Fertility problems: assessment and treatment

NICE guideline: short version

Draft for consultation May 2016

This guideline covers investigations to establish the causes of fertility problems, medical and surgical treatments to restore fertility, and assisted reproduction techniques.

Who is it for?

- Healthcare professionals who care for people with fertility problems.
- Providers of services for people with fertility problems..
- People with fertility problems, their families and carers.

This guideline will update NICE guideline CG156 (published February 2013).

We have reviewed the evidence but made no change to the recommended actions in 1 recommendation on intrauterine insemination. It is marked as **[2016]**. You are invited to comment on the evidence review and the committee's conclusions, which are contained in the addendum.

We have not updated recommendations shaded in grey, and cannot accept comments on them.

See Update information for a full explanation of what is being updated.

Evidence for the 2004 and 2013 recommendations is in the full version of the 2013 guideline.

Contents

Recommendations

People have the right to be involved in discussions and make informed decisions about their care, as described in your care.

Making decisions using NICE guidelines explains how we use words to show the strength (or certainty) of our recommendations, and has information about prescribing medicines (including off-label use), professional guidelines, standards and laws (including on consent and mental capacity), and safeguarding.

1.1 Principles of care

1.1.1 Providing information

1.1.1.1 Couples who experience problems in conceiving should be seen together because both partners are affected by decisions surrounding investigation and treatment. **[2004]**

1.1.1.2 People should have the opportunity to make informed decisions regarding their care and treatment via access to evidence-based information. These choices should be recognised as an integral part of the decision-making process. Verbal information should be supplemented with written information or audio-visual media. **[2004]**

1.1.1.3 Information regarding care and treatment options should be provided in a form that is accessible to people who have additional needs, such as people with physical, cognitive or sensory disabilities, and people who do not speak or read English. **[2004]**

1.1.2 Psychological effects of fertility problems

1.1.2.1 When couples have fertility problems, both partners should be informed that stress in the male and/or female partner can affect the couple's relationship and is likely to reduce libido and frequency of intercourse which can contribute to the fertility problems. **[2004, amended 2013]**

1.1.2.2 People who experience fertility problems should be informed that they may find it helpful to contact a fertility support group. **[2004]**

1.1.2.3 People who experience fertility problems should be offered counselling because fertility problems themselves, and the investigation and treatment of fertility problems, can cause psychological stress. **[2004]**

1.1.2.4 Counselling should be offered before, during and after investigation and treatment, irrespective of the outcome of these procedures. **[2004]**

1.1.2.5 Counselling should be provided by someone who is not directly involved in the management of the individual's and/or couple's fertility problems. **[2004, amended 2013]**

1.1.3 Generalist and specialist care

1.1.3.1 People who experience fertility problems should be treated by a specialist team because this is likely to improve the effectiveness and efficiency of treatment and is known to improve people's satisfaction with treatment. **[2004, amended 2013]**

1.2 Initial advice to people concerned about delays in conception

1.2.1 Chance of conception

1.2.1.1 People who are concerned about their fertility should be informed that over 80% of couples in the general population will conceive within 1 year if:

- the woman is aged under 40 years **and**
- they do not use contraception and have regular sexual intercourse.

Of those who do not conceive in the first year, about half will do so in the second year (cumulative pregnancy rate over 90%). **[2004, amended 2013]**

1.2.1.2 Inform people who are using artificial insemination to conceive and who are concerned about their fertility that:

- over 50% of women aged under 40 years will conceive within 6 cycles of intrauterine insemination (IUI)
- of those who do not conceive within 6 cycles of intrauterine insemination, about half will do so with a further 6 cycles (cumulative pregnancy rate over 75%). **[new 2013]**

1.2.1.3 Inform people who are using artificial insemination to conceive and who are concerned about their fertility that using fresh sperm is associated with higher conception rates than frozen–thawed sperm. However, intrauterine insemination, even using frozen–thawed sperm, is associated with higher conception rates than intracervical insemination. **[new 2013]**

1.2.1.4 Inform people who are concerned about their fertility that female fertility and (to a lesser extent) male fertility decline with age. **[new 2013]**

1.2.1.5 Discuss chances of conception with people concerned about their fertility who are:

- having sexual intercourse (see table 1) **or**
- using artificial insemination (see table 2). **[new 2013]**

1.2.2 Frequency and timing of sexual intercourse or artificial insemination

1.2.2.1 People who are concerned about their fertility should be informed that vaginal sexual intercourse every 2 to 3 days optimises the chance of pregnancy. **[2004, amended 2013]**

1.2.2.2 People who are using artificial insemination to conceive should have their insemination timed around ovulation. **[new 2013]**

1.2.3 Alcohol

1.2.3.1 Women who are trying to become pregnant should be informed that drinking no more than 1 or 2 units of alcohol once or twice per week and

avoiding episodes of intoxication reduces the risk of harming a developing fetus. **[2004]**

1.2.3.2 Men should be informed that alcohol consumption within the Department of Health's recommendations of 3 to 4 units per day for men is unlikely to affect their semen quality. **[2004, amended 2013]**

1.2.3.3 Men should be informed that excessive alcohol intake is detrimental to semen quality. **[2004]**

1.2.4 Smoking

1.2.4.1 Women who smoke should be informed that this is likely to reduce their fertility. **[2004]**

1.2.4.2 Women who smoke should be offered referral to a smoking cessation programme to support their efforts in stopping smoking. **[2004]**

1.2.4.3 Women should be informed that passive smoking is likely to affect their chance of conceiving. **[2004]**

1.2.4.4 Men who smoke should be informed that there is an association between smoking and reduced semen quality (although the impact of this on male fertility is uncertain), and that stopping smoking will improve their general health. **[2004]**

1.2.5 Caffeinated beverages

1.2.5.1 People who are concerned about their fertility should be informed that there is no consistent evidence of an association between consumption of caffeinated beverages (tea, coffee and colas) and fertility problems[1]. **[2004]**

1.2.6 Obesity

1.2.6.1 Women who have a body mass index (BMI) of 30 or over should be informed that they are likely to take longer to conceive. **[2004, amended 2013]**

[1] Also see recommendation 1.10.5.3 about caffeine intake and IVF treatment.

