

NHG Guideline Subfertility

Second revision

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Introduction

The NHG Guideline on Subfertility provides recommendations for the diagnosis and management in the event of a desired pregnancy failing to occur. Subfertility is defined as the absence of pregnancy after more than twelve months of unprotected intercourse aimed at achieving conception.¹ If the desire for pregnancy has existed for less than one year, this is not considered as subfertility yet and – usually – good information is sufficient, because the chance of pregnancy is high. This guideline was revised as part of a project in which the guidelines concerning subfertility for gynaecologists, urologists and clinical chemists were also developed or revised.² The guidelines were adjusted to correspond to each other and agreements were made about task division and referral. If abnormalities are found during the anamnesis, physical examination or additional examinations, referral to a gynaecologist for further diagnosis and/or treatment is indicated. If this is not the case, the chance of spontaneous pregnancy determines the choice of treatment. In order to estimate this chance, a prediction model has been used in this guideline and in the relevant guidelines for second-line practitioners.³ Using this model, the chance of a pregnancy in the next year can be estimated based on information about the

Background

Epidemiology

The number of new cases of subfertility registered in general practice is 9.0 per 1,000 women aged 25 to 44 years.⁴ The prevalence in this age category is 22 per 1,000 women per year. The figures for women are similar to the figures for 'couples'. Approximately 5% of all couples will remain childless against their wishes.⁵

Aetiology

The most common causes of subfertility are ovulation abnormalities (24%), strongly decreased quality of sperm (20%), abnormalities in the interaction between sperm and cervical mucus (15%) and tubal pathology (including severe endometriosis) (11%).⁶ The cause remains unexplained in 30% of cases.

Less frequent causes are azoospermia, con-

genital abnormalities of the genitals and sexual problems. A regular cycle – in other words a cycle with a regular duration of 21 to 35 days – is virtually always ovulatory. The woman's age is the most important prognostic factor for the chance of pregnancy. The chance of pregnancy decreases annually for women over the age of 30 years.⁷ To a much lesser extent, the man's age also affects the chance of pregnancy.⁸ Fertility problems can be present in both the man's family and the woman's family.^{9,10} Exposure of sperm to an elevated temperature, for example with retractile testes or fever, appears to reduce the quality of the sperm. A varicocele also causes an increase in temperature in the scrotum, but an unfavourable effect on the chance of pregnancy has never been demonstrated.¹¹ Surgical treatment of a varicocele to increase the chance of pregnancy is not effective.

Diagnostic recommendations

The doctor's assistant should indicate when making an appointment for the consultation concerning subfertility that both partners should preferably be present during the consultation: subfertility affects the couple and not only the man or the woman. If a couple visits their general practitioner with a desire to become pregnant with a subsequent child following previous referral due to subfertility, the action that is taken depends on the history.¹² The gynaecologist can be consulted about the treatment policy.

The absence of a pregnancy is often painful for a couple. It is therefore important that the general practitioner considers emotional aspects such as the significance of not being able to have (any more) children and the consequences on sexuality and the relationship.

History

For all couples, the general practitioner asks about:

- the duration of desire for pregnancy;
- the number of months of unprotected intercourse;
- duration and regularity of the cycle (possible indicator of oligomenorrhoea or amenorrhoea);
- the frequency of intercourse during the fertile period.

For couples that have had a desire for pregnancy for more than one year, the general practitioner will ask about the following:

- any previous pregnancies and the out-

come of these pregnancies;

- descendants from any previous relationship(s) (increases the chance of pregnancy);
- prior use of a depot contraceptive;¹³
- a previous STD (Chlamydia infection, gonorrhoea), an episode of salpingitis (fallopian tube infection)¹⁴ or other infection in the lower abdomen (perforated appendicitis), lower abdominal surgery;¹⁵
- pain symptoms in the lower abdomen (can point to endometriosis);¹⁶
- knowledge about the fertile part of the cycle (at which point in the cycle does intercourse take place);
- relevant problems in the living or working environment, such as extended periods from home or irregular working hours;
- use of medicines such as valproic acid, treatment with cytostatics or radiotherapy,¹⁷ exposure to harmful substances¹⁸ for the woman;
- problems with intercourse for the woman (can point to vaginismus, endometriosis, sexual abuse);
- problems with erection and ejaculation for the man (actual intra-vaginal ejaculation).¹⁹

Key messages

- Subfertility is defined as the absence of pregnancy after more than twelve months of unprotected intercourse aimed at achieving conception.
- Subfertility should lead to anamnesis and physical examination for ovulation abnormalities and the patency of the fallopian tubes.
- Additional examinations include a sperm analysis and a Chlamydia antibody test.
- The couple is referred to the gynaecologist for further diagnostic tests and treatment in the event of:
 - abnormal findings (ovulation abnormalities, indications for tubal pathology or a strongly reduced quality of sperm);
 - a chance of pregnancy < 30% in the next year;
 - woman's age ≥ 38 years.
- In case of a chance of pregnancy between 30 and 40%, the general practitioner will consult with the couple about whether to refer or not.
- A watchful waiting policy is maintained for 6 months to 1 year in the event of normal findings and a chance of pregnancy > 40%.

In the case of *oligomenorrhoea* or *amenorrhoea*, the general practitioner will ask about the duration of this condition and will look at possible causes, such as:

- stress, low body weight, significant weight loss or intense exercise;
- acne, hirsutism or obesity (can point to polycystic ovarian syndrome);
- galactorrhoea (can point to hyperprolactinaemia);
- climactic symptoms.

Refer to the NHG Clinical Practice Guideline on Amenorrhoea for the further diagnosis and treatment options.

If the sperm analysis is abnormal (refer to the 'Additional examination' section), the general practitioner will ask the man about:

- current symptoms of the genitalia;
- a febrile illness in the past twelve weeks;
- smoking, use of alcohol or drugs;
- previous STD (Chlamydia infection, gonorrhoea, epididymitis or (mumps) orchitis);

Patient contribution

The NHG Guidelines provide guidance for treatment by the GP; therefore, the GP holds a central position. However, patient factors always influence treatment. For practical reasons, this aspect is not emphasized repeatedly in this guideline, but is mentioned explicitly at this point. Wherever possible, the GP creates a treatment plan in consultation with the patient, taking the patient's specific situation into account and acknowledging the patient's own responsibilities, with adequate information provision being a prerequisite for success.

GP's considerations

The GP's personal insight is a key aspect in all guidelines. Weighing relevant factors in specific situations can justify reasoned deviations from the treatment policy described below. Nonetheless, this guideline is meant to serve as a standard and aid.

Delegating tasks

NHG Guidelines are written for GPs. This does not mean the GP must perform all tasks personally. Certain tasks may be delegated to the doctor's assistant, practice support staff or practice nurse, as long as they are provided with support in the form of clear working agreements, defining the conditions under which the GP must be consulted, and as long as the GP retains quality control. As the decision on whether or not to delegate is strongly dependent on the local situations, the guidelines do not contain any concrete recommendations in this area.

- use of medicines (ACE inhibitors, antidepressants, sulphasalazine or anabolic steroids),²⁰ treatment with cytostatics or radiotherapy, exposure to harmful substances (lead, pesticides);¹⁸
- cryptorchidism, trauma or surgery in the genital region.

Physical examination

For the *woman*, the general practitioner will focus on:²¹

- physique, growth of body hair and anatomical abnormalities of the external genitalia (indicating congenital or functional abnormalities of the genital tract);
- hirsutism (can point to hyperandrogenism, for example the polycystic ovarian syndrome);
- abdominal surgery scars;
- significant excess weight or lack of weight.²²

The general practitioner will then perform:

- a speculum examination (can provide indications for anatomical abnormalities and vaginismus);
- vaginal examination (location and size of the uterus and the adnexa. This can provide indications for anatomical abnormalities, endometriosis, myomas and vaginismus).

The *man* will undergo physical examination if the sperm analysis is abnormal (refer to the 'Additional examination' section). The examination then consists of inspection and palpation of the external genitalia. Watch out for the shape, the volume, the location and the consistency of the testis, abnormalities of the epididymis and the presence of the vas deferens. Small, soft testicles in an adult male can point to insufficient gonadotrophic stimulation. Absence of a testicle in the scrotum can point to cryptorchidism. The detection of a varicocele does not have any consequences on the management (refer to the 'Aetiology' section).

Additional investigations

If the diagnosis of subfertility (desire for pregnancy existing for more than twelve months) has been confirmed, the following examinations will take place:

- Sperm analysis in the laboratory.²³ The sperm is abnormal in the case of azoospermia and a VCM (volume x concentration x percentage progressively moving spermatozoa) < 3 x 10⁶. In the case of abnormal sperm, the examination is repeated after several weeks, with the best result determining the management (refer to the 'Sperm analysis' section).

