in the case of the controllable factors.

Not all of the choices and information provided make a worthwhile contribution to autonomy. Making choices can also be a burden, especially if people have difficulty processing relevant information properly. Good preconception care therefore demands a high level of communication skills on the part of care providers. They must be capable of providing health education that is aimed at changing behaviour in a number of areas. They must also have the ability to give targeted advice, especially with regard to risk factors that are readily controllable by their clients or by others. In other areas, a care provider should simply be able to provide information that is non-directive but helps the clients to make their own choices. Information about genetic diagnosis, about different reproductive options, and about opportunities for genetic screening should be provided in a phased manner so that the clients can exercise control over the topics that are discussed.

It is not possible to predict precisely what impact preconception care will have on social attitudes to responsibility, and to what extent it forces parents to view pregnancy from a medical perspective when they might rather have avoided this. It is also difficult to estimate how distressing information about complex risks and the associated choices will be. Preconception care programmes should therefore be regularly evaluated and these consequences should be considered. This assessment could perhaps be linked to outcome research on the health effects of preconception care.

When making an ethical assessment, it is also important to consider whether the proposed medical intervention is also justifiable from a social standpoint, in view of the costs that it entails. A precise assessment of the costs and benefits of a preconception care programme and a comparison with the present-day situation requires a detailed cost-effectiveness analysis. However, this falls outside the remit of this advisory report. Certain elements of preconception care are already known to be cost-effective (e.g. personal advice and counselling on folic acid supplementation and smoking cessation), and it will clearly be more cost-effective to provide a combined care package than to offer various elements separately. However, there are still no evidence-based cost-effectiveness data to support an integrated and comprehensive package of care.

7.3.2 *Conclusions regarding legal aspects*

Preconception care is designed to promote the health of mother and child and to extend the range of options available to recipients. The specific nature of preconception care stems from the fact that this type of care will usually be provided unsolicited both through collective and individual measures. This means that the delivery of preconception care must be accompanied by adequate safeguards.

From a legal standpoint, the delivery of preconception care is governed not only by general legal principles but also by constitutional rights and specific rules of law as enshrined in the Medical Treatment Agreement Act (WGBO) and the Personal Data Protection Act (WBP). It is important that information should be delivered in such a way that the right to self-determination (as enshrined in the WGBO) is not infringed.

A distinction needs to be made between information about those risk factors that are controllable and those that are not. The way in which the information should be delivered is partly determined by its complexity. Whereas lifestyle advice can be delivered in a directive manner, information that relates to non-controllable, genetic factors (e.g. the possibility of preconceptual carrier screening) must be provided in a non-directive and phased manner. It is also possible that the complexity of the information may impose greater demands on the provider. The unsolicited provision of preconceptual carrier screening requires explicit informed consent.

The right to privacy plays a role at various stages of preconception care. This applies first and foremost in the case of the collective measures, where a potential conflict may arise between the ‘care’ and the ‘interference’ aspects of preconception care. In addition, it is important that personal medical data obtained in the course of preconception care are adequately protected and do not fall into

the hands of third parties. Adequate steps should be taken to ensure medical confidentiality and the protection of personal data.

Chapter 8

Towards a programme of preconception care in the Netherlands

In this chapter the Committee discusses its views on the value of preconception care, what this care should comprise (given the current level of knowledge) and what quality criteria it should meet. In addition, it reviews the choices that will need to be made when implementing preconception care in the Netherlands.

8.1 The Committee's view on the value of preconception care

As should be evident from the preceding chapters, preconception care is a multi-faceted concept. Its aim is twofold: on the one hand to promote the health of the expectant mother and her child and on the other hand to provide timely options where there is an increased risk of an unfavourable pregnancy outcome. The channels through which these goals are pursued include individual education about lifestyle, chronic illness and use of medication, genetic aspects, working conditions and environmental factors, risk assessment, counselling and – where appropriate – medical and other interventions, including the possibility of genetic screening and collective measures. The effectiveness and efficiency of various preventive and medical interventions have now been established in relation to preconception care. However, this has yet to be conclusively demonstrated in the case of a number of other interventions, which will be discussed in more detail later.

All things considered, the Committee believes that preconception care clearly provides substantial health benefits for the expectant mother and child or alterna-

tively greater reproductive autonomy for the would-be parent(s). It therefore recommends that general individual preconception care should be introduced in the Netherlands and that collective and specialist individual preconception care should be reinforced where necessary.

Apart from the direct health benefits for individual parents and children, the Committee also feels that preconception care serves an important public health role over and above its impact on the pregnancy outcome. Other potential benefits include:

- Most standard, lifestyle-oriented programmes are aimed at people with fairly severe problems. In the case of people who wish to have a child, the cut-off point for interventions aimed at lifestyle factors (e.g. alcohol and smoking) is lower ('zero tolerance'). Lifestyle guidelines that are provided during preconception care can therefore assist in the overall prevention of unhealthy lifestyles.
- Compliance is greater in connection with interventions aimed at prospective parents. In other words, parents-to-be are more motivated to stop smoking because this is in the interests of their future child.
- Preconception care has implications for attitudes towards responsibility for health, not only among future parents but also among employers, etc. The government endorses these responsibilities.

8.2 Quality criteria and desirable care components

The Committee argues that preconception care is the entire raft of measures (knowledge expansion *and* interventions) aimed at promoting the health of the expectant mother and her child, which if they are to be effective should preferably be undertaken prior to conception. This section discusses the quality criteria that preconception care should meet and the essential components of this care.

8.2.1 Quality criteria

Besides being embedded in an ethical-legal framework, the Committee believes that preconception care must satisfy a number of other partly inter-related quality criteria:

- effectiveness
- efficiency
- optimal coverage (ideally, all couples or women who want to have children should be included)

- equity of access (low psychological and financial threshold for requesting a consultation)
- ease of access (not having to travel far for a consultation, no waiting lists)
- fair and smooth referral system (if necessary, after risk assessment)
- good links with prenatal and neonatal care
- effective communication.