1.2.6.2 Women who have a BMI of 30 or over and who are not ovulating should be informed that losing weight is likely to increase their chance of conception. **[2004, amended 2013]**

1.2.6.3 Women should be informed that participating in a group programme involving exercise and dietary advice leads to more pregnancies than weight loss advice alone. **[2004]**

1.2.6.4 Men who have a BMI of 30 or over should be informed that they are likely to have reduced fertility. **[2004, amended 2013]**

1.2.7 Low body weight

1.2.7.1 Women who have a BMI of less than 19 and who have irregular menstruation or are not menstruating should be advised that increasing body weight is likely to improve their chance of conception. **[2004]**

1.2.8 Tight underwear

1.2.8.1 Men should be informed that there is an association between elevated scrotal temperature and reduced semen quality, but that it is uncertain whether wearing loose-fitting underwear improves fertility. **[2004]**

1.2.9 Occupation

1.2.9.1 Some occupations involve exposure to hazards that can reduce male or female fertility and therefore a specific enquiry about occupation should be made to people who are concerned about their fertility and appropriate advice should be offered. **[2004]**

1.2.10 Prescribed, over-the-counter and recreational drug use

1.2.10.1 A number of prescription, over-the-counter and recreational drugs interfere with male and female fertility, and therefore a specific enquiry about these should be made to people who are concerned about their fertility and appropriate advice should be offered. **[2004]**

1.2.11 Complementary therapy

1.2.11.1 People who are concerned about their fertility should be informed that the effectiveness of complementary therapies for fertility problems has not

been properly evaluated and that further research is needed before such interventions can be recommended. **[2004]**

1.2.12 Folic acid supplementation

1.2.12.1 Women intending to become pregnant should be informed that dietary supplementation with folic acid before conception and up to 12 weeks' gestation reduces the risk of having a baby with neural tube defects. The recommended dose is 0.4 mg per day. For women who have previously had an infant with a neural tube defect or who are receiving anti-epileptic medication or who have diabetes (see Diabetes in pregnancy: management from preconception to the postnatal period [NICE guideline NG3]), a higher dose of 5 mg per day is recommended. **[2004, amended 2013]**

1.2.13 Defining infertility

1.2.13.1 People who are concerned about delays in conception should be offered an initial assessment. A specific enquiry about lifestyle and sexual history should be taken to identify people who are less likely to conceive. **[2004]**

1.2.13.2 Offer an initial consultation to discuss the options for attempting conception to people who are unable to, or would find it very difficult to, have vaginal intercourse. **[new 2013]**

1.2.13.3 The environment in which investigation of fertility problems takes place should enable people to discuss sensitive issues such as sexual abuse. **[2004]**

1.2.13.4 Healthcare professionals should define infertility in practice as the period of time people have been trying to conceive without success after which formal investigation is justified and possible treatment implemented. **[new 2013]**

1.2.13.5 A woman of reproductive age who has not conceived after 1 year of unprotected vaginal sexual intercourse, in the absence of any known cause of infertility, should be offered further clinical assessment and investigation along with her partner. **[new 2013]**

1.2.13.6 A woman of reproductive age who is using artificial insemination to conceive (with either partner or donor sperm) should be offered further clinical assessment and investigation if she has not conceived after 6 cycles of treatment, in the absence of any known cause of infertility. Where this is using partner sperm, the referral for clinical assessment and investigation should include her partner. **[new 2013]**

1.2.13.7 Offer an earlier referral for specialist consultation to discuss the options for attempting conception, further assessment and appropriate treatment where:

- the woman is aged 36 years or over
- there is a known clinical cause of infertility or a history of predisposing factors for infertility. **[new 2013]**

1.2.13.8 Where treatment is planned that may result in infertility (such as treatment for cancer), early fertility specialist referral should be offered. **[2004, amended 2013]**

1.2.13.9 People who are concerned about their fertility and who are known to have chronic viral infections such as hepatitis B, hepatitis C or HIV should be referred to centres that have appropriate expertise and facilities to provide safe risk-reduction investigation and treatment. **[2004]**

1.3 Investigation of fertility problems and management strategies

1.3.1 Semen analysis

1.3.1.1 The results of semen analysis conducted as part of an initial assessment should be compared with the following World Health Organization reference values[2]:

- semen volume: 1.5 ml or more
- pH: 7.2 or more

[2] Please note the reference ranges are only valid for the semen analysis tests outlined by the World Health Organization.

- sperm concentration: 15 million spermatozoa per ml or more
- total sperm number: 39 million spermatozoa per ejaculate or more
- total motility (percentage of progressive motility and non-progressive motility): 40% or more motile or 32% or more with progressive motility
- vitality: 58% or more live spermatozoa
- sperm morphology (percentage of normal forms): 4% or more. **[2004, amended 2013]**

1.3.1.2 Screening for antisperm antibodies should not be offered because there is no evidence of effective treatment to improve fertility. **[2004]**

1.3.1.3 If the result of the first semen analysis is abnormal, a repeat confirmatory test should be offered. **[2004]**

1.3.1.4 Repeat confirmatory tests should ideally be undertaken 3 months after the initial analysis to allow time for the cycle of spermatozoa formation to be completed. However, if a gross spermatozoa deficiency (azoospermia or severe oligozoospermia) has been detected the repeat test should be undertaken as soon as possible. **[2004]**

1.3.2 Post-coital testing of cervical mucus

1.3.2.1 The routine use of post-coital testing of cervical mucus in the investigation of fertility problems is not recommended because it has no predictive value on pregnancy rate. **[2004]**

1.3.3 Ovarian reserve testing

1.3.3.1 Use a woman's age as an initial predictor of her overall chance of success through natural conception (see figure 1) or with in vitro fertilisation (IVF) (see figure 2). **[new 2013]**