- A Chlamydia antibody test (CAT)²⁴ If the anamnesis provides indications for tubal pathology, such as (recurrent) previous infections or lower abdominal surgery, this is an indication for referral and the CAT can be omitted.

Registration of the basal temperature curve (BTC) to demonstrate ovulation is not useful in the case of a regular cycle, as such a cycle is almost always ovulatory.

The post-coital test (as a facultative test instead of the sperm analysis) has been removed, because it is very rarely performed in primary care and there are doubts about the reliability of this test in primary care.²⁵

Other additional examinations, such as determination of the FSH and TSH levels are not useful.²⁶

Sperm analysis

The quality of the sperm can be reduced by:

- a raised temperature, such as a febrile illness;
- exposure to chemical substances, such as paint fumes and pesticides.

Conditions for optimum quality of the sperm analysis:

The sperm must be:

- submitted to the laboratory within one hour;
- transported without becoming too warm or too cold (preferably in an inner pocket);
- collected in a container supplied by the laboratory (do not use a condom);
- obtained by masturbation (prior abstinence is not necessary).

Evaluation

Subfertility is defined as the absence of pregnancy after more than twelve months of unprotected intercourse aimed at achieving conception. The duration of the subfertility corresponds to the duration of the desire for pregnancy: the diagnosis of subfertility means that a couple has been subfertile for one year.

The management depends on the outcomes of the anamnesis, physical examination and additional examinations.

Abnormal findings are defined as:

- indications for an anovulatory disorder: an irregular cycle (cycle duration longer than 35 days) or amenorrhoea for more than six months;
- indications for tubal pathology based on the anamnesis, as with (recurrent) previous infections (PID, a perforated appendicitis) and lower abdominal surgery, or an abnormal CAT;

- azoospermia or a strongly reduced sperm quality (VCM < 3 x 10⁶) based on repeated sperm analysis;
- other problems, such as sexual problems that mean that intra-vaginal intercourse does not take place or anatomical abnormalities that make intercourse or pregnancy impossible.

In these cases, the couple is referred to the gynaecologist for further diagnostic tests and treatment.

In the case of *normal findings*, the management depends on the chance of pregnancy. The chance of pregnancy depends strongly on the age of the woman and the quality of the sperm. Use the prognostic score model to calculate the individual chance of pregnancy in the next year (see www.nhg.org). The pregnancy percentages from the prognostic model have been summarised in *table 1* and *table 2* (*table 1*: women who have not been pregnant before; *table 2*: women who have been pregnant before).

- *Chance of spontaneous pregnancy > 40%*: advise the couple to wait 6 to 12 months. This is in accordance with the management in secondary care. Referral takes place after 18 months to 2 years of subfertility.
- *Chance of pregnancy between 30 and 40%*: consult with the couple about referral to secondary care. The woman's age (and the number of years that the woman has left to become pregnant) plays an important role in this decision. Certainly for women under the age of 32 years, it is important to discuss whether it would not be preferable to keep trying for a spontaneous pregnancy for some time, due to the still considerable chances of pregnancy and the fact that there is still plenty of time. For couples with these chances of pregnancy, the chance of a pregnancy with treatment in secondary care does not appear to be greater than with a watchful waiting policy for 6 months to 1 year.²⁷ In addition, there are also disadvantages associated with fertility treatment: the treatment is lengthy (2 to 3 years) and forms a heavy burden on many couples.
- *Chance of pregnancy < 30%*: refer the couple to the gynaecologist.
- *Woman's age ≥ 38 years*: refer the couple to the gynaecologist.

Treatment recommendations

Education

If the *desire for pregnancy is shorter than 12 months*, explain that the chance of spontaneous pregnancy in the next few months is significant. A normal cycle is very likely to be ovulatory. Approximately 70% of women

are pregnant after six months of unprotected intercourse, 80% after one year and 90% after two years.²⁸ These percentages are lower for women over the age of 35 years. The couple is advised to return for further diagnostic tests if the woman fails to become pregnant after more than 12 months.

In the case of subfertility and normal findings in the diagnostic phase, information is given about:

*The most fertile period for the woman and the frequency of intercourse*²⁹

- Ovulation takes place approximately 14 days before the first day of the next expected menstruation.
- For a regular cycle of 28 days, this is approximately on day 14 after the first day of the previous menstruation.
- In the case of a regular cycle of 28 days,

Table 1 The chance of pregnancy in couples who have been subfertile for one year, according to age of the woman and percentage of progressively moving spermatozoa in the man, where the woman in question has not been pregnant before.

Age (years)	Progressively moving spermatozoa (%)				
	20%	30%	40%	50%	60%
20	40	42	45	48	50
25	36	38	40	43	45
26	35	37	39	42	44
27	34	36	38	41	43
28	33	35	38	40	42
29	32	34	37	39	42
30	31	34	36	38	41
31	31	33	35	37	40
32	29	31	33	35	37
33	27	29	31	33	35
34	25	27	29	31	33
35	23	25	27	29	31
36	22	23	25	27	29
37	20	22	23	25	27

- Instructions for use of the tables:
- The tables can only be used if the menstrual cycle is regular, the CAT is negative and the VCM > 3 x 10⁶.
- Consult the prognostic model on www.nhg.org if the percentage of progressively moving spermatozoa or the age of the woman falls outside of the table.
- The percentages in the table are indicative of the actual chance of pregnancy and should therefore be presented to the couple as an estimated chance.
- The choice of treatment policy (wait-and-see or referral and the accompanying choice of colours) has been determined based on agreements between first-line and second-line practitioners.
- Refer to the gynaecologist if the age of the woman ≥ 38 years.

Green: expectative approach for six to twelve months

Yellow: expectative approach or referral based on the woman's age and in consultation with the couple

Red: referral

Table 2 The chance of pregnancy in couples who have been subfertile for one year, according to age of the woman and percentage of progressively moving spermatozoa in the man, where the woman in question has been pregnant before.

Age (years)	Progressively moving spermatozoa (%)				
	20%	30%	40%	50%	60%
20	63	63	66	69	72
25	54	57	60	63	66
30	49	52	55	58	61
31	48	51	54	57	59
32	45	48	51	54	57
33	43	45	48	51	54
34	40	43	45	48	51
35	38	40	43	45	48
36	36	38	40	43	45
37	33	36	38	40	43

- Instructions for use of the tables:
- The tables can only be used if the menstrual cycle is regular, the CAT is negative and the VCM > 3 x 10⁶.
- Consult the prognostic model on www.nhg.org if the percentage of progressively moving spermatozoa or the age of the woman falls outside of the table.
- The percentages in the table are indicative of the actual chance of pregnancy and should therefore be presented to the couple as an estimated chance.
- The choice of treatment policy (wait-and-see or referral and the accompanying choice of colours) has been determined based on agreements between first-line and second-line practitioners.
- Refer to the gynaecologist if the age of the woman ≥ 38 years.

Green: expectative approach for six to twelve months

Yellow: expectative approach or referral based on the woman's age and in consultation with the couple

Red: referral

virtually all pregnancies are achieved by intercourse on days 8 to 14 of the cycle (the 6 days preceding ovulation).

- An intercourse frequency of 2 to 3 times per week during this period is sufficient for a good chance of pregnancy.
- The consistency and clarity of the cervical mucus is a good indicator of the fertile period; normal pre-ovulatory cervical mucus is crystal clear and can be stretched very far (up to 10 cm or more).
- LH tests have no added benefit in the majority of women; these test only become positive 1 or 2 days before ovulation, meaning that potentially fertile days are missed.
- Recording of the basal temperature curve (BTC)³⁰ and LH tests can be used to recognise the moment of ovulation and the fertile period.

The role of lifestyle factors and body weight

- Smoking appears to reduce the chance of pregnancy for women.³¹ It is also important to stop smoking due to the risk of

damage to the unborn child. In men, there is a link between smoking and a reduced sperm quality. The clinical relevance of this is unclear.

- It has not been demonstrated that the use of alcohol reduces fertility in women.³² However, limiting the use of alcohol is indicated due to possible damage to the unborn child. In men, excessive use of alcohol can result in sexual dysfunction and a decrease in potency.
- The use of drugs and anabolic steroids decreases the quality of sperm in men.^{20,33}
- Women with a BMI ≥ 30 become pregnant less quickly.^{22,34}

Further pre-conception lifestyle advice falls outside the scope of this guideline, but can be of importance to couples with a desire for pregnancy.³⁵

In addition to oral information, the general practitioner can give the patient the NHG Patient Letters on subfertility. There are letters on problems with becoming pregnant, general; fertility tests for women; and fertility tests for men. Please visit ww.nhg.org for an overview of all NHG Patient Letters.