The Committee recommends that these quality criteria should be monitored from the moment that implementation and execution of the preconception care programme begin. It would also be advisable to set up and carry out cost-effectiveness research from the outset. The aim of all these measures is to ensure that preconception care is – and remains – up to date and efficient. Other extremely important considerations are that preconception care should be integrated into the continuum of care alongside prenatal and neonatal care, that it should be properly coordinated with the 'pre-primary', primary, secondary and tertiary sectors, and that there should be a good referral system.

8.2.2 Components of preconception care

Given the current level of knowledge, the Committee believes that individual preconception care in the Netherlands should at least incorporate the following components:

- general advice on a healthy diet (chapter 3)
- folic acid supplementation, starting at least four weeks before the desired conception and continuing for eight weeks thereafter (chapter 3)
- vitamin D supplementation for women with a non-Western background, pending further research into the effectiveness and efficiency of this measure (chapter 3)
- individual advice and, if necessary, active counselling aimed at cessation of smoking, alcohol and drug use (chapter 3)
- if necessary, advice on adapting the work situation, in consultation with an occupational health and safety specialist (chapter 4)
- if necessary, advice on adjusting use of medication for people with a chronic illness (including use of over-the-counter medication). This must always be undertaken by or in consultation with the relevant medical specialist(s) (chapter 5)
- advice on optimal treatment of pre-existing illnesses and previous pregnancy complications. This should likewise always be provided by or in consultation with the relevant medical specialist(s) (chapter 5)

- advice on infectious diseases (and preconceptual testing for these) and vaccinations (chapter 5)
- identification of risks arising from the medical history of the future parents and their family members and, if necessary, provision of genetic counselling and information on carrier screening (chapters 5 and 6)
- identification of parental wishes as regards the information they wish to receive and also their ability to understand the information that is provided (chapter 7).

The elements listed above are to be regarded as a minimum requirement given the current level of knowledge. Further regular consultation will be needed within scientific bodies and national committees in order to ensure that the content of preconception care remains in step with scientific advances.

8.2.3 Couples with a non-Western background

Couples (and the women in particular) with a non-Western background deserve special attention when preconception care is introduced. This applies to vitamin D status (chapter 3), infectious diseases and vaccination status, chronic disorders and use of medication (chapter 5), and hereditary factors (the possible consequences of a consanguineous marriage and carrier screening – especially for haemoglobinopathies, chapter 6). It ought to be possible to advise this group at a preconception consultation to ensure that they make use of prenatal care early in the pregnancy. During such a consultation it should also be possible to explain what antenatal care comprises and how it works. At present, many non-Western women often only see the midwife late in their pregnancy[278]. Owing to possible language problems, consideration should be given to the possibility of providing information material in several languages (e.g. Arabic, Berber, Turkish and English) and enlisting the services of bilingual and bicultural consultants (VETCs). The effectiveness of this form of preconception care for these target groups needs to be further investigated, both in a general sense and, more specifically, with regard to the use of VETCs.

8.3 Integration of the different elements

The Committee does not envisage preconception care being introduced piecemeal in the Netherlands, but advocates an integrated strategy whereby the different elements can all be discussed at the same time. The arguments for an integrated approach are as follows:

- Integrated preconception care is expected to be more efficient (and more cost-effective) than the fragmented delivery of individual components.
- An integrated approach is expected to provide maximum health gain, since any interventions can then be coordinated.
- The information and advice that obstetric caregivers currently give prospective parents during the first visit (much of which would be better provided prior to pregnancy) largely consist of the same components as those that are being proposed for preconception care and thus they already form an integrated package.
- As preconception care will almost inevitably influence the way in which responsibilities are perceived, this care needs to be embedded and delivered very carefully and in a phased manner, and not fragmented over a large variety of activities from different care providers that are difficult to control.

8.4 Towards a programme of preconception care

8.4.1 Arguments for such a programme

Besides the integration of different information and care components into a single preconception care package, the Committee also advocates the adoption of a programmatic approach. The arguments for this approach are as follows:

- General individual preconception care will only satisfy the aforementioned quality criteria (notably coverage and ease of access) if a programmatic approach is adopted.
- Without a programmatic approach it will be difficult to reach certain risk groups (e.g. people with a low socio-economic status or people with non-Western backgrounds). For these groups in particular, this care must not only be easily accessible, but it must also be offered in a proactive manner. Merely offering preconceptual counselling on an opportunistic basis is therefore undesirable.
- The aforementioned health gain for the future mother and her child is such that one would also expect it to be apparent at the public-health level. This will only happen if preconception care is offered systematically and over a period of many years, if it is generally accessible and if it reaches a large number of people.
- There is a need for a well coordinated and documented continuum of care, with clear agreements between the relevant professional groups, which will be difficult to achieve in the absence of a programmatic approach.

8.4.2 *Organisational considerations*

The essence of general individual preconception care is support at the 'pre-primary' and primary care level, i.e. assistance from a community child health doctor, GP and midwife. This care must be available to all couples who want to have a child. It will comprise both general dietary and lifestyle advice and risk assessment in relation to pre-existing disorders, use of medication, working conditions and genetic make-up.