1.3.3.2 Use one of the following measures to predict the likely ovarian response to gonadotrophin stimulation in IVF:

- total antral follicle count of less than or equal to 4 for a low response[3] and greater than 16 for a high response[4]
- anti-Müllerian hormone of less than or equal to 5.4 pmol/l for a low response[5] and greater than or equal to 25.0 pmol/l for a high response[6]
- follicle-stimulating hormone greater than 8.9 IU/l for a low response and less than 4 IU/l for a high response[7]. **[new 2013]**

1.3.3.3 Do not use any of the following tests individually to predict any outcome of fertility treatment:

- ovarian volume
- ovarian blood flow
- inhibin B
- oestradiol (E2). **[new 2013]**

1.3.4 Regularity of menstrual cycles

1.3.4.1 Women who are concerned about their fertility should be asked about the frequency and regularity of their menstrual cycles. Women with regular monthly menstrual cycles should be informed that they are likely to be ovulating. **[2004]**

1.3.4.2 Women who are undergoing investigations for infertility should be offered a blood test to measure serum progesterone in the mid-luteal phase of their cycle (day 21 of a 28-day cycle) to confirm ovulation even if they have regular menstrual cycles. **[2004, amended 2013]**

1.3.4.3 Women with prolonged irregular menstrual cycles should be offered a blood test to measure serum progesterone. Depending upon the timing of menstrual periods, this test may need to be conducted later in the cycle

[3] Follicles of ≤5 mm measured by transvaginal ultrasound on day 3 of cycle: low response was <4 oocytes.
[4] Follicles of 2–10 mm measured by transvaginal ultrasound on day 3 of cycle: high response was ≥15 oocytes or ≥20 oocytes.
[5] Beckman Coulter assay: poor response defined as <4 oocytes or cancellation.
[6] Beckman Coulter or DSL assays: defined high response as ≥15 oocytes to >21 oocytes.
[7] Long protocol of down-regulation: low response defined as <4 oocytes or cancellation; high response defined as >20 oocytes.

(for example day 28 of a 35-day cycle) and repeated weekly thereafter until the next menstrual cycle starts. **[2004]**

1.3.4.4 The use of basal body temperature charts to confirm ovulation does not reliably predict ovulation and is not recommended. **[2004]**

1.3.4.5 Women with irregular menstrual cycles should be offered a blood test to measure serum gonadotrophins (follicle-stimulating hormone and luteinising hormone). **[2004]**

1.3.5 Prolactin measurement

1.3.5.1 Women who are concerned about their fertility should not be offered a blood test to measure prolactin. This test should only be offered to women who have an ovulatory disorder, galactorrhoea or a pituitary tumour. **[2004]**

1.3.6 Thyroid function tests

1.3.6.1 Women with possible fertility problems are no more likely than the general population to have thyroid disease and the routine measurement of thyroid function should not be offered. Estimation of thyroid function should be confined to women with symptoms of thyroid disease. **[2004]**

1.3.7 Endometrial biopsy

1.3.7.1 Women should not be offered an endometrial biopsy to evaluate the luteal phase as part of the investigation of fertility problems because there is no evidence that medical treatment of luteal phase defect improves pregnancy rates. **[2004]**

1.3.8 Investigation of suspected tubal and uterine abnormalities

1.3.8.1 Women who are not known to have comorbidities (such as pelvic inflammatory disease, previous ectopic pregnancy or endometriosis) should be offered hysterosalpingography (HSG) to screen for tubal occlusion because this is a reliable test for ruling out tubal occlusion, and

it is less invasive and makes more efficient use of resources than laparoscopy. **[2004]**

1.3.8.2 Where appropriate expertise is available, screening for tubal occlusion using hysterosalpingo-contrast-ultrasonography should be considered because it is an effective alternative to hysterosalpingography for women who are not known to have comorbidities. **[2004]**

1.3.8.3 Women who are thought to have comorbidities should be offered laparoscopy and dye so that tubal and other pelvic pathology can be assessed at the same time. **[2004]**

1.3.8.4 Women should not be offered hysteroscopy on its own as part of the initial investigation unless clinically indicated because the effectiveness of surgical treatment of uterine abnormalities on improving pregnancy rates has not been established. **[2004]**

1.3.9 Testing for viral status

1.3.9.1 People undergoing IVF treatment should be offered testing for HIV, hepatitis B and hepatitis C (for donor insemination see recommendation 1.14.3.1). **[2004, amended 2013]**

1.3.9.2 People found to test positive for one or more of HIV, hepatitis B, or hepatitis C should be offered specialist advice and counselling and appropriate clinical management. **[2004, amended 2013]**

1.3.10 Viral transmission

1.3.10.1 For couples where the man is HIV positive, any decision about fertility management should be the result of discussions between the couple, a fertility specialist and an HIV specialist. **[new 2013]**

1.3.10.2 Advise couples where the man is HIV positive that the risk of HIV transmission to the female partner is negligible through unprotected sexual intercourse when all of the following criteria are met:

- the man is compliant with highly active antiretroviral therapy (HAART)

- the man has had a plasma viral load of less than 50 copies/ml for more than 6 months
- there are no other infections present
- unprotected intercourse is limited to the time of ovulation. **[new 2013]**

1.3.10.3 Advise couples that if all the criteria in recommendation 1.3.10.2 are met, sperm washing may not further reduce the risk of infection and may reduce the likelihood of pregnancy. **[new 2013]**

1.3.10.4 For couples where the man is HIV positive and either he is not compliant with HAART or his plasma viral load is 50 copies/ml or greater, offer sperm washing. **[new 2013]**

1.3.10.5 Inform couples that sperm washing reduces, but does not eliminate, the risk of HIV transmission. **[new 2013]**

1.3.10.6 If couples who meet all the criteria in recommendation 1.3.10.2 still perceive an unacceptable risk of HIV transmission after discussion with their HIV specialist, consider sperm washing. **[new 2013]**