Couples with subfertility can contact patient association Freya (www.freya.nl) for support and – if they have decided to stop treatment – the regional offices of FIOM (www.fiom.nl).

Drug treatment

Medicinal stimulation of ovulation using clomifene is not recommended in general practice, due to the limited indication and

the limited experience with clomifene in primary care.³⁶

Referral

The general practitioner discusses referral to the gynaecologist with the couple in the case of (see *figure 1*):

- amenorrhoea for a period of six months (even if the diagnosis of subfertility has not been made yet);
- subfertility for 1 year and abnormal findings:
 - other indications for ovulation abnormalities (oligomenorrhoea);
 - indications in the anamnesis for possible tubal pathology, previous infections or lower abdominal surgery or an abnormal CAT;
 - azoospermia or a strongly reduced sperm quality based on repeated sperm analysis ($VCM < 3 \times 10^6$);
 - other problems, such as sexual problems and anatomical abnormalities that make intercourse or pregnancy impossible.
- subfertility for 1 year and normal findings if:
 - chance of pregnancy $< 30\%$;
 - woman's age ≥ 38 years;
- subfertility persisting for more than 2 years.

In the case of a chance of pregnancy between 30 and 40% (with subfertility for 1 year and normal findings), the general practitioner will consult with the couple about whether to refer or not.

In the discussion about the referral, the fol-

lowing points will be discussed:

- the couple's expectations;
- a general explanation of what the couple can expect (see *table 3*);
- the impact of the subfertility course in secondary care on employment;³⁷
- possible guidance by the general practitioner during the sometimes lengthy and difficult period of examinations and possible treatment.

Factors such as shortened life expectancy, child abuse/neglect, psychological instability, cognitive limitations and increased risk of congenital defects can be contra-indications for (referral for) fertility-promoting treatments. The general practitioner will discuss this in detail with the couple. This can involve controversial situations; consultation with the gynaecologist is indicated prior to referral.

Guidance of couples with long-term subfertility problems

A couple whose desire for pregnancy remains unfulfilled can have a long way to go before all technical possibilities have been exhausted. The general practitioner offers all couples the opportunity – if they wish – to discuss the experiences and expectations on a regular basis. In this case, make appointments with the couple for follow-up consultations upon completion of the diagnostic tests and before the start of new treatments. The examinations or treatments can sometimes result in emotional tension,⁴² relationship problems or problems at work.³⁷ Sometimes, decisions (new job, moving house) are postponed to cre-

Table 3 Treatment options in secondary care.

Treatment	Indication, efficacy
Ovulation induction ²⁶	<ul style="list-style-type: none"> - ovulation disorders (particularly PCOS); - duration of treatment: 6 – 12 months; - pregnancy percentage: 30 – 40%; - increased risk of multiple pregnancies.
Tube surgery ³⁸	<ul style="list-style-type: none"> - mild and moderate tubal pathology; - 40 – 60% chance of pregnancy in most favourable case; - increased risk of ectopic pregnancy (EUG).
Intra-uterine insemination (IUI) ³⁹	<ul style="list-style-type: none"> - unexplained subfertility and decreased quality of sperm AND chance of pregnancy $< 30\%$; - performed either with or without mild hyperstimulation; - usually 4 – 6 cycles; - pregnancy percentage of 7.3% per cycle, of which 9.5% multiple pregnancies.
In vitro fertilisation (IVF) ⁴⁰	<ul style="list-style-type: none"> - bilateral tubal pathology; - if IUI has proved unsuccessful; - woman's age ≥ 38 years; - reticent approach in women > 41 years, upper limit of treatment at 45 years; - pregnancy percentage of 20% after 1 cycle and almost 60% after 3 cycles.
Intra-cytoplasmic sperm injection (ICSI) ⁴¹	<ul style="list-style-type: none"> - severely reduced sperm quality; - possibly with surgically obtained sperm (TESE/MESA/PESA) in the event of azoospermia; - only applied in a study setting; - pregnancy percentage similar to IVF.
Egg cell donation	<ul style="list-style-type: none"> - women with premature ovarian failure; - pregnancy percentage: 10 – 20% per cycle (depending on the age of the donor).

ate enough space for a possible pregnancy. The decision to stop treatment is an active decision. The processing of the probability or certainty that a couple will never have a biological child is similar to a grieving process. Discuss the options for foster care and adoption.⁴³

Guideline development method

In March 2008, a working group consisting of six general practitioners, one general practitioner in training and one gynaecologist started revising the NHG Guideline on Subfertility. The working group consisted of the following members: R.J. Hinloopen, general practitioner in Utrecht; C.C.A.N. van Oppen, general practitioner in Koog aan de Zaan; A.M. Silvijs, general practitioner in Leiden; Dr K.M. van Asselt, general practitioner in Kockengen; and Dr P.J.Q. van der Linden, gynaecologist in Deventer.

The members of the working group did not report any conflicts of interest.

In May 2009, fifty general practitioners were asked to comment. Their addresses were selected randomly from the database of NHG members. Fifteen comment forms were returned.

The following acted as referees: Dr J.J.L.M. Dekker, Prof. J.A. Land, Dr H. Visser and Dr E. Scheenjes,

gynaecologists; L. Smeenk, E. Brands, A. Bruinsma, Dr F.P. Hohman and Prof. T. Lagro-Janssen, general practitioners; A. Brand and D. Soeters, on behalf of the NHG Clinical Practice Guidelines Advisory Board; J. Engeldorp Gastelaars, on behalf of the KNMP-WINAp; Prof. J.M.A. Sitsen, physician – clinical pharmacologist on behalf of the Health Care Insurance Board (CVZ); Dr T. Brand and M.M. Maussault-Panis, occupational health physicians on behalf of the NVAB; and P. Leusink, general practitioner and sexologist NVVS. Listing as a referee does not mean that the referee supports every detail of the content in the Clinical Practice Guideline.

The draft guideline was authorised by the NHG Authorisation Committee in November 2009.

The working group was supported by J.A.M. van Balen, general practitioner and staff member of the department of Guideline Development and Research of the NHG. Dr Tj. Wiersma was involved as the senior staff member from this department.

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Notes

Note 1

Definition of subfertility

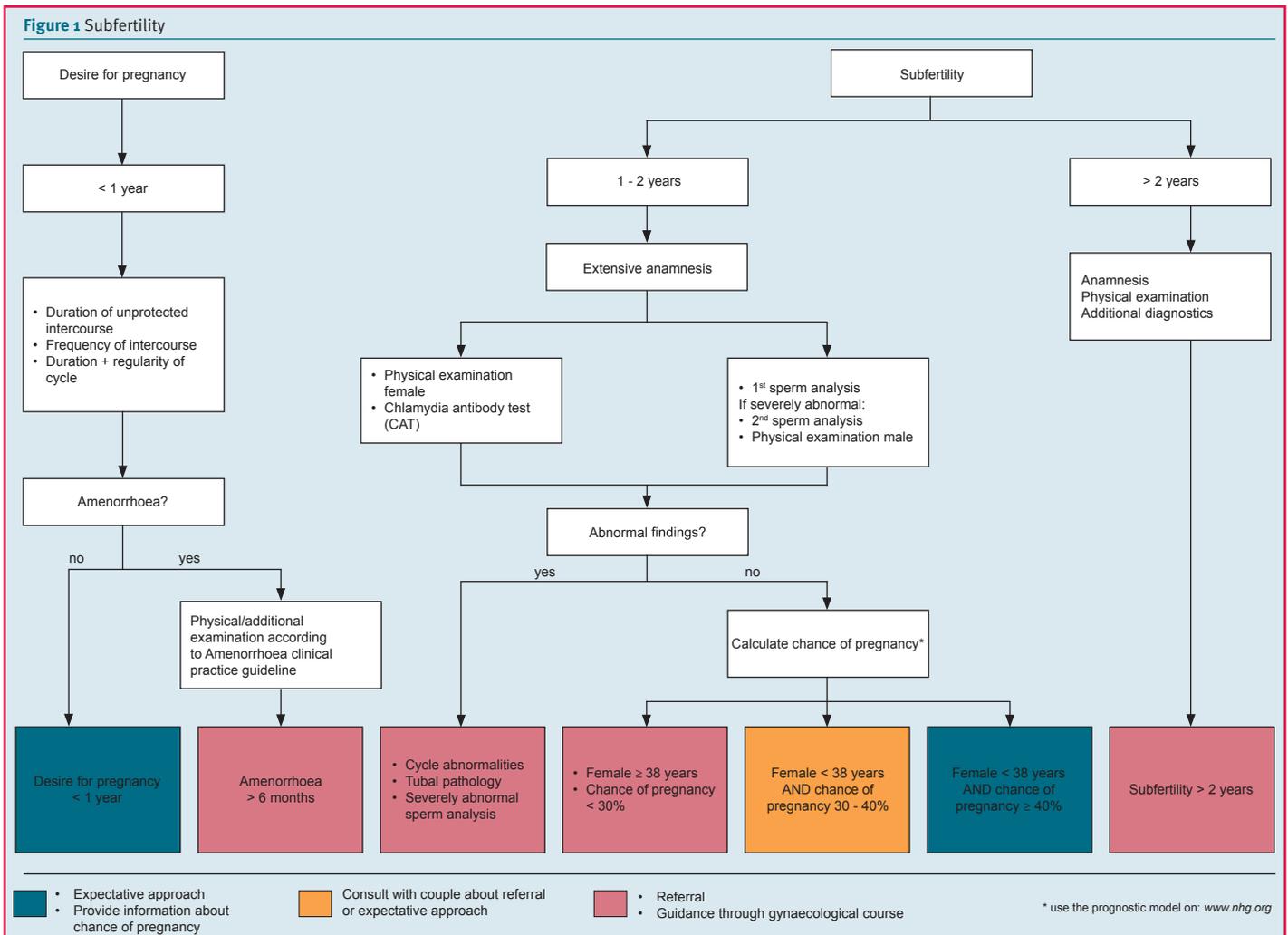
A period of one year of unprotected intercourse is used to define subfertility. The English literature also uses the terms infertility and infecundity. This latter term also encompasses recurrent miscarriages and the consequences of DES for women. The definition of subfertility in this guideline corresponds to the definition in the guidelines on subfertility by the Dutch Society of Obstetrics and Gynaecology [NVOG 2004a].