Given the desire to make preconception care part of the chain of prenatal and neonatal care, obstetric caregivers (i.e. midwives and GPs who are actively involved in obstetrics) are obvious candidates to deliver general individual preconception consultations – particularly as they are also the first port of call for prenatal care. Another reason is that obstetric caregivers already play a major role in the provision of dietary information (which is relevant to the preconception phase) and risk assessment during a pregnant woman's first visit. Earlier in this advisory report it was indicated that much of this information would be better provided prior to conception. Van Heesch *et al.* (2006) discovered that 84 per cent of the 102 midwives in their survey were willing to provide preconception care in future.[279]

From the ease-of-access standpoint, however, general practice may perhaps be the most appropriate setting for preconceptual counselling. Women with a non-Western background, in particular, tend not to consult a midwife, whereas they do visit the GP.[278] Moreover, all Dutch citizens are (in principle) registered with a GP, which allows for an active, personal approach to the target group through periodic offers of care. A visit to the GP is also more 'anonymous'. If a couple visits the midwife, it is obvious that they wish to have children, whereas they may prefer to keep this wish to themselves and avoid running the risk of bumping into someone they know during a visit to the midwife. Furthermore, the GP holds his patient's medical record, which provides him with information about the medical history of the individual concerned and, ideally, also that of his or her family members.

Gaytant *et al.* (1998) and Poppelaars *et al.* (2004) surveyed practices and future interest among 200 GPs and 303 recently married couples in the Netherlands.[280-282] Although little use was being made of the theoretical possibility of preconception consultation at the time of this study, interest was shown in the introduction of preconception clinics. Preconception care also fits in well with recent plans for GPs to become more involved in preventive research.

There could be a role for the child health services in the preconceptual counselling of women who already have a baby prior to a subsequent pregnancy and possibly also in connection with the transition from the child health services to adult (or adolescent) healthcare. Here too there is scope for a proactive, individually tailored, periodic approach to the target group, since the municipal health authorities (GGDs), where the community child health doctors and paediatricians operate, have access to the municipal personal records database. There might also be a role in the future for the proposed new youth and family centres (CJG) for example if their remit were to be extended to embrace preventive medical care. And, of course, there are a host of feasible collaborations between all of the professional groups that have been mentioned, particularly if they are all located at a health centre.

If the risk assessment conducted in the course of general individual preconception care should reveal that future parents are at increased risk of a less favourable pregnancy outcome, they should be referred to the appropriate specialist(s). A gynaecologist, clinical geneticist, neurologist, specialist in internal medicine/endocrinologist and/or occupational health physician can then provide care that is specifically aimed at reducing this increased risk. Effective coordination is crucially important here. In many cases, the gynaecologist will be the appropriate specialist to assume this coordinating role. Furthermore, it is important for women with a chronic illness that their doctors, who will frequently be medical specialists, should finally come to realise that they ought to be giving disease-specific preconceptual advice to all women of child-bearing age. For general preconceptual advice (e.g. to take folic acid), further risk assessment, etc., the woman must be referred to a gynaecologist if it is obvious that, in view of her personal risk profile, she will also come under his supervision if she becomes pregnant. In other cases, the couple must be referred for general individual preconception care.

General individual preconception care must be organised and maintained at the local level. If the care providers themselves assume responsibility for this, the result is likely to be a wide range of organisational forms. This also raises the possibility of comparing different organisational forms with regard to their ability to satisfy different quality criteria, although further attention may need to be paid to the matter of standardising the content of the care and adapting it to scientific developments. Consideration can therefore also be given to local organisational forms at the central level.

There will, in any event, be a need for a local, or at least regional, care director or coordinator. The following bodies have been mooted within the Committee as potential candidates for this role: the municipal health authorities, the regional

primary-care support structures (ROS), and the university medical centres (UMCs). Here too a choice will need to be made as to whether it is necessary to consider having the same type of body uniformly assuming the role of director throughout the country, or whether diversity is also acceptable in this case. The former option (i.e. uniformity) is probably preferable from a manageability standpoint.

8.4.3 *Knowledge infrastructure*

Quality control and guideline formulation

By analogy with prenatal care, the Committee believes that preconception care has no chance of succeeding without proper record-keeping and guidelines for referral between different care providers.[283] Medically-related quality indicators and guidelines for general individual preconception care can be established by a joint nationwide working party made up of the relevant health professionals from the 'pre-primary' and primary sector (midwives, GPs and community child health doctors). Gynaecology, clinical genetics and occupational medicine (and perhaps even other specialisms) would also need to be represented on this working party in order to accommodate record-keeping practices in the secondary and tertiary sectors. The existing Preconception Care working group of the Foundation for Preconception Care* could serve as a starting point for this kind of working party, providing it is adequately resourced.

The quality indicators and guidelines for specialist preconception care should be formulated by the respective scientific organisations. When the guidelines are developed, it will also be possible to indicate what particular tasks are to be performed by each professional group (by analogy with prenatal care) and to describe the different possible routes of referral. In particular, the Committee requests that consideration should also be given to the role of the occupational health physician. Finally, the Committee urges that all medical specialist guidelines (and especially those relating to chronic disorders) should include a section on preconception care.

* The expert working group on Preconception Care is engaged in various matters relating to preconception care, including the formulation of guidelines.

Monitoring and data collection

In order to investigate the coverage, effectiveness and efficiency of preconception care, it would be necessary to assemble a specific set of key data nationwide. This data can also be used for quality control and to assess compliance with the guidelines. Such a system has also been set up in connection with prenatal screening.

Based on the data collected, one would then compare the pregnancy outcomes *with* preconception care with those from current prenatal care *without* preconception care (outcome research based on case control or cohort research). Then it would be possible to examine how the new care concept functions, how it fits in with prenatal and neonatal care, and how satisfactory the different elements in the preconception care package are.

Research topics

Since our knowledge of the effectiveness of preconception care is currently confined to certain elements only, it is extremely important that we should also pave the way for further effectiveness and cost-effectiveness studies when introducing this new care concept. In this way it will be possible to optimise the care package by incorporating new elements or removing those elements that prove insufficiently effective or efficient.