1.3.10.7 Inform couples that there is insufficient evidence to recommend that HIV negative women use pre-exposure prophylaxis, when all the criteria in recommendation 1.3.10.2 are met. **[new 2013]**

1.3.10.8 For partners of people with hepatitis B, offer vaccination before starting fertility treatment. **[new 2013]**

1.3.10.9 Do not offer sperm washing as part of fertility treatment for men with hepatitis B. **[new 2013]**

1.3.10.10 For couples where the man has hepatitis C, any decision about fertility management should be the result of discussions between the couple, a fertility specialist and a hepatitis specialist. **[new 2013]**

1.3.10.11 Advise couples who want to conceive and where the man has hepatitis C that the risk of transmission through unprotected sexual intercourse is thought to be low. **[new 2013]**

1.3.10.12 Men with hepatitis C should discuss treatment options to eradicate the hepatitis C with their appropriate specialist before conception is considered. **[new 2013]**

1.3.11 Susceptibility to rubella

1.3.11.1 Women who are concerned about their fertility should be offered testing for their rubella status so that those who are susceptible to rubella can be offered vaccination. Women who are susceptible to rubella should be offered vaccination and advised not to become pregnant for at least 1 month following vaccination. **[2004, amended 2013]**

1.3.12 Cervical cancer screening

1.3.12.1 To avoid delay in fertility treatment a specific enquiry about the timing and result of the most recent cervical smear test should be made to women who are concerned about their fertility. Cervical screening should be offered in accordance with the national cervical screening programme guidance. **[2004]**

1.3.13 Screening for *Chlamydia trachomatis*

1.3.13.1 Before undergoing uterine instrumentation women should be offered screening for *Chlamydia trachomatis* using an appropriately sensitive technique. **[2004]**

1.3.13.2 If the result of a test for *Chlamydia trachomatis* is positive, women and their sexual partners should be referred for appropriate management with treatment and contact tracing. **[2004]**

1.3.13.3 Prophylactic antibiotics should be considered before uterine instrumentation if screening has not been carried out. **[2004]**

1.4 Medical and surgical management of male factor fertility problems

1.4.1 Medical management (male factor infertility)

1.4.1.1 Men with hypogonadotrophic hypogonadism should be offered gonadotrophin drugs because these are effective in improving fertility. **[2004]**

1.4.1.2 Men with idiopathic semen abnormalities should not be offered anti-oestrogens, gonadotrophins, androgens, bromocriptine or kinin-enhancing drugs because they have not been shown to be effective. **[2004]**

1.4.1.3 Men should be informed that the significance of antisperm antibodies is unclear and the effectiveness of systemic corticosteroids is uncertain. **[2004]**

1.4.1.4 Men with leucocytes in their semen should not be offered antibiotic treatment unless there is an identified infection because there is no evidence that this improves pregnancy rates. **[2004]**

1.4.2 Surgical management (male factor infertility)

1.4.2.1 Where appropriate expertise is available, men with obstructive azoospermia should be offered surgical correction of epididymal blockage because it is likely to restore patency of the duct and improve fertility. Surgical correction should be considered as an alternative to surgical sperm recovery and IVF. **[2004]**

1.4.2.2 Men should not be offered surgery for varicoceles as a form of fertility treatment because it does not improve pregnancy rates. **[2004]**

1.4.3 Management of ejaculatory failure

1.4.3.1 Treatment of ejaculatory failure can restore fertility without the need for invasive methods of sperm retrieval or the use of assisted reproduction

procedures. However, further evaluation of different treatment options is needed. **[2004]**

1.5 Ovulation disorders

Classification of ovulatory disorders

The World Health Organization classifies ovulation disorders into 3 groups.

- Group I: hypothalamic pituitary failure (hypothalamic amenorrhoea or hypogonadotrophic hypogonadism).
- Group II: hypothalamic-pituitary-ovarian dysfunction (predominately polycystic ovary syndrome).
- Group III: ovarian failure.

1.5.1 WHO Group I ovulation disorders

1.5.1.1 Advise women with WHO Group I anovulatory infertility that they can improve their chance of regular ovulation, conception and an uncomplicated pregnancy by:

- increasing their body weight if they have a BMI of less than 19 **and/or**
- moderating their exercise levels if they undertake high levels of exercise. **[new 2013]**

1.5.1.2 Offer women with WHO Group I ovulation disorders pulsatile administration of gonadotrophin-releasing hormone or gonadotrophins with luteinising hormone activity to induce ovulation. **[2013]**

1.5.2 WHO Group II ovulation disorders

In women with WHO Group II ovulation disorders receiving first-line treatment for ovarian stimulation:

1.5.2.1 Advise women with WHO Group II anovulatory infertility who have a BMI of 30 or over to lose weight (see recommendation 1.2.6.3). Inform them that this alone may restore ovulation, improve their response to ovulation

induction agents, and have a positive impact on pregnancy outcomes. **[new 2013]**

1.5.2.2 Offer women with WHO Group II anovulatory infertility one of the following treatments, taking into account potential adverse effects, ease and mode of use, the woman's BMI, and monitoring needed:

- clomifene citrate **or**
- metformin[8] **or**
- a combination of the above. **[new 2013]**

1.5.2.3 For women who are taking clomifene citrate, offer ultrasound monitoring during at least the first cycle of treatment to ensure that they are taking a dose that minimises the risk of multiple pregnancy. **[2013]**

1.5.2.4 For women who are taking clomifene citrate, do not continue treatment for longer than 6 months. **[new 2013]**

1.5.2.5 Women prescribed metformin[8] should be informed of the side effects associated with its use (such as nausea, vomiting and other gastrointestinal disturbances). **[2004]**

In women with WHO Group II ovulation disorders who are known to be resistant to clomifene citrate:

1.5.2.6 For women with WHO Group II ovulation disorders who are known to be resistant to clomifene citrate, consider one of the following second-line treatments, depending on clinical circumstances and the woman's preference:

- laparoscopic ovarian drilling **or**
- combined treatment with clomifene citrate and metformin[8] if not already offered as first-line treatment **or**

[8] At the time of publication (February 2013), metformin did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. The patient should provide Informed consent, which should be documented. See the General Medical Council's Good practice in prescribing medicines - guidance for doctors for further information.