Note 2

Other guidelines on subfertility

These include the guidelines/protocols for the following subjects:

- Unexplained infertility (Dutch Society of Obstetrics and Gynaecology, NVOG).
- IUI (NVOG)
- IVF (NVOG)
- Male subfertility (NVOG and the Netherlands Association for Urology, NVU)
- Sperm analysis (NVOG, Association of Clinical Embryologists (KLEM) and the Netherlands Society for Clinical Chemistry and Laboratory Medi-



cine, NVKC)

- Network guideline Subfertility (NHG, NVOG, NVU, KLEM and NVKC)

The abovementioned guidelines/protocols are expected to be published on the websites of the relevant associations in the course of 2010.

Note 3

Prognostic model

Three prediction models were developed during the 1990s to predict the chance of pregnancy in subfertile women [Eimers 1994, Collins 1995, Snick 1997]. None of these models were validated prospectively in primary care and therefore the use of these models to estimate the chance of pregnancy was not advised in the guideline published in 1998. Hunault integrated the three models into a new prediction model, which includes the following variables: age of the woman, duration of the subfertility, nature of the subfertility (primary or secondary), motility of the sperm, referral status (primary or secondary care) and PCT (optional) [Hunault 2004]. This integrated model was recently validated in a prospective cohort study [Van der Steeg 2007]. This study included 3,021 couples referred by the general practitioner (average duration of subfertility was 1.7 years). These couples had an anamnesis collected, sperm analysis and PCT performed and checks for an ovulation disorder or tubal pathology. The cycle was presumed to be ovulatory if the cycle was regular (duration 23 to 35 days; inter-cycle variation < 8 days). The ovulation was confirmed by means of a basal temperature curve or a mid-luteal progesterone determination or monitored by ultrasound. Couples in which the man had strongly abnormal sperm quality (VCM < 3×10^6) were excluded. Tubal pathology was confirmed by means of a CAT or hysterosalpingography. If the CAT was negative, it was assumed that there was no tubal pathology. In the study, couples with a chance of pregnancy > 40% were advised to follow an expectative approach for 6 months. Couples were monitored for 12 months: 18% of the couples had a spontaneous, progressing pregnancy in this year; 27% of the couples in which the woman did not become pregnant received no additional treatment; 44% of the couples started treatment. A calibration analysis, in which the association between the average number of expected and observed spontaneous pregnancies was determined, revealed an association of 0.82 (95% CI: 0.6 to 1.0; $p = 0.08$). The observed number of pregnancies corresponded well with the number of predicted pregnancies: for the 977 couples with an expected chance of pregnancy of 30 to 40% (32% of the couples), the pregnancy percentage after 1 year was 30%, and for the 611 couples with a chance of pregnancy $\geq 40\%$ (20% of the couples), the pregnancy percentage after 12 months was 46%. The study included a lot of couples with a pregnancy chance in the middle range of about 30 to 40% (for whom the decision to refer or not to refer is important). Therefore, the reliability of the prediction model is highest in this range. As couples with a very high or very low chance of pregnancy were included far less often,

the model may be less reliable for these groups. However, a less accurate estimate of the chance of pregnancy in these groups is not a problem, because the management for these couples is clear (very high chance of pregnancy = watchful waiting policy; very low chance of pregnancy = refer).

Considering the inclusion criteria and exclusion criteria, it can be assumed that the population as described in this study corresponds closely to the population seen by the general practitioner and that it is therefore applicable in primary care. The management recommended in this guideline only differs slightly concerning the additional examinations described in this study where ovulation disorders are concerned: the guideline does not recommend BCT and mid-luteal progesterone determination for a normal cycle length, but states that one can assume that there are no ovulation disorders if the cycle duration is 21 to 35 days. This means that a small percentage of women with a normal cycle duration and an ovulation disorder can be missed.

This guideline has chosen to use the pregnancy percentage to determine whether referral to secondary care is indicated. The previous guideline based the decision to refer to secondary care exclusively on age. In addition to age, the prognostic model by Hunault includes several other variables in order to make a sound decision on whether or not to refer to secondary care. Although the chance of pregnancy as predicted by this model may differ slightly from the actual chance of pregnancy for a primary care population, the use of the model provides a much better estimate than the previous prediction models. Furthermore, the use of this model also fits more closely with the management in secondary care, where the management is also determined based on this model.

Note 4

Incidence and prevalence

The figures mentioned in the main text were obtained from the Continuous Morbidity Registration (CMR) in Nijmegen. An incidence of 9.0 was found for subfertility in the age category from 25 to 44 years over the registration period from 1985 to 2006 [Van de Lisdonk 2008]. The prevalence was 22 per 1000 women per year. In the CMR, the figures for this CMR code under women most closely match the extent of the problem of subfertility and can therefore be applied to 'couples'. The number of new cases of subfertility registered in the second National Study is 5.7 per 1000 women aged 25 to 44 years, and 1.8 and 0.2 per 1000 men aged 25 to 44 years and 45 to 64 years, respectively. In this study, subfertility was defined as 2 years of unwanted childlessness [Van der Linden 2004].

Note 5

Unwanted childlessness

The percentage of unwanted childlessness in the general population is 3% for women trying to become pregnant before the age of 30 years, and 8% for women trying to become pregnant after the age of 30 years [Steenhof 2000].

Note 6

Causes

A review article listing the causes of subfertility in primary, secondary and tertiary care lists the following percentages for primary care, based on the study by Snick, which examined the chance of spontaneous pregnancy in 726 subfertile couples in the region of Walcheren: severely reduced quality of sperm 20%, ovulation disorder 24%, abnormalities in the interaction between sperm and cervical mucous 15%, tubal pathology (also severe endometriosis) 11% and unexplained (including slight and mild endometriosis) 30% [Evers 2002, Snick 1997].

Note 7

Age of the woman

Fertility decreases rapidly over the age of 30 years: the fertility at the age of 35 and 40 is 50% and 10%, respectively, of the fertility at the age of 25 [Van Noord-Zaadstra 1991].

A prospective cohort study of couples without previously known fertility problems lists the following percentages of subfertility: 8% of women aged 19 to 26 years, 13 to 14% of women aged 27 to 34 years, and 18% of women aged 35 to 39 years. These figures apply to an intercourse frequency of at least twice a week. The percentages are 15%, 22 to 24% and 29%, respectively, for an intercourse frequency of once a week [Dunson 2004].

There is a large spread in the age at which fertility decreases. Subfertility can precede early menopause, pointing to a common underlying cause, including genetic factors [Kok 2003, Van Asselt 2004a, Van Asselt 2004b]. Menopause before the age of 45 years in the mother can be an indication of early decreased fertility. Despite these indications, there is no simple test for ovarian ageing and for the time being the knowledge of early hereditary menopause does not have any consequences on the management that should be followed.