The Committee feels that the following topics from the present preconception care package (listed in order of appearance in the report) require further investigation:

- Optimal level of vitamin D supplementation for women with a non-Western background (from chapter 3)
- Vaccination (or revaccination) for whooping cough, measles and rubella. The question here is whether the National Vaccination Programme should include revaccination of women of child-bearing age, which would make this a collective measure, or whether a future child will be adequately protected if the prospective mother and/or immediate or extended family members and caregivers are revaccinated prior to conception (from chapter 5)
- Carrier screening for CF and haemoglobinopathies (from chapter 6)
- Effects of preconception care on public attitudes to responsibility for the future child and reproductive autonomy (from chapter 7)
- Research into the best way of alerting the target group to the existence of preconception care (from this chapter)
- Effectiveness of communication and education (from this chapter)

- Outcome research on the effectiveness (and efficiency) of integrated preconception care for improved pregnancy outcomes and reduced perinatal mortality (from this chapter)
- Health services research into the composition of the care package, coverage and organisational structures (from this chapter).

Training and continuing education

If the full integration of preconception care into the healthcare system is to be successful then medical disciplines need to be aware of this care concept. This needs to be considered in all medical – and possibly also paramedical and nursing – curricula and continuing education programmes, especially within those professional groups that will ultimately be providing preconception care. Furthermore, medical specialists and occupational health physicians, in particular, will need to be more aware of the fact that women of child-bearing age (and men) may wish to have children and therefore that it may be necessary to treat their illness and/or adapt their working conditions.

In order to increase knowledge about preconception care among the public at large, the education system could also devote more attention to preparation for reproduction, alongside existing instruction as part of health or sex education.

8.4.4 Communication and education

Preconception care starts with communication and information about optimising the health of the future parents. This falls under the heading of Health Education (Dutch abbreviation: GVO), which is a scientific discipline in its own right. It is beyond the Committee's expertise and the scope of this advisory report to analyze the scientific evidence underlying the different forms of instruction.

However, the Committee would like to highlight a number of basic principles that can be applied in order to make educational activities and materials more effective. These have previously been formulated for the purposes of mass-media education (see the Health Council advisory report *Plan de campagne*), but have a wider application:[284]

Carefully analyze the health problem in question, as well as any related behaviour, and the associated personal and environmental determinants

- Formulate clear, reasonable targets
- Combine education with other types of interventions
- Make use of theoretical and empirical knowledge in this area and exploit the potential of new communication and information technologies

- Test and verify the effectiveness of mass-media and individual educational activities by means of monitoring and research.

Individual preconception care

Good educational materials are extremely important. Several such teaching aids have already been developed within the existing initiatives, such as the website Zwangerwijzer.nl and the *Kinderwens* section of the municipal health authorities' *Groeigids*.[29,38] The quality of new teaching materials should be ensured and that of the existing ones maintained. Nationwide coordination can play an important role here, alongside education on prenatal screening.

Experience has been gathered in various preconception care projects with different ways of approaching the target group. Broadly speaking, there are three techniques for alerting people to the possibility of preconception care. Firstly, by mentioning it on the internet or in the telephone directory, so that the care providers can be located by those who need them. *Zwangerwijzer.nl* is one example of this approach. Secondly via announcements in the media or house-to-house leafleting. The Maastricht clinic and the Rotterdam pilot are publicised in this way. And thirdly, one can selectively invite people who are potential candidates on account of their age. One example of this approach is carrier screening for cystic fibrosis. In the CF carrier screening project there was not found to be any difference in attendance between people who had been invited by the GP and those invited by the GGD.[225] What has never been investigated is whether a single invitation is sufficient, or whether this needs to be repeated a number of times and if so, how many?

Collective preconception care

When preconception care is introduced as a new care concept nationwide, information campaigns (media-based or otherwise) can inform the general public about the existence of preconception care and why it is wise to seek a consultation. An initiative encouraging people to seek a preconception consultation must then be followed up immediately.

8.4.5 National control

It is impossible to set up a programme of general individual preconception care without an authoritative central body in charge of quality control, continuing education, record-keeping, monitoring and, if necessary, devising local organisa-

tional forms. The Committee believes that this will be the first step towards achieving the stated goal. The bodies mooted within the Committee as candidates for this role are GGD-Nederland [the national association of municipal health authorities], the national association of primary-care organisations (LVG), the RIVM centre for population screening (CVB) and the Dutch Foundation for Preconception Care. As this is a policy matter, the Committee refrains from making a concrete proposal but does note major differences between the various candidates in terms of current focus and capacity.

8.4.6 *Capacity*

The availability of sufficient professional capacity is crucially important to the success of preconception care. It is not clear whether there is sufficient capacity in the 'pre-primary' sector (child health services) to accommodate preconception care.

The GPs are already wrestling with a capacity problem. It is therefore necessary either to add extra capacity in this setting or possibly to forge new alliances.

The midwives are already adding preconception care consultations to their responsibilities. As there is currently a slight surplus of midwives[285], there is probably sufficient capacity available within this profession for the delivery of preconception care.

The specialists will possibly receive more referrals from preconception care by GPs and midwives, though it is not possible to estimate at this stage exactly how many more. It might be possible to reduce the number of problem pregnancies by detecting and eliminating risk factors at an early stage. On the other hand, the number could also increase if more women with a chronic illness were to become pregnant. The effects on the demand for curative care are therefore still difficult to estimate. The Committee proposes that a record be kept of referral patterns so that extra capacity can be released in good time if necessary.

The 'capacity body' for further training in medicine and dentistry (known simply as the *Capaciteitsorgaan*) would be able to make an estimate of the additional capacity required for preconception care.

8.4.7 *Funding*

It is beyond this Committee's remit to undertake a detailed analysis of the financial aspects of preconception care. However, it does wish to emphasise that the success of the programme will hinge on this care being financially accessible to everyone who wants to have a child.