- gonadotrophins. **[new 2013]**

1.5.2.7 Women with polycystic ovary syndrome who are being treated with gonadotrophins should not be offered treatment with gonadotrophin-releasing hormone agonist concomitantly because it does not improve pregnancy rates, and it is associated with an increased risk of ovarian hyperstimulation. **[2004]**

1.5.2.8 The use of adjuvant growth hormone treatment with gonadotrophin-releasing hormone agonist and/or human menopausal gonadotrophin during ovulation induction in women with polycystic ovary syndrome who do not respond to clomifene citrate is not recommended because it does not improve pregnancy rates. **[2004]**

1.5.2.9 The effectiveness of pulsatile gonadotrophin-releasing hormone in women with clomifene citrate-resistant polycystic ovary syndrome is uncertain and is therefore not recommended outside a research context. **[2004]**

1.5.3 Hyperprolactinaemic amenorrhoea - dopamine agonists

1.5.3.1 Women with ovulatory disorders due to hyperprolactinaemia should be offered treatment with dopamine agonists such as bromocriptine. Consideration should be given to safety for use in pregnancy and minimising cost when prescribing. **[2004]**

1.5.4 Monitoring ovulation induction during gonadotrophin therapy

1.5.4.1 Women who are offered ovulation induction with gonadotrophins should be informed about the risk of multiple pregnancy and ovarian hyperstimulation before starting treatment. **[2004]**

1.5.4.2 Ovarian ultrasound monitoring to measure follicular size and number should be an integral part of gonadotrophin therapy to reduce the risk of multiple pregnancy and ovarian hyperstimulation. **[2004]**

1.6 Tubal and uterine surgery

1.6.1 Tubal microsurgery and laparoscopic tubal surgery

1.6.1.1 For women with mild tubal disease, tubal surgery may be more effective than no treatment. In centres where appropriate expertise is available it may be considered as a treatment option. **[2004]**

1.6.2 Tubal catheterisation or cannulation

1.6.2.1 For women with proximal tubal obstruction, selective salpingography plus tubal catheterisation, or hysteroscopic tubal cannulation, may be treatment options because these treatments improve the chance of pregnancy. **[2004]**

1.6.3 Surgery for hydrosalpinges before in vitro fertilisation treatment

1.6.3.1 Women with hydrosalpinges should be offered salpingectomy, preferably by laparoscopy, before IVF treatment because this improves the chance of a live birth. **[2004]**

1.6.4 Uterine surgery

1.6.4.1 Women with amenorrhoea who are found to have intrauterine adhesions should be offered hysteroscopic adhesiolysis because this is likely to restore menstruation and improve the chance of pregnancy. **[2004]**

1.7 Medical and surgical management of endometriosis

1.7.1 Medical management (ovarian suppression) of endometriosis

1.7.1.1 Medical treatment of minimal and mild endometriosis diagnosed as the cause of infertility in women does not enhance fertility and should not be offered. **[2004, amended 2013]**

1.7.2 Surgical ablation

1.7.2.1 Women with minimal or mild endometriosis who undergo laparoscopy should be offered surgical ablation or resection of endometriosis plus

laparoscopic adhesiolysis because this improves the chance of pregnancy. **[2004]**

1.7.2.2 Women with ovarian endometriomas should be offered laparoscopic cystectomy because this improves the chance of pregnancy. **[2004]**

1.7.2.3 Women with moderate or severe endometriosis should be offered surgical treatment because it improves the chance of pregnancy. **[2004]**

1.7.2.4 Post-operative medical treatment does not improve pregnancy rates in women with moderate to severe endometriosis and is not recommended. **[2004]**

1.8 Unexplained infertility

1.8.1 Ovarian stimulation for unexplained infertility

1.8.1.1 Do not offer oral ovarian stimulation agents (such as clomifene citrate, anastrozole or letrozole) to women with unexplained infertility. **[new 2013]**

1.8.1.2 Inform women with unexplained infertility that clomifene citrate as a stand-alone treatment does not increase the chances of a pregnancy or a live birth. **[new 2013]**

1.8.1.3 Advise women with unexplained infertility who are having regular unprotected sexual intercourse to try to conceive for a total of 2 years (this can include up to 1 year before their fertility investigations) before IVF will be considered. **[new 2013]**

1.8.1.4 Offer IVF treatment (see recommendations 1.11.1.3–4) to women with unexplained infertility who have not conceived after 2 years (this can include up to 1 year before their fertility investigations) of regular unprotected sexual intercourse. **[new 2013]**

1.9 Intrauterine insemination

1.9.1 Intrauterine insemination

1.9.1.1 Consider unstimulated intrauterine insemination as a treatment option in the following groups as an alternative to vaginal sexual intercourse:

- people who are unable to, or would find it very difficult to, have vaginal intercourse because of a clinically diagnosed physical disability or psychosexual problem who are using partner or donor sperm
- people with conditions that require specific consideration in relation to methods of conception (for example, after sperm washing where the man is HIV positive)
- people in same-sex relationships. **[new 2013]**

1.9.1.2 For people in recommendation 1.9.1.1 who have not conceived after 6 cycles of donor or partner insemination, despite evidence of normal ovulation, tubal patency and semenalysis, offer a further 6 cycles of unstimulated intrauterine insemination before IVF is considered. **[new 2013]**

1.9.1.3 For people with unexplained infertility, mild endometriosis or mild male factor infertility, who are having regular unprotected sexual intercourse:

- advise them to try to conceive for a total of 2 years (this can include up to 1 year before their fertility investigations) before IVF will be considered
- do not routinely offer intrauterine insemination, either with or without ovarian stimulation (exceptional circumstances include, for example, when people have social, cultural or religious objections to IVF). **[2016]**