Note 8

Age of the man

A retrospective study in the general population ($n=6188$) of women selected randomly from population records in Europe shows that the effect of the man's age on fertility is much more limited than the woman's age [De La Rochebrochard 2003]. The effect of the man's age becomes more relevant with increasing age of the woman. If the man is older than 40 years and the woman is aged between 35 and 39 years, the chance of having a child is smaller than for a man under the age of 40 years with a woman of the same age (OR 3.0; 95% CI: 1.6 to 5.9).

Note 9

Hereditary female subfertility

Decreased fertility can be hereditary [ESHRE 2008]. Causes such as endometriosis, polycystic ovarian syndrome, myomas and early menopause are considered complex genetic conditions. Family studies show that these conditions occur more often in mothers and sisters of affected women, but an unam-

biguous hereditary pattern has not been found (yet). It is assumed that several genetic variations and mutations are responsible.

Endometriosis occurs 6 times more often in first-degree relatives of patients with endometriosis than in women from families without endometriosis. This figure is 2.5 for first-degree relatives of women with myomas. PCOS occurs 2 times more often in both women if they are monozygotic twins than if they are dizygotic twins. The age at which menopause is confirmed is very similar between mothers and daughters. Causes of an early menopause are heterogeneous and largely unknown [Van Asselt 2004a]. Female relatives of men with fragile X syndrome have a greater chance of menopause before the age of 40 years.

Note 10

Hereditary male subfertility

Various studies have examined whether subfertility has a hereditary cause. The extent is limited, but subfertile brothers are slightly more common for men with reduced spermatogenesis (OR 3.2; 95% CI: 1.6 to 6.4) [Gianotten 2004]. The method of inheritance is not clear; it is likely that several (genetic) factors are the cause.

There are a number of specific genetic causes that are known to cause male subfertility [Ferlin 2007]. As far as chromosomes are concerned, Klinefelter syndrome is the most important (10% of all men with azoospermia). In addition, Y deletions are important, as genes that are important for spermatogenesis are located on the Y chromosome. The most important gene mutation that causes subfertility is a defect in the cystic fibrosis gene. This gene defect is found in 60 to 70% of men in whom the vas deferens is absent. Often there are no other symptoms of cystic fibrosis. As a result of modern reproductive techniques, it is possible that hereditary causes of male subfertility are passed on to the next generation.

Note 11

Quality of the semen: temperature increase

An increase in temperature is associated with decreased sperm production [Weber 1995]. A systematic review demonstrated that the surgical treatment of a varicocele does not result in a greater chance of pregnancy in subfertile couples (8 studies; OR 1.10; 95% CI: 0.73 to 1.68) [Evers 2008].

Note 12

Desire for pregnancy after previous fertility treatment

It is unlikely that couples wishing to have a second child will first visit the general practitioner if the woman previously became pregnant after fertility treatment in secondary care. They will usually go directly to secondary care. However, there are situations in which the primary care can play a role. For example, women regularly become pregnant spontaneously during the diagnostic phase: spontaneous pregnancy occurs in 21 to 62% of cases during examination for subfertility without any treatment [Col-

lins 1983]. In that case, the secondary care will also maintain a watchful waiting policy for a new desire for pregnancy. The gynaecologist can be consulted about the management.

Note 13

Contraceptives

Hormonal contraceptives

The chance of pregnancy after stopping with depot preparations is significantly reduced: fertility only reaches levels similar to that of oral contraceptive/IUD users 24 months after stopping the depot contraceptive [Phillips 2001].

In women who used a low-dose pill, the chance of pregnancy was slightly lower during the first three cycles after stopping – despite normal ovulatory cycles – compared to women who had not used contraceptives [Wiegratz 2006]. There was no difference after six months. A comparative study showed that after the removal of a hormone-coated IUD the percentage of pregnancy was the same as after the removal of a copper-coated IUD [French 2004].

Copper-coated IUD

Many doctors and patients still have doubts about the effects of the copper-coated IUD on fertility. The notion that the IUD reduces fertility, as a result of an increased risk of infection or by some other mechanism, is not supported by study data. A prospective cohort study (n=957; as part of a RCT of two different IUDs) shows that for women who had the IUD removed due to a desire for pregnancy (n=109), the cumulative chance of pregnancy after 12 months was 86% (95% CI: 0.81 to 0.94), and 96% after 24 months (95% CI: 0.93 to 1.0) [Hov 2007]. This was irrespective of the parity, age and duration of IUD use. In the group where the IUD was removed due to complications (pain, bleeding, expulsion, etc.), 94 of the 96 women became pregnant (98%).

Similar results were found in a cohort study of the fertility in nullipara (n=1071) following the removal of the copper-coated IUD compared to stopping oral contraceptives or barrier methods [Doll 2001]. After 18 months, 70% of the former pill users, 67% of the former IUD users and 76% of the former barrier users had given birth.

Conclusion: prior use of a copper-coated IUD does not affect fertility. It should be noted that the placement of an IUD carries a small risk of *pelvic inflammatory disease* (PID). Women with an increased risk of an STD are therefore advised to have STD testing prior to placement of an IUD and to seek treatment if necessary before insertion of the IUD.

Note 14

PID

The risk of subfertility after PID is based on estimates. A cohort study of 1844 women found a percentage of 16%, varying from 13% after one PID to 40% after three or more episodes [Weström 1992]. In the control group of 657 women, 2.7% remained childless against their wishes. The risk of subfertility increased with increasing severity of the PID. There are no more recent figures. A small follow-up study

of 39 women revealed a lower risk of infertility (89% of the women became pregnant with an average follow-up of 125 months and 59% carried the pregnancy to term). This could possibly be attributed to faster treatment [Heinonen 2003].

Note 15

Lower abdominal surgery

An uncomplicated appendectomy does not increase the risk of subfertility. In the event of complications, such as a ruptured appendix, the risk of infertility increases by a factor of 3 to 5 [Trimbos-Kemper 1982, Mueller 1986, Powley 1965, Puri 1984]. Ovarian cystectomy, wedge resection of the ovary, enucleation of myomas, Caesarean section, tubal surgery and laparotomy have been described as (contributing) causes of tubal pathology.

Note 16

Endometriosis

Endometriosis is common in women with subfertility: the reported prevalence is 20 to 50% [Haney 1993, Olive 1993]. For moderate to severe endometriosis (stage III and IV), the NVOG guideline on unexplained subfertility advises to start with IVF treatment immediately. For minimal and mild endometriosis (stage I and II), the NVOG guideline indicates that surgical treatment (laparoscopic ablation, with or without adhesiolysis) can be considered.

Note 17

Use of medication by the woman

The most important medicines in this respect are cytostatics [Aronson 2006, Trottmann 2007]. Radiotherapy can also cause infertility. Opinion varies about the consequences of diethylstilbestrol (DES) on the chances of conception [Kaufman 1986, Stolck 1982, Huikeshoven 1984, Herbst 1981, Senekjian 1988]. DES daughters can have more ectopic pregnancies, miscarriages and premature births as a result of anatomical abnormalities, possibly in combination with hormonal imbalances. Valproic acid can lead to subfertility by causing hyperandrogenism (possibly resulting in anovulation and PCOS).

The book by the Health Base Foundation (created in cooperation with the RIVM) entitled *Medicines, pregnancy and breastfeeding* can be used or the Teratology Information Centre (TIS) of the RIVM can be contacted for advice about the possible harmful effects of medicines on fertility. It is likely that substances that are harmful for the initial phases of pregnancy are also risky in the period that there is a desire for pregnancy [Health Base Foundation/RIVM 2007].

Note 18

Harmful substances at work

Occupational exposure to solvents, pesticides, metals and welding fumes can reduce fertility [Roeleveld 2006, Sallmén 2006]. Commonly listed chemical substances are: dibromochloropropane (DBCP), ethylene dibromide (EDB), some ethylene glycol ethers, carbon disulphide (CS₂), substances released during welding, lead, mercury and chrome. Refer to the

occupational health physician if there is a possibility of exposure to harmful substances. He/she can determine whether there are indeed reprotoxic, mutagenic or carcinogenic substances. The employer is legally obliged to clarify the risks of harmful substances on fertility and take preventative measures if necessary. Information can also be obtained from the Netherlands Centre for Occupational Diseases (NCvB).

In addition, the NVAB guideline Pregnancy, Postpartum Period and Work contains information about harmful substances in the work situation. It is likely that substances that are harmful for the initial phases of pregnancy are also risky in the period that there is a desire for pregnancy [Netherlands Society of Occupational Medicine 2007].

Note 19

Sexual disorders

Premature or delayed ejaculation (ejaculatio praecox and retardata) can occur, as well as the feeling of achieving orgasm without ejaculation taking place (retrograde ejaculation). Lack of knowledge, inexperience and ejaculation before insertion (ejaculatio ante portas) can all be reasons that intra-vaginal contact does not take place, even though the couple think they are having intercourse. There is a lot of embarrassment concerning these issues.