Monitoring and quality control are also extremely important in order to establish and maintain the efficiency of the programme.

8.5 Conclusion and recommendation

Having weighed the available evidence, the Committee's recommendation in this advisory report is that a programme of preconception care should, indeed, be introduced. This programme should offer an integrated package of care consisting of various elements and comprising a solid knowledge infrastructure and good quality control. A number of policy choices still need to be made before such a programme can be introduced, notably with regard to organisation and funding. These choices are also indicated in the advisory report.

Chapter 9

General conclusions and recommendations

This chapter will provide brief answers to the questions posed in the Minister's request for advice and general conclusions and recommendations will be formulated in the light of these answers. Specific and detailed conclusions and recommendations can be found in the individual chapters.

9.1 Current level of scientific knowledge

Question 1: Is it possible to provide an overview of scientific research results of relevance to the promotion of the health of mother and child, together with an assessment of the evidence on which these findings are based?

Chapters 3, 4, 5 and 6 provide a systematic review of findings from health promotion research relating to food, alcohol, tobacco and other recreational drugs (chapter 3), working conditions (chapter 4), illness, use of medication and other health-related factors (chapter 5), and genetic risk factors (chapter 6). All of these topics are considered exclusively and specifically in a preconception setting. Through its systematic, evidence-based search strategy and selection of the scientific literature, the Committee has confined its attention to those topics for which the highest level of evidence was available. This may mean that other topics of relevance to preconception care have been overlooked in this advisory report. For a more comprehensive overview, the Committee refers readers to the forthcoming evidence-based report of the Clinical Committee of the Select Panel

on Preconception Care (scheduled for publication in autumn 2007), which has also included topics for which less robust evidence is available.

In the Committee's opinion, there is sufficient evidence to conclude that preconception care in relation to food, alcohol, tobacco and other recreational drugs, working conditions, support for prospective mothers with a chronic illness and use of medication offers significant added value compared with the existing prenatal care in these areas. Preconception care has been shown to be cost-effective in certain specific areas (e.g. counselling on smoking cessation, personal advice on folic acid supplements and preconception care for diabetic women).

Although the adopted literature search strategy (using "preconception care" as the limiting search term) did not produce much literature about genetic factors, the Committee felt compelled to include this topic in the advisory report in view of its importance. In individuals with a personal or family history of hereditary disorders, the Committee believes that preconceptual counselling increases the reproductive autonomy of future parents and offers them additional options. Generally speaking, the Committee also feels that information about carrier screening for cystic fibrosis and haemoglobinopathies is compatible with preconception care and adds significant value to prenatal and neonatal screening.

All things considered, it therefore recommends the systematic introduction of preconception care as a new care concept in the Netherlands.

9.2 Current application of research findings

Question 2: To what extent are the above-mentioned research findings being applied in present-day practice in the Netherlands and other Western countries?

Preconception care is growing in importance in the Netherlands, as evidenced by the substantial number of initiatives in this area, which are reviewed in chapter 2. Abroad too, preconception care is being put into practice in various ways, albeit frequently in the form of disparate and uncoordinated initiatives. In particular, Hungary, Hong Kong and the United States either have in place – or are working on – integrated programmes of generally accessible preconception care. Where such schemes are in place, the results are good.

9.3 Achieving optimal preconception care coverage and the players involved

Question 3: How can we optimise the coverage of education about risks, health promotion and possible interventions before and during pregnancy, and which professional groups/agencies (e.g. the child health services) should be involved?

This question is mainly answered in chapter 8. Based on the scientific evidence for the effectiveness of counselling and intervention in various areas, the Committee concludes that the most appropriate form is an integrated programme of preconception care. In other words, the components that have been discussed (food, alcohol, tobacco and other recreational drugs, illness, medication, working conditions, information about preconceptual carrier screening and counselling) should be provided in a single package in order to guarantee that no component is neglected and all are accessible. This will involve organising preconception care as part of a continuum (as in the case of prenatal care), within which guidelines are developed for patterns of referral and comprehensive records are kept.

During the initial period, at least, preconception care will need to be actively brought to the attention of the public by means of information campaigns, and also, for example, by the periodically issuing invitations to women of child-bearing age.

Professional groups that could potentially be involved include the child health services, midwives, GPs, medical specialists and occupational health physicians. In addition, the healthcare insurers, the Foundation for Preconception Care, the municipal health authorities, the regional support structures, professional associations, UMCs and the RIVM might also have a role to play. It would be good to involve health education experts in the development of a communications strategy.

9.4 Ethical considerations

Question 4: What ethical questions and controversies need to be considered in connection with preconception care?

In the Committee's view, the focus should be on the interests of the individual couple and their child as far as health benefits and autonomy are concerned. Any health benefits and cost savings at the public-health level are important spin-offs.

Within the ethical debate over preconception care, the Committee makes the distinction between controllable risk factors (such as lifestyle) and non-controllable risk factors (such as hereditary disorders in the family).

As far as the controllable risk factors are concerned, the Committee concludes that a fairly directive approach can be adopted when providing counselling and making recommendations on possible interventions. The primary concern here is the future child, and there is a clear health benefit to be gained. Much of this advice is now actually given during the first visit to the obstetric caregiver. As far as working conditions are concerned, although they are certainly controllable, the employee frequently has little influence over them, in which case the onus of responsibility must lie with the employer.

As regards non-controllable genetic risk factors, the Committee recommends a non-directive approach. The aim is not to achieve health benefits but to promote reproductive autonomy. This means giving prospective parents with a family history of hereditary disorders a greater range of options when deciding whether or not to embark on a pregnancy by providing them with sound information. This applies both to information on genetic disorders experienced by the parents-to-be or their families, and information on the possibility of preconceptual carrier screening. The Committee also believes that this information, in particular, can be provided in a phased manner. In this way, couples can indicate how much information they wish to receive, thus affording maximum protection to the right not to know.