1.10 Prediction of IVF success

1.10.1 Female age

1.10.1.1 Inform women that the chance of a live birth following IVF treatment falls with rising female age (see figure 2). **[2013]**

1.10.2 Number of previous treatment cycles

1.10.2.1 Inform people that the overall chance of a live birth following IVF treatment falls as the number of unsuccessful cycles increases. **[new 2013]**

1.10.3 Previous pregnancy history

1.10.3.1 People should be informed that IVF treatment is more effective in women who have previously been pregnant and/or had a live birth. **[2004, amended 2013]**

1.10.4 Body mass index

1.10.4.1 Women should be informed that female BMI should ideally be in the range 19–30 before commencing assisted reproduction, and that a female BMI outside this range is likely to reduce the success of assisted reproduction procedures. **[2004]**

1.10.5 Lifestyle factors

1.10.5.1 People should be informed that the consumption of more than 1 unit of alcohol per day reduces the effectiveness of assisted reproduction procedures, including IVF. **[2004, amended 2013]**

1.10.5.2 People should be informed that maternal and paternal smoking can adversely affect the success rates of assisted reproduction procedures, including IVF treatment. **[2004, amended 2013]**

1.10.5.3 People should be informed that maternal caffeine consumption has adverse effects on the success rates of assisted reproduction procedures, including IVF treatment. **[2004, amended 2013]**

1.11 Access criteria for IVF

1.11.1 Criteria for referral for IVF

1.11.1.1 When considering IVF as a treatment option for people with fertility problems, discuss the risks and benefits of IVF in accordance with the current Human Fertilisation and Embryology Authority (HFEA) Code of Practice. **[new 2013]**

1.11.1.2 Inform people that normally a full cycle of IVF treatment, with or without intracytoplasmic sperm injection (ICSI), should comprise 1 episode of ovarian stimulation and the transfer of any resultant fresh and frozen embryo(s). **[new 2013]**

1.11.1.3 In women aged under 40 years who have not conceived after 2 years of regular unprotected intercourse or 12 cycles of artificial insemination (where 6 or more are by intrauterine insemination), offer 3 full cycles of IVF, with or without ICSI. If the woman reaches the age of 40 during treatment, complete the current full cycle but do not offer further full cycles. **[new 2013]**

1.11.1.4 In women aged 40–42 years who have not conceived after 2 years of regular unprotected intercourse or 12 cycles of artificial insemination (where 6 or more are by intrauterine insemination), offer 1 full cycle of IVF, with or without ICSI, provided the following 3 criteria are fulfilled:

- they have never previously had IVF treatment
- there is no evidence of low ovarian reserve (see recommendation 1.3.3.2)
- there has been a discussion of the additional implications of IVF and pregnancy at this age. **[new 2013]**

1.11.1.5 Where investigations show there is no chance of pregnancy with expectant management and where IVF is the only effective treatment, refer the woman directly to a specialist team for IVF treatment. **[new 2013]**

1.11.1.6 In women aged under 40 years any previous full IVF cycle, whether self- or NHS-funded, should count towards the total of 3 full cycles that should be offered by the NHS. **[new 2013]**

1.11.1.7 Take into account the outcome of previous IVF treatment when assessing the likely effectiveness and safety of any further IVF treatment. **[new 2013]**

1.11.1.8 Healthcare providers should define a cancelled IVF cycle as one where an egg collection procedure is not undertaken. However, cancelled cycles due to low ovarian reserve should be taken into account when considering suitability for further IVF treatment. **[new 2013]**

1.12 Procedures used during IVF treatment

1.12.1 Pre-treatment in IVF

1.12.1.1 Advise women that using pre-treatment (with either the oral contraceptive pill or a progestogen) as part of IVF does not affect the chances of having a live birth. **[new 2013]**

1.12.1.2 Consider pre-treatment in order to schedule IVF treatment for women who are not undergoing long down-regulation protocols. **[new 2013]**

1.12.2 Down regulation and other regimens to avoid premature luteinising hormone surges in IVF

1.12.2.1 Use regimens to avoid premature luteinising hormone surges in gonadotrophin-stimulated IVF treatment cycles. **[new 2013]**

1.12.2.2 Use either gonadotrophin-releasing hormone agonist down-regulation or gonadotrophin-releasing hormone antagonists as part of gonadotrophin-stimulated IVF treatment cycles. **[new 2013]**

1.12.2.3 Only offer gonadotrophin-releasing hormone agonists to women who have a low risk of ovarian hyperstimulation syndrome. **[new 2013]**

1.12.2.4 When using gonadotrophin-releasing hormone agonists as part of IVF treatment, use a long down-regulation protocol. **[new 2013]**

1.12.3 Controlled ovarian stimulation in IVF

1.12.3.1 Use ovarian stimulation as part of IVF treatment. **[new 2013]**

1.12.3.2 Use either urinary or recombinant gonadotrophins for ovarian stimulation as part of IVF treatment. **[new 2013]**

1.12.3.3 When using gonadotrophins for ovarian stimulation in IVF treatment:

- use an individualised starting dose of follicle-stimulating hormone, based on factors that predict success, such as:
  - age
  - BMI
  - presence of polycystic ovaries
  - ovarian reserve
- do not use a dosage of follicle-stimulating hormone of more than 450 IU/day. **[new 2013]**

1.12.3.4 Offer women ultrasound monitoring (with or without oestradiol levels) for efficacy and safety throughout ovarian stimulation. **[new 2013]**

1.12.3.5 Inform women that clomifene citrate-stimulated and gonadotrophin-stimulated IVF cycles have higher pregnancy rates per cycle than natural cycle IVF. **[2013]**

1.12.3.6 Do not offer women natural cycle IVF treatment. **[2013]**

1.12.3.7 Do not use growth hormone or dehydroepiandrosterone (DHEA) as adjuvant treatment in IVF protocols. **[new 2013]**