Erectile dysfunction is common in men with subfertility: in a questionnaire study of 206 couples with subfertility and 190 fertile couples, 24% of the subfertile group had erectile dysfunction, compared to 14% of the control couples (measured using the International Index of Erectile Function, IIEF) [Drosdzol 2008]. A similar percentage (22%) was found in another study of 121 subfertile couples [Shindel 2008].

Note 20

Use of medication by the man

Irreversible azoospermia often occurs after chemotherapy or genital radiotherapy.

The following medicines can influence the quality of the sperm: ACE inhibitors, tricyclic anti-depressants, anti-epileptic medicines (carbamazepine, oxcarbazepine, valproic acid), calcium antagonists, spironolactone, hormonal preparations (androgens, including anabolic steroids, anti-androgens, progestagens and oestrogens) and sulfasalazine (sulfasalazine can be replaced by mesalazine). In the event of decreased quality of sperm, one should consider stopping the abovementioned medicines. In the case of use of anabolic steroids, it is known that the quality of sperm usually returns to normal within 4 months after stopping use (all 11 men in a group of 41 male steroid users who had stopped using anabolic steroids for more than 4 months had normal sperm parameters) [Knuth 1989].

Note 21

Physical examination of the woman

An abnormal build and abnormalities in the development of secondary sexual characteristics can point to structural or functional disorders of the genital tract

[Heineman 2004]. The most common cause is Turner syndrome (in addition to short stature, typical Turner signs are a short, broad neck, a shield-like chest and cubiti valgi). Hirsutism, obesity and acne can point to polycystic ovarian syndrome. Scars on the abdomen can point to abdominal surgery (with possible adhesions).

The physical examination can reveal congenital anatomical abnormalities, such as a fusion of the labia and septa in the vagina. Acquired disorders, such as uterine myomatosis and endometriosis (evidenced by a blue swelling in the rear fornix, an adnex tumour next to the uterus that is poorly mobile just like the uterus, and painful, lumpy, thickened sacro-uterine ligaments) can be found. If the internal examination is very painful or not possible, this can point to endometriosis or vaginismus.

Note 22

Excess weight and low weight

A review article on excess weight and subfertility showed that various case-control studies and cohort studies demonstrate that excess weight reduces fertility [Kuchenbecker 2006]. The most obvious cause of subfertility with excess weight is anovulation. Excess weight also influences the pregnancy chances in subfertile women who do ovulate. For a BMI above 29, every increase in BMI by one point results in a 4% decreased chance of pregnancy (HR 0.96; 95% CI: 0.91 to 0.99) [Van der Steeg 2008].

Low weight can also reduce fertility. A case-control study based on the Nurses Health Study found a U-shaped relationship between BMI and decreased fertility. A BMI < 20 or > 24 increases the risk of subfertility. Exercise appears to decrease the risk of subfertility [Rich-Edwards 2002].

Note 23

Sperm analysis

The previous version of the guideline indicated that sperm analysis could also take place in the own practice. However, the evaluation of sperm quality is not a simple task: even when performed in a laboratory, there is significant inter-test and intra-test variation, mainly associated with differences in expertise of the technician performing the test. If a sperm analysis is performed in the general practice, this result will always have to be confirmed by means of a laboratory evaluation. As all general practice laboratories can now perform sperm analysis, it is not recommended to perform the test in the own practice any more.

To date, the WHO criteria were used to define male

subfertility. However, the problem is that validation of the WHO criteria is lacking and the interpretation of the five partially linked variables is difficult.

The prospective cohort study on the validation of the prognostic model (see note 3) looked at the predictive value of the results of the sperm analysis for the chance of spontaneous pregnancy [Van der Steeg 2007]. The results of this are summarised in table 4.

The prognostic model shows that the percentage of progressively moving spermatozoa appears to have the most important prognostic significance and the other sperm parameters do not appear to contribute to the chance of pregnancy. Therefore, the advice is not to refer purely based on poor semen parameters, but to use the percentage of progressively moving spermatozoa in the prognostic model and only refer to secondary care in the case of a low chance of pregnancy. In addition, referral should take place with a VCM < 3 x 10⁶ (due to the fact that the prognostic model does not apply to these couples). Referral does not need to take place for other abnormal sperm parameters. A gynaecologist can be consulted in the case of severely abnormal sperm parameters. Therefore, women with a positive CAT should undergo additional diagnostic tests (hysterosalpingography or laparoscopy) to diagnose tubal pathology. The specificity and negative predictive value (NPV) are good (MIF: specificity 74 to 95%, NPV 90 to 93%; ELISA: specificity 77 to 87%, NPV 88 to 91%); the chance that a woman with a negative CAT does NOT have tubal pathology is high. There is no information available about the diagnostic value of an elevated CAT in primary care.

Note 24

Chlamydia antibody titre (CAT)

There are many serological tests for demonstrating antibodies against Chlamydia. Micro-immunofluorescence (MIF) is the gold standard. In addition to MIF tests, there are also enzyme immuno-assays in use to provide serological evidence of previously experienced Chlamydia infections. Most laboratories in the Netherlands prefer to use these latter tests (MIF tests are very labour intensive and very subjective in reading the results). The test is performed in serum. The limit varies per test used and per laboratory.

The sensitivity and positive predictive value (PPV) of the CAT in secondary care for diagnosing bilateral tubal pathology compared to laparoscopy as the gold standard are relatively low (MIF: sensitivity 47 to 71%, PPV 35 to 65%; ELISA: sensitivity 37 to 55%, PPV 29

Table 4 Relationships between sperm parameters and pregnancy chances.

	normal	chance of pregnancy
Volume	> 2 ml	decreasing gradually if ≤ 2 ml
Concentration	> 40 x 10 ⁶ /ml	decreasing gradually if ≤ 40 x 10 ⁶ /ml
VCM*	linear correlation with chance of pregnancy (less motility, less chance)	
Morphology	> 20%	decreasing gradually if ≤ 20%
Total number of spermatozoa	> 200 x 10 ⁶	decreasing gradually if ≤ 200 x 10 ⁶

* VCM (volume x concentration x percentage progressively moving spermatozoa)

to 45%) [Land 2003]. Therefore, the test is not able to predict tubal pathology very well.

Note 25

Post-coital test

The guideline from 1998 included the post-coital test as a facultative test that could be performed in the own practice instead of the sperm analysis.

Research into the diagnostic value of the post-coital test in secondary care provided varying results [Hull 1982, Oei 1996, Snick 1997, Glazener 1987]. In the prognostic model, validated by Van der Steeg in a population referred by the general practitioner or by own initiative, the PCT appeared to be an independent predictor of the chance of pregnancy (the chances of pregnancy were 7 to 8% higher for a positive PCT compared to the situation where the PCT was not performed). Research into the value of the PCT in primary care is not available: it is expected that the test properties will be less reliable in primary care than in secondary care. In particular, one practical problem is the timing of the test. If not timed properly, the test can give a false negative result. A negative PCT is therefore of little value. In that case, the PCT will have to be repeated in secondary care, with ultrasound visualisation of egg ripening.

The PCT was included in the guideline as an optional test at the time, because the test was not technically complicated and because the PCT had formed part of the standard examination in secondary care for decades. However, in the past ten years this test has hardly been used in primary care. As the test is very rarely performed in primary care, and because the test probably provides less reliable results in primary care, it was decided not to include the test in the current version of the guideline.

Note 26

Additional laboratory tests

Routine determination of thyroid function is not useful. Testing of thyroid function should only be considered if there are also other symptoms that could point to a thyroid function abnormality.

The determination of FSH in men to distinguish between obstructive and non-obstructive causes of azoospermia does not have any effect on the management in general practice. There are no unambiguous guidelines as yet for FSH determination in women over the age of 35 years to evaluate the chance of a possible early menopause. Therefore, it is not recommended.

Note 27

Watchful waiting in primary care versus referral to secondary care

A randomised Dutch study of 253 couples with unexplained subfertility (average duration of subfertility 2 years) with a pregnancy chance of 30 to 40% shows that the chance of an ongoing pregnancy is as great with a watchful waiting policy as it is with IUI with ovarian hyperstimulation (27% versus 23%; RR 0.85; 95% CI: 0.63 to 1.1) [Steures 2008].