Possible feelings of social pressure and medicalisation can be prevented by offering preconception care on a voluntary basis. Thus anyone may attend a consultation, but it is not compulsory.

9.5 Specific requirements

Question 5: Given the level of support that is needed for efficient implementation, what specific requirements should preconceptual information meet?

The Committee believes that preconception care must satisfy a number of quality requirements, which are described in Chapter 8:

- The various components should be effective and incorporated in evidence-based guidelines. When new insights are gained into a possible intervention, its effectiveness should be investigated and, if it proves ineffective, it should be removed from the preconception care package.

- Efficiency is a further important quality criterion in addition to effectiveness. As this programme will be population-wide, cost-effectiveness is important in order to ensure that it remains affordable.
- Preconception consultations should be generally accessible. The psychological and financial threshold for requesting a consultation should be as low as possible.
- This means that future parents should ideally be able to have a consultation in their own town/city and there should be no waiting lists.
- Ideally, the programme will cover all people who want to have children. It should, in any event, be accessible to people from groups with an increased risk of a less favourable pregnancy outcome (e.g. couples from groups with a low socio-economic status and women with epilepsy or diabetes).
- If preconception care as a whole is to be successful, any referrals that may be necessary after risk assessment should be conducted in a fair and prompt manner.
- The programme mentioned in the reply to question 3 should link up well with prenatal and neonatal care services, not only in terms of knowledge infrastructure and the information and education provided but also as regards the care itself.

9.6 Final observation

Child care begins before pregnancy. This is the single most important, evidence-based message of this advisory report. Preconception care can help to achieve this goal.

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Annexes

Annex **A**

The request for advice

On 5 November 2004 the Minister of Health, Welfare and Sport addressed the following request for advice to the President of the Health Council of the Netherlands (letter reference: PG/ZP2.518.824, 5.11.2004).

In my opening address to the assembled experts at the Bilderberg Conference on 'Preconception Care for Prospective Parents' on 29th January 2004, I expressed the wish to enter into a discussion with them about how we can improve the information given to prospective parents about preconception care (annex 1). The aim of preconception care is to enable couples to prepare themselves in the best possible way for pregnancy, in order to reduce the risk of hereditary and congenital disorders. To achieve this goal, sufficient information should be provided about risks, health promotion and possible interventions. At present, this information is still extremely fragmented.

On 1st October 2004 the Dutch Foundation for Preconception Care was founded, comprising the following six participating organisations: the Dutch Genetic Alliance (VSOP), the Royal Dutch Organisation of Midwives (KNOV), the Dutch Association for Community Genetics (NAGC), the Dutch Society for Obstetrics and Gynaecology (NVOG), the Dutch Society for Clinical Genetics (VKGN) and the national association of municipal health authorities (GGD-Nederland). These organisations are seeking to establish how to gain better access to couples who want to have children, in order to improve the information that they receive. Earlier in the year, on 7th April 2004, the VSOP had produced an advisory report on preconception care (annex 2), in which it proposed that the Foundation be charged with the task of considering the precise content and structure of preconception care, and that the Health Council should be asked to advise on the implementation of preconception care, espe-

cially in relation to those aspects that are still surrounded by significant scientific and/or ethical uncertainty or controversy.

On 29th June 2004, during the debate over the policy on prenatal screening, the Lower House adopted the motion tabled by member Ormel and others, requesting the government to seek to require manufacturers of contraceptives to include on their packaging the advice that women should start taking folic acid as soon as they stop using contraceptives with a view to becoming pregnant. In response, State Secretary Ross-Van Dorp has agreed to look into how she might fulfil this request (annex 3). In the meantime, plans are being made to stage a folic acid campaign during the period 2005-2007. The precise details of such a campaign have yet to be worked out, however. I am keen that this initiative should, as closely as possible, reflect current expert thinking on the broad-based implementation of preconception care in the Netherlands (as indicated earlier) – and that this care should amount to more than just prophylactic folic acid.

Research has shed light on factors that have a major bearing on good pregnancy outcomes and measures that promote the health of mother and child. Research into risks has shown that some are associated with the lifestyle and that smoking and alcohol consumption, in particular, have an adverse impact on pregnancy. Other risks stem from use of medication and exposure to substances that are not normally harmful. Some of the available knowledge in these areas is already being applied, but application is not universal and it is frequently inadequate. We know, for example, that folic acid is only being taken by some of the women who should be using it. Others only start taking it at a later stage, namely when they are already pregnant (and they have sought advice from a midwife or GP). Similarly, women usually only get information about infections stemming from such sources as raw food and cat litter trays after they have become pregnant. Information about hereditary diseases, too, is being under-utilised. What is important is knowledge about this type of disorder within the family, an understanding of the risks of consanguinity and awareness of carrier status (e.g. in the case of such disorders as cystic fibrosis and sickle cell disease).

Ignorance has been identified as the main reason why the available knowledge is either not applied or only applied at a late stage. If we improve education about risks, prospective parents can do more to promote a favourable pregnancy outcome. As things currently stand, this information only reaches some of the individuals concerned. Application of this information requires sufficient support both from prospective parents and from the relevant professional groups and such sectors as the child health services. Acceptance of preconception care is, after all, a necessary condition for efficient implementation – and in order to gain the requisite level of support, it is necessary to ensure that the services provided are of a high quality.