1.12.4 Triggering ovulation in IVF

1.12.4.1 Offer women human chorionic gonadotrophin (urinary or recombinant) to trigger ovulation in IVF treatment. **[new 2013]**

1.12.4.2 Offer ultrasound monitoring of ovarian response as an integral part of the IVF treatment cycle. **[2013]**

1.12.4.3 Clinics providing ovarian stimulation with gonadotrophins should have protocols in place for preventing, diagnosing and managing ovarian hyperstimulation syndrome. **[2004]**

1.12.5 Oocyte and sperm retrieval in IVF

1.12.5.1 Women undergoing transvaginal retrieval of oocytes should be offered conscious sedation because it is a safe and acceptable method of providing analgesia. **[2004]**

1.12.5.2 The safe practice of administering sedative drugs published by the Academy of Medical Royal Colleges should be followed. **[2004]**

1.12.5.3 Women who have developed at least 3 follicles before oocyte retrieval should not be offered follicle flushing because this procedure does not increase the numbers of oocytes retrieved or pregnancy rates, and it increases the duration of oocyte retrieval and associated pain. **[2004]**

1.12.5.4 Surgical sperm recovery before ICSI may be performed using several different techniques depending on the pathology and wishes of the man. In all cases, facilities for cryopreservation of spermatozoa should be available. **[2004]**

1.12.5.5 Assisted hatching is not recommended because it has not been shown to improve pregnancy rates. **[2004]**

1.12.6 Embryo transfer strategies in IVF

1.12.6.1 Women undergoing IVF treatment should be offered ultrasound-guided embryo transfer because this improves pregnancy rates. **[2004]**

1.12.6.2 Replacement of embryos into a uterine cavity with an endometrium of less than 5 mm thickness is unlikely to result in a pregnancy and is therefore not recommended. **[2004]**

1.12.6.3 Women should be informed that bed rest of more than 20 minutes' duration following embryo transfer does not improve the outcome of IVF treatment. **[2004]**

1.12.6.4 Evaluate embryo quality, at both cleavage and blastocyst stages, according to the Association of Clinical Embryologists (ACE) and UK National External Quality Assessment Service (UK NEQAS) for Reproductive Science Embryo and Blastocyst Grading schematic (see figure 3). **[new 2013]**

1.12.6.5 When considering the number of fresh or frozen embryos to transfer in IVF treatment:

- For women aged under 37 years:
  - In the first full IVF cycle use single embryo transfer.
  - In the second full IVF cycle use single embryo transfer if 1 or more top-quality embryos are available. Consider using 2 embryos if no top-quality embryos are available.
  - In the third full IVF cycle transfer no more than 2 embryos.
- For women aged 37–39 years:
  - In the first and second full IVF cycles use single embryo transfer if there are 1 or more top-quality embryos. Consider double embryo transfer if there are no top-quality embryos.
  - In the third full IVF cycle transfer no more than 2 embryos.
- For women aged 40–42 years consider double embryo transfer. **[new 2013]**

1.12.6.6 For women undergoing IVF treatment with donor eggs, use an embryo transfer strategy that is based on the age of the donor. **[new 2013]**

1.12.6.7 No more than 2 embryos should be transferred during any one cycle of IVF treatment. **[2013]**

1.12.6.8 Where a top-quality blastocyst is available, use single embryo transfer. **[new 2013]**

1.12.6.9 When considering double embryo transfer, advise people of the risks of multiple pregnancy associated with this strategy. **[new 2013]**

1.12.6.10 Offer cryopreservation to store any remaining good-quality embryos after embryo transfer. **[new 2013]**

1.12.6.11 Advise women who have regular ovulatory cycles that the likelihood of a live birth after replacement of frozen–thawed embryos is similar for embryos replaced during natural cycles and hormone-supplemented cycles. **[2013]**

1.12.7 Luteal phase support after IVF

1.12.7.1 Offer women progesterone for luteal phase support after IVF treatment. **[new 2013]**

1.12.7.2 Do not routinely offer women human chorionic gonadotrophin for luteal phase support after IVF treatment because of the increased likelihood of ovarian hyperstimulation syndrome. **[2013]**

1.12.7.3 Inform women undergoing IVF treatment that the evidence does not support continuing any form of treatment for luteal phase support beyond 8 weeks' gestation. **[new 2013]**

1.12.8 Gamete intrafallopian transfer and zygote intrafallopian transfer

1.12.8.1 There is insufficient evidence to recommend the use of gamete intrafallopian transfer or zygote intrafallopian transfer in preference to IVF in couples with unexplained fertility problems or male factor fertility problems. **[2004]**

1.13 Intracytoplasmic sperm injection

1.13.1 Indications for intracytoplasmic sperm injection

1.13.1.1 The recognised indications for treatment by ICSI include:

- severe deficits in semen quality

- obstructive azoospermia
- non-obstructive azoospermia.

In addition, treatment by ICSI should be considered for couples in whom a previous IVF treatment cycle has resulted in failed or very poor fertilisation. **[2004]**

1.13.2 Genetic issues and counselling

1.13.2.1 Before considering treatment by ICSI, people should undergo appropriate investigations, both to establish a diagnosis and to enable informed discussion about the implications of treatment. **[2004, amended 2013]**

1.13.2.2 Before treatment by ICSI consideration should be given to relevant genetic issues. **[2004]**

1.13.2.3 Where a specific genetic defect associated with male infertility is known or suspected couples should be offered appropriate genetic counselling and testing. **[2004]**

1.13.2.4 Where the indication for ICSI is a severe deficit of semen quality or non-obstructive azoospermia, the man's karyotype should be established. **[2004]**

1.13.2.5 Men who are undergoing karyotype testing should be offered genetic counselling regarding the genetic abnormalities that may be detected. **[2004]**

1.13.2.6 Testing for Y chromosome microdeletions should not be regarded as a routine investigation before ICSI. However, it is likely that a significant proportion of male infertility results from abnormalities of genes on the Y chromosome involved in the regulation of spermatogenesis, and couples should be informed of this. **[2004]**