A Dutch cohort study of 1391 couples, referred by the

general practitioner due to subfertility (average duration of subfertility was 15 months) who were monitored for 5 years, showed that 72% of the women had an ongoing pregnancy during the follow-up period [Brandes 2009]. Women with a pregnancy chance > 40% (45%) were assigned a watchful waiting policy, nearly one third of the couples were treated with ovulation induction and one third with IUI, 25% started with IVF treatment. Nearly half (46%) of the pregnancies occurred spontaneously. The contribution made by IVF was relatively small: 15% of the pregnancies were the result of IVF treatment (of the couples who started with IVF, 60% had an ongoing pregnancy). Both studies support a watchful waiting policy for 6 to 12 months in primary care.

Note 28

Pregnancy chance with a desire for pregnancy shorter than twelve months

The percentages as listed in the main text were obtained from obstetric/gynaecology textbooks and are also generally used by gynaecologists for informing patients [Heineman 2004].

There are several studies that support these percentages. A prospective observational study over 12 months of 200 couples with a desire for pregnancy shows that 30, 58, 73 and 82% of the women were pregnant after 1, 3, 6 and 12 months, respectively [Zinaman 1996]. In this study the couples were informed about timing intercourse. Similar studies with smaller numbers of patients showed similar figures [Wilcox 1988, Hilgers 1992].

A more recent study of 346 couples shows even higher percentages: 38, 68, 81 and 92% of the women were pregnant after 1, 2, 3, 6 and 12 months, respectively [Gnoth 2003]. It should be noted that – for this study – only cycles in which intercourse took place at least once during the fertile period were included.

Note 29

Timing of intercourse

The most fertile period in the menstrual cycle is the period 5 to 6 days prior to ovulation [Wilcox 1995]. For a regular cycle of 28 days, ovulation takes place on approximately day 14 after the first day of the previous menstruation and therefore the most fertile period is between days 8 and 14 of the cycle. For a regular cycle longer than 28 days, the ovulation shifts and the fertile period will also move back by the number of days that the cycle is longer (for a normal cycle of 35 days, the fertile period is between days 15 and 21). The fertile period cannot be indicated properly for an irregular cycle [Wilcox 2000]. With an intercourse frequency of 2 times per week, intercourse will take place at least 1 or 2 times during the fertile period and there is a good chance of conception [Stanford 2002, Agarwal 1994].

If this frequency is not feasible for some reason, it may be useful to provide advice about timing intercourse, although opinions differ on this matter [Agarwal 1994, Snick 2005]. There are various methods for timing intercourse. They differ in terms of the accuracy for determining the fertile period.

- *Evaluation of vaginal cervical mucus*: low cost, some training required to distinguish various types of cervical mucus, harder to evaluate with physiologically high levels of discharge. A prospective cohort study of 197 women in a centre for natural family planning revealed that the chance of pregnancy was 0.3% (95% CI: 0.06 to 0.88) with intercourse with the most unfavourable type of cervical mucus (absence or hardly any cervical mucus) and 29% (95% CI: 21 to 37%) with intercourse with the most favourable type (thread-like, clear) [Scarpa 2006]. A similar study in 782 women revealed that the chance of conception with intercourse during the fertile period was $\geq 17\%$ with a favourable type of cervical mucus, compared to $\leq 13\%$ with an unfavourable type of cervical mucus [Bigelow 2004].
- *Basal temperature curve (BTC)*: low cost, some explanation required, discipline required for execution, can be influenced by infections, variation in circadian rhythm, etc. When compared to ovulation detection by ultrasound, for a spontaneous cycle in 101 subfertile women, the BTC had a sensitivity of 0.77 and a specificity of 0.33, and a positive and negative predictive value of 94% and 10%, respectively. A normal, biphasic curve makes ovulation extremely probable, but it cannot accurately predict the moment of ovulation (the increase in basal temperature curve takes place from 8 days prior to ovulation to 4 days after ovulation) [Guermami 2001]. In addition, potentially fertile days will be missed, as the greatest chance of conception exists in the period 5 to 6 days before the increase in temperature on the BTC, up to 1 day after this increase.
- *Urine tests for LH*: very reliable with regards to predicting ovulation. Sensitivity was 1.00, specificity 0.25, positive and negative predictive value of 0.97 and 1.00, respectively, compared to ovulation detection by ultrasound [Guermami 2001]. However, this test only becomes positive 1 to 2 days before ovulation (because this is when the LH peak occurs in the blood; approximately 12 hours later it becomes visible in the urine), which means that potentially fertile days are missed [Tanabe 2001, Eichner 2004].
- *Urine tests for LH and oestradiol*: these tests combine the concentration of LH and oestradiol in the urine with a 'calendar' of the last cycles (provided by the woman). Days are indicated as 'low', 'high' and 'peak', referring to the degree of fertility. In a prospective study of 53 healthy female volunteers (149 cycles), ovulation was detected during the two days of peak fertility in 91% of the cycles [Behre 2000]. This is due to the combination of LH detection and oestradiol detection. The oestradiol surges several days before the LH peak and is therefore a better marker of the potentially fertile period. The test can only be used in women with a cycle duration of 21 to 42 days, but can be beneficial if regular intercourse cannot be achieved [Robinson 2007]. The costs of the test are relatively high. In the Netherlands, such tests

are only available via internet. The tests that measure urine concentrations of LH and oestradiol for the purpose of contraception are available. These tests are sometimes also used by women for timing of intercourse.

Conclusion: both evaluation of discharge and LH tests can be used to time intercourse. The position of LH-oestradiol tests is not yet clear. Use of the basal temperature curve to time intercourse is not recommended.

Note 30

Basal temperature curve

The basal temperature curve (BTC) can be recorded to pinpoint ovulation and the fertile period. The woman is instructed to measure the rectal temperature every morning before getting out of bed; a BTC form and instruction text can be provided if necessary. A normal, biphasic curve (increase of at least 0.3 °C for 12 days or more) makes ovulation very probably; the increase in temperature is the result of an increase in progesterone. The temperature is dependent on the corpus luteum, but is also influenced by factors such as emotions, viral diseases and varying circadian rhythms [Billings 1972]. If the BTC cannot be interpreted or is not biphasic, the registration can be repeated for one or two cycles.

Note 31

Smoking

The negative effect of smoking on fertility in women has been studied many times [Wilks 2004]. In a meta-analysis including 12 studies, an OR was calculated for subfertility of 1.6 (95% CI: 1.34 to 1.91) for 10,928 smoking and 19,179 non-smoking women [Augood 1998]. The authors did indicate that the population was heterogeneous. Possible confounding factors could include: the definition of subfertility, the validity of self-reporting of smoking, selection of participants and exclusion of unplanned pregnancies. A large cross-sectional study of 8559 couples with a desire for pregnancy, which appeared after the meta-analysis, with the time to conception as endpoint showed a similar trend: both active and passive smoking resulted in a longer time to conception [Hull 2000]. This study also found a longer time to conception for couples in which only the man was a (heavy) smoker (≥ 20 cigarettes per day). However, it is not clear whether this is the result of decreased fertility in the man due to smoking or an indirect effect because the woman's fertility was reduced by the passive smoking. It appears that smoking cannot explain male subfertility. A negative effect of smoking on the quality of sperm has been found [Ramlau-Hansen 2007, Hassa 2006, Pasqualotto 2006].

Conclusion: smoking appears to reduce fertility in women. In men there is a link between smoking and reduced sperm quality.

Smoking affects not only the chance of pregnancy, but also increases the risk of miscarriages and ectopic pregnancy [Practice Committee of the American Society for Reproductive Medicine 2006]. In addition, the chance of success with IVF is also lower for smok-

ers. Furthermore, smoking is also associated with a low birth weight and SIDS. The Health Council of the Netherlands therefore advises couples – both men and women – to stop smoking [Health Council of the Netherlands 2007].

Note 32

Alcohol

A prospective study of 7393 Swedish women found a relative risk of subfertility of 1.58 (95% CI: 1.07 to 2.34) in women who reported a high level of alcohol consumption (> 14 units/week) compared to women who reported moderate consumption (5 to 14 units/week) [Eggert 2004]. A Danish prospective study of 7760 women found no link between the use of alcohol and infertility in women under the age of 30 years. In women over the age of 30 years, there was a relative risk of 2.26 (95% CI: 1.19 to 4.32) of infertility with the use of more than 7 units of alcohol/week compared to women who consumed less than 1 unit of alcohol/week [Tolstrup 2003]. An important limitation of both abovementioned studies was that they could not correct for confounders such as smoking and other lifestyle factors and PID/Chlamydia infection.

Conclusion: there is no convincing evidence that social use of alcohol reduces fertility in women.