This prompts me to raise the following questions with regard to preconception care:

- Is it possible to provide an overview of research results of relevance to the promotion of the health of mother and child, together with an assessment of the evidence on which these findings are based?
- To what extent are the above-mentioned research findings being applied in present-day practice in the Netherlands and other Western countries?
- How can we optimise the coverage of education about risks, health promotion and possible interventions before and during pregnancy, and which professional groups/agencies (e.g. the child health services) should be involved?
- What ethical questions and controversies need to be considered in connection with preconception care?
- Given the level of support that is needed for efficient implementation, what specific requirements should preconceptual information meet?

Yours sincerely,
(signed)
The Minister of Health, Welfare and Sport
H. Hoogervorst

Annex **B**

The committee

- Prof. L.P. ten Kate, Emeritus Professor of Clinical Genetics, VU University Medical Center, Amsterdam, *Chairman*
- Prof. W.J.J. Assendelft, Professor of Family Medicine, Leiden
- Dr. T. Brand, occupational health physician, Coronel Institute, Academic Medical Centre, Amsterdam
- P.C. Groeneveld, Directorate of Public Health, Ministry of Health, Welfare and Sport, The Hague, *adviser*
- Prof. R.A. Hirasing, Professor of Community Child Health, VU University Medical Center, Amsterdam / consultant, TNO Quality of Life, Leiden
- A.M. van Huis, midwife, Academic Medical Centre, Amsterdam
- Prof. L.T.W. de Jong-van den Berg, Professor of Social Pharmacy and Pharmaco-epidemiology, University of Groningen
- Prof. M. Offringa, Professor of Clinical Epidemiology and Paediatrics, Academic Medical Centre, Amsterdam
- Y. Poortman, biologist, Secretary General, International Genetic Alliance of Parent and Patient Organisations, former Executive Director of VSOP, Soestdijk
- Prof. C.T.R.M. Schrander-Stumpel, Professor of Clinical Genetics, University of Maastricht
- Prof. E.A.P. Steegers, Professor of Obstetrics and Prenatal Medicine, Erasmus MC, Rotterdam
- Dr. D. Stemerding, lecturer, science and society, University of Twente

- Prof. S.P. Verloove-Vanhorick, Professor of Preventive and Curative Paediatric Health Care, LUMC / consultant, TNO Quality of Life, Leiden
- Dr. M.F. Verweij, ethicist, University of Utrecht
- Dr. P.A. Bolhuis, Health Council, *Secretary (until 1st January 2006)*
- Dr. V.W.T. Ruiz van Haperen, Health Council, *Secretary (as of 1st February 2006)*

With special thanks to Dr. M. Deutekom of the Dutch Cochrane Centre in Amsterdam for her assistance in the systematic literature search, selection and processing and to L.F. Stultiens of the Health Council for her contribution to the section on legal aspects in chapter 7.

The Health Council and interests

Members of Health Council Committees are appointed in a personal capacity because of their special expertise in the matters to be addressed. Nonetheless, it is precisely because of this expertise that they may also have interests. This in itself does not necessarily present an obstacle for membership of a Health Council Committee. Transparency regarding possible conflicts of interest is nonetheless important, both for the President and members of a Committee and for the President of the Health Council. On being invited to join a Committee, members are asked to submit a form detailing the functions they hold and any other material and immaterial interests which could be relevant for the Committee's work. It is the responsibility of the President of the Health Council to assess whether the interests indicated constitute grounds for non-appointment. An advisorship will then sometimes make it possible to exploit the expertise of the specialist involved. During the establishment meeting the declarations issued are discussed, so that all members of the Committee are aware of each other's possible interests.

Annex **C**

Justification of working methods

literature search and formulation of conclusions with levels of evidence

Staff at the Dutch Cochrane Centre and Medical Library, Academic Medical Centre, Amsterdam

- Dr. M. Deutekom, DCC
- Dr. M. van de Paardt, Medical Library, AMC
- Dr. R.J.P.M. Scholten, Director, DCC

Databases

- PubMed/Medline
- EMBase
- Cochrane Database of Systematic Reviews
- PsychLit

Strategy

1 Central premise: preconception care (as a selection criterion)
2 Inventory of available international advice, position papers, policy statements on preconception care (‘grey literature’)
3 Use of this and other literature arising from this inventory (providing the abstract is of high quality)
4 Search for systematic reviews (SRs)

5 Relevant references from these reviews also used
6 Supplemented with literature provided by Committee members and other experts
7 Literature classified by topic / risk factor
8 For major topics, the quality of the SRs was determined and summarised (e.g. alcohol, folic acid)
9 For other, 'smaller' topics, in the absence of SRs we looked for large studies (cohort, case-control studies). If these were available, we considered whether evidence-based conclusions could be drawn. For some topics, the Committee was merely able to establish that there were still no SRs and that, if it was not possible to draw an unequivocal, evidence-based conclusion from the available individual studies (e.g. due to the methodological heterogeneity of the studies), further research will be required.
10 Finally, the conclusions were translated into 'recommendations', based on evidence. This was an explicit process, whereby the Committee considered the evidence in relation to other relevant factors, such as consumer and patient preferences, availability of specific expertise, organisational aspects, social consequences or costs. Based on the overall consensus from its deliberations, the Committee formulated its recommendations.

Filters used in the search strategy: preconception care and systematic review

Preconception care:
Search term: ((preconception care[mesh] OR preconception* OR prepregnancy* OR pre-pregnancy* OR periconception* OR peri-conception*))

Systematic review:
(Source: University of Rochester): Filter: ((((((((((“Meta-Analysis”[MeSH Terms] OR meta-analysis[pt]) OR medline[tiab]) OR ((((metaanalyses[tiab] OR metaanalysis[tiab]) OR metaanalytic[tiab]) OR metaanalytical[tiab]) OR metaanalytically [tiab])) OR “meta analysis”[All Fields]) OR (((((overview[tiab] OR overview/literature[tiab]) OR overviewed[tiab]) OR overviewer[tiab]) OR overviewing[tiab]) OR overviews[tiab])) OR clinical trial[pt]) OR multicenter study[pt]) OR evaluation studies[pt]) OR validation studies [pt]) OR review[pt]) OR (systematic review[All Fields] OR systematic reviews[All Fields]))

Search period

The selection of grey literature took place on an ongoing basis, between May 2005 and June 2007.