In men, the use of alcohol results in erectile dysfunction and loss of libido. The effect on the quality of sperm is less obvious. A review article of nine studies on the effect of the use of alcohol in men on the quality of sperm only showed a (varying) effect on various sperm parameters in three of the nine studies [Marinelli 2004]. In one of the studies, the quality of sperm was better in men with moderate use of alcohol than in men who did not drink alcohol. The studies were of moderate quality: alcohol was often included as a secondary measure of outcome and there was insufficient correction for confounders such as smoking. Very few individuals with excessive use of alcohol were included. We can conclude that it has not been demonstrated that the social use of alcohol in men has a negative effect on the quality of sperm.

Note 33

Drugs

In men, the use of cannabis resulted in decreased sperm concentration and decreased sperm motility [Nudell 2002]. Opiates decrease libido by a direct inhibitory effect on the hypothalamus. Cocaine and amphetamines affect sexual functions, both stimulatory (priapism) and negative (erectile dysfunction). A negative effect of drug abuse on fertility in women has not been demonstrated clearly. Older studies of moderate quality provide contradictory results: on the one hand an increased risk of infertility was reported in women using marijuana, on the other hand the time to conception was shorter for women who used marijuana [Mueller 1990, Joesoef 1993]. Use of cocaine produced similar results in these studies.

Note 34

Weight loss and exercise in people with excess weight

Although it is clear that excess weight is associated with a decreased chance of pregnancy, the proof that weight loss or exercise increases the chance of pregnancy has not been substantiated properly. Studies are currently being performed to determine this. Smaller studies are promising. In a prospective, non-randomised study of anovulatory women (n=18) – clomiphene resistant – with subfertility of at least two years, twelve of the thirteen women who completed the intervention programme became ovulatory and eleven women became pregnant following intervention consisting of a diet and an exercise programme [Clark 1995]. No one became ovulatory in the control group (the drop-outs, n=5). Intervention studies have not been performed in women who ovulate.

Note 35

Pre-conceptional lifestyle advice

This includes advice about the use of vitamins (folic acid, vitamin A, vitamin D), medicines that could be harmful for the pregnancy (anti-depressants, ACE inhibitors), smoking, infectious diseases (vaccination against Rubella), employment conditions and psychosocial problems [De Jonge 2008].

Note 36

Ovulation induction

Ovulation induction does not increase the chances of pregnancy in couples with unexplained subfertility [Bhattacharya 2008].

The NVOG guideline Anovulation and Desire for Pregnancy does recommend treatment with clomiphene citrate for women with anovulation and normal FSH and oestradiol levels (these are often women with PCOS) [NVOG 2004b]. In this case, clomiphene citrate 50 to 150 mg/day is given for 5 days per cycle. If ovulation is achieved, the treatment is continued for a maximum of 6 to 12 cycles. Approximately 60 to 85% of women become regularly ovulatory on treatment with clomiphene. Women who become ovulatory on treatment with clomiphene citrate are treated for 6 to 12 cycles; 30 to 40% of these women become pregnant. There is an increased risk of multiple pregnancies (8% of pregnancies). Side effects associated with the use of clomiphene citrate include vision problems, dizziness and headache. Use of clomiphene citrate in primary care is not recommended due to the limited indication and the lack of experience with clomiphene in primary care.

Note 37

Effect of fertility treatment on work

Treatment of subfertility in secondary care can result in significant absenteeism and loss of productivity due to frequent hospital visits. A Dutch study showed that for a first IVF treatment, the absenteeism was 33 hours per woman and the loss of productivity was EUR 596 [Bouwman 2008]. There is no illness from an employment law point of view. However, for an IVF treatment, it seems reasonable to consider the

woman unfit to work on the day of egg retrieval and the day of embryo transfer [Netherlands Society of Occupational Medicine 2007].

Openness towards co-workers and the employers can provide support. The working times and activities could then also be adjusted. Unfortunately, open communication with the employer is not always possible.

The general practitioner can inform the couple about making use of the employment conditions consultation of the occupational health physician. The occupational health physician can play a role as independent mediator in the dialogue between employee and employer.

Note 38

Tubal surgery

Pregnancy chances following tubal surgery are very varied and depend – among other factors – on pre-operative selection, severity of tubal damage, age of the woman and duration of the subfertility [NVOG 2005]. If the most favourable cases are selected, pregnancy percentages of 40 to 60% are achieved following salpingostomy. Due to the very slight chance of pregnancy, severe tubal pathology forms a contra-indication for surgery. In the case of mild and moderate tubal pathology, a decision must be made between micro-surgical treatment (possibly performed laparoscopically) and in vitro fertilisation (IVF). Results of tubal surgery in the form of pregnancy can be expected up to approximately 2 years after surgery (90% within 15 months). Partially due to this fact, an age limit of 38 to 40 years is generally maintained. Tubal surgery carries an increased risk of ectopic pregnancy (average 2 to 8%, depending on the type of surgery).

Note 39

Intra-uterine insemination

Couples with unexplained subfertility, as well as couples with relatively unexplained subfertility based on reduced quality of sperm who have a chance of spontaneous pregnancy of less than 30% or who do not achieve spontaneous pregnancy after an extended period of trying are initially eligible for intra-uterine insemination (IUI). IVF is only offered immediately if the women is 38 years or older.

In an IUI cycle, sperm is processed in a laboratory and

the motile spermatozoa are concentrated in a small volume that can be injected directly into the uterus at a well-timed moment.

IUI is applied with and without ovarian hyperstimulation: IUI with mild stimulation is slightly more effective than IUI without stimulation [Verhulst 2006]. A disadvantage of stimulation is the risk of ovarian hyperstimulation syndrome and multiple pregnancies. Both methods are applied.

In a retrospective study of 64% of the Dutch hospitals, the percentage of ongoing pregnancies per cycle in 2003 was 7.4%, with 9.5% multiple pregnancies [Steures 2007].

Note 40

IVF

Couples of whom the woman has bilateral tubal pathology, couples who are not pregnant after 4 cycles of IUI with stimulation or 6 cycles without stimulation and couples of whom the woman is aged 38 years or older are eligible for IVF. There is a hesitance to treat women over the age of 41 years, due to the low chance of pregnancy; the upper limit for treatment is 45 years.

The IVF results of the Dutch IVF centres since 1996 can be found on www.nvog.nl. This registration reflects the percentage of ongoing pregnancies per started cycle [NVOG 2007]. The percentage of ongoing pregnancies over the last 5 years was between 19 and 21%. A Dutch longitudinal study of 1,456 couples who received IVF/ICSI in the period 1996 to 2000 found a cumulative birth percentage of 59.1% after 3 years [Witsenburg 2005].

Note 41

ICSI

Intra-cytoplasmic sperm injection (ICSI) is a form of IVF, in which one sperm cell is injected into the egg cell [Kremer 2008]. In the case of oligospermia, the sperm can be isolated from the ejaculate and in the case of azoospermia, the sperm can be obtained surgically from the epididymis (via an open micro-surgical procedure – MESA, or a biopsy – PESA) or the testes (TESE). Initially there was uncertainty about a possible increased risk of the presence of chromosomal abnormalities in men with oligospermia or azoospermia and the risk of birth defects in the descendants with the use of ICSI. Therefore, the deci-

sion was made in the Netherlands in 1996 to stop the clinical use of ICSI with surgically obtained sperm. Following the publication of various international studies with reassuring results about the health of children born following treatment with ICSI, the use of ICSI with surgically obtained sperm (MESA, PESA and TESE) is permitted in a study context.

Note 42

Emotional strain

The emotional impact of subfertility, and particularly IVF treatment, on women is significant [Verhaak 2007]. This is not clear in men. A questionnaire study (The Primary Care Evaluation of Mental Disorders (PRIME-MD), based on the DSM-IV), of 545 couples being treated for subfertility shows that 11% of the women and 5% of the men suffered severe depression, and 15% of the women and 5% of the men had an anxiety disorder [Volgsten 2008]. A prospective cohort study of 384 couples undergoing IVF showed that 17% of the couples did not complete the treatment. The most important reason given for this was the high psychological and physical burden (in 28% of the couples) [Verberg 2008]. Women with pre-existing psychological problems stopped IVF treatment at an earlier stage [Smeenk 2004]. Women with psychological problems have more absenteeism from work [Bouwman 2008].

The FIOm has a lot of experience in helping couples who have exhausted all options for fertility problems.

Note 43

Adoption

It is a good idea to discuss the possibility of adoption with couples at an early stage. The adoption process is very lengthy (3 to 6 years) and the adoption agencies set various requirements for the couple. For example, the age of the prospective adoptive parent may not exceed 41 years and the age difference between the parents and the adopted child usually may not exceed 40 years. A general requirement is that the medical treatment must be completed before an adoption procedure can be started. It is also possible to start an adoption procedure as a single parent. It is important to realise when discussing adoption that some couples will not consider adoption as an alternative to having their own biological child.

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