The systematic literature search for systematic reviews and large studies, with the term preconception care as the selection criterion, included all of the literature in the specified databases up until October 2006.

In some areas, the literature has been supplemented with articles from the period October 2006 – May 2007.

Level of evidence found in the literature

Source: CBO: Levels of Evidence (http://www.cbo.nl/product/richtlijnen/handleiding_ebro/article20060207153532/view)

	Intervention	Diagnostic accuracy	Harm/adverse events[a], etiology, prognosis
A1	Systematic review of at least two independent studies of A2-level		
A2	Double-blind randomised clinical trial of good quality and sufficient power	Comparison between an index test and a reference test (the gold standard) with previously defined cut-off points and independent assessment of test and gold standard, including sufficient numbers of consecutive patients having the index and reference test	Prospective cohort study, with sufficient power, adequately controlled for confounding, and sufficient, non-selective follow-up
B	Other comparative study (without those aspects mentioned in A2), case-control or cohort study	Other comparison between an index test and a reference test (without those aspects mentioned in A2)	Other prospective cohort study (without those aspects mentioned in A2), retrospective cohort study, or case-control study
C	Non-comparative study		
D	Expert opinion		

[a] This classification is only applicable when controlled trials would not be feasible for ethical or other reasons. In other conditions, the classification for intervention should be applied.

Formulation of conclusions from the literature

Based on the available evidence, conclusions were then formulated, together with an indication of the level of evidence, which was classified as follows:

Level of evidence for the conclusions

Level 1	Based on one systematic review (A1) or at least two independently performed level-A2studies
Level 2	Based on one level-A2 study or at least two independently performed level-B studies
Level 3	Based on one level-B or C study
Level 4	Based on the opinion of experts, e.g. members of the working party

With thanks to Dr. D.T. Ubbink (DCC), Dr. A. Goossens (DCC) and Dr. L. Hooft (DCC) for their advice with regard to the search strategy and their assistance in the selection of the literature.

Annex **D**

Abbreviations and glossary

D.1 Abbreviations

ACE	Angiotensin-converting enzyme
ACOG	American College of Obstetricians and Gynecologists
ADA	American Diabetes Association
AIDS	Acquired immunodeficiency syndrome
BMI	Body mass index (weight in kilograms divided by the square of the length in metres)
CDC	Centers for Disease Control and Prevention (Atlanta, GA, USA)
CF	Cystic fibrosis
CI	Confidence interval
DCC	Dutch Cochrane Centre
DES	Diethylstilboestrol
DNA	Deoxyribonucleic acid
EBRO	Evidence-based guideline development
EFSA	European Food Safety Agency
EU	European Union
EURAP	European Registry of Antiepileptic Drugs and Pregnancy
EUROCAT	European Registration Of Congenital Anomalies and Twins

GP	General practitioner
GR	Health Council of the Netherlands
HELLP	Haemolysis, Elevated Liver enzymes, Low Platelets
HIV	Human immunodeficiency virus
ICSI	Intra-cytoplasmatic sperm injection
IOM	Institute of Medicine (Washington DC, US)
IVF	In-vitro fertilisation
KNOV	Royal Dutch Organisation of Midwives
MeSH	Medical Subject Headings
MMWR	Morbidity and Mortality Weekly Report (published by CDC)
NACG	Netherlands Association for Community Genetics
NFD	Dutch Diabetes Federation
NVOG	Dutch Society for Obstetrics and Gynaecology
OR	Odds ratio
PGD	Pre-implantation genetic diagnosis
PKU	Phenylketonuria
RIVM	Dutch National Institute of Public Health and the Environment
RR	Relative risk
RVP	National Vaccination Programme
RVZ	Council for Public Health and Health Care
STDs	Sexually transmissible diseases
SSRI	Selective serotonin reuptake inhibitor
TIS	Teratology Information Service
UMC	University Medical Centre
VKGN	Dutch Society for Clinical Genetics
VSOP	Dutch Genetic Alliance
VWS	The Dutch Ministry of Health, Welfare and Sport

D.2 Glossary

Aneuploidy
: State in which a foetus has an abnormal number of chromosomes

Autosomal
: Referring to chromosomes other than the X and Y sex-determining chromosomes

Congenital
: Inborn / present at birth

Convulsions
: Violent spasms

Ectopic pregnancy
: A pregnancy that develops outside of the uterus

Founder effect
: An unusually high frequency of a gene (and a reduction in the gene pool) in a particular population derived from a small set of unrepresentative ancestors

Genetic drift
: A change in the frequencies of genetic traits or allele frequencies over generations (caused entirely by statistical variation, and not by natural selection or founder effect)

Glycaemic control
: Control over blood sugar levels in patients with diabetes

Haemoglobinopathies
: Collective term for conditions involving an abnormal haemoglobin (the protein which binds oxygen in the blood)

Periconceptional
: Relating to the period extending from 4 weeks before to 4 weeks after conception (in which a woman will usually not know that she is pregnant)

Placenta previa
: Condition in which the placenta is implanted in the lower segment of the uterus

Pre-eclampsia
: Hypertension during pregnancy, in combination with protein in the urine and/or an accumulation of fluid

Reproductive autonomy
: The ability and opportunity to make one's own, well-considered decisions concerning procreation

Rickets
: A disease resulting from a lack of vitamin D and characterised by efective bone growth

Spina bifida
: A congenital defect in which the spinal column is imperfectly closed

Vitamin deficiency
: An insufficient quantity of a certain vitamin in the body