1.13.3 Intracytoplasmic sperm injection versus IVF

1.13.3.1 Couples should be informed that ICSI improves fertilisation rates compared to IVF alone, but once fertilisation is achieved the pregnancy rate is no better than with IVF. **[2004]**

1.14 Donor insemination

1.14.1 Indications for donor insemination

1.14.1.1 The use of donor insemination is considered effective in managing fertility problems associated with the following conditions:

- obstructive azoospermia
- non-obstructive azoospermia
- severe deficits in semen quality in couples who do not wish to undergo ICSI. **[2004, amended 2013]**

1.14.1.2 Donor insemination should be considered in conditions such as:

- where there is a high risk of transmitting a genetic disorder to the offspring
- where there is a high risk of transmitting infectious disease to the offspring or woman from the man
- severe rhesus isoimmunisation. **[2004, amended 2013]**

1.14.2 Information and counselling

1.14.2.1 Couples should be offered information about the relative merits of ICSI and donor insemination in a context that allows equal access to both treatment options. **[2004]**

1.14.2.2 Couples considering donor insemination should be offered counselling from someone who is independent of the treatment unit regarding all the physical and psychological implications of treatment for themselves and potential children. **[2004]**

1.14.3 Screening of sperm donors

1.14.3.1 Units undertaking semen donor recruitment and the cryopreservation of donor spermatozoa for treatment purposes should follow the 'UK guidelines for the medical and laboratory screening of sperm, egg and embryo donors' (2008)[9] describing the selection and screening of donors. **[2004, amended 2013]**

1.14.3.2 All potential semen donors should be offered counselling from someone who is independent of the treatment unit regarding the implications for themselves and their genetic children, including any potential children resulting from donated semen. **[2004]**

1.14.4 Assessments to offer the woman

1.14.4.1 Before starting treatment by donor insemination (for conditions listed in recommendations 1.14.1.1 and 1.14.1.2) it is important to confirm that the woman is ovulating. Women with a history that is suggestive of tubal damage should be offered tubal assessment before treatment. **[2004, amended 2013]**

1.14.4.2 Women with no risk factors in their history should be offered tubal assessment after 3 cycles if treatment by donor insemination (for conditions listed in recommendations 1.14.1.1 and 1.14.1.2) has been unsuccessful. **[2004, amended 2013]**

1.14.5 Intrauterine insemination versus intracervical insemination

1.14.5.1 Couples using donor sperm should be offered intrauterine insemination in preference to intracervical insemination because it improves pregnancy rates. **[2004]**

[9] This recommendation has been updated to reflect a new guideline issued by the joint working party of Association of Biomedical Andrologists (ABA), Association of Clinical Embryologists (ACE), British Andrology Society (BAS), British Fertility Society (BFS) and Royal College of Obstetricians and Gynaecologists (RCOG).

1.14.6 Unstimulated versus stimulated donor insemination

1.14.6.1 Women who are ovulating regularly should be offered a minimum of 6 cycles of donor insemination (for conditions listed in recommendations 1.14.1.1 and 1.14.1.2) without ovarian stimulation to reduce the risk of multiple pregnancy and its consequences. **[2004, amended 2013]**

1.15 Oocyte donation

1.15.1 Indications for oocyte donation

1.15.1.1 The use of donor oocytes is considered effective in managing fertility problems associated with the following conditions:

- premature ovarian failure
- gonadal dysgenesis including Turner syndrome
- bilateral oophorectomy
- ovarian failure following chemotherapy or radiotherapy
- certain cases of IVF treatment failure.

Oocyte donation should also be considered in certain cases where there is a high risk of transmitting a genetic disorder to the offspring. **[2004]**

1.15.2 Screening of oocyte donors

1.15.2.1 Before donation is undertaken, oocyte donors should be screened for both infectious and genetic diseases in accordance with the 'UK guidelines for the medical and laboratory screening of sperm, egg and embryo donors' (2008)[9]. **[2004, amended 2013]**

1.15.3 Oocyte donation and 'egg sharing'

1.15.3.1 Oocyte donors should be offered information regarding the potential risks of ovarian stimulation and oocyte collection. **[2004]**

1.15.3.2 Oocyte recipients and donors should be offered counselling from someone who is independent of the treatment unit regarding the physical

and psychological implications of treatment for themselves and their genetic children, including any potential children resulting from donated oocytes. **[2004]**

1.15.3.3 All people considering participation in an 'egg-sharing' scheme should be counselled about its particular implications. **[2004]**

1.16 People with cancer who wish to preserve fertility

1.16.1 Cryopreservation of semen, oocytes and embryos

1.16.1.1 When considering and using cryopreservation for people before starting chemotherapy or radiotherapy that is likely to affect their fertility, follow recommendations in 'The effects of cancer treatment on reproductive functions' (2007)[10]. **[2013]**

1.16.1.2 At diagnosis, the impact of the cancer and its treatment on future fertility should be discussed between the person diagnosed with cancer and their cancer team. **[new 2013]**

1.16.1.3 When deciding to offer fertility preservation to people diagnosed with cancer, take into account the following factors:

- diagnosis
- treatment plan
- expected outcome of subsequent fertility treatment
- prognosis of the cancer treatment
- viability of stored/post-thawed material. **[new 2013]**

1.16.1.4 For cancer-related fertility preservation, do not apply the eligibility criteria used for conventional infertility treatment. **[new 2013]**

1.16.1.5 Do not use a lower age limit for cryopreservation for fertility preservation in people diagnosed with cancer. **[new 2013]**

[10] Royal College of Physicians, The Royal College of Radiologists, Royal College of Obstetricians and Gynaecologists. (2007) The effects of cancer treatment on reproductive functions: guidance on management. Report of a Working Party. London: RCP.

1.16.1.6 Inform people diagnosed with cancer that the eligibility criteria used in conventional infertility treatment do not apply in the case of fertility cryopreservation provided by the NHS. However, those criteria will apply when it comes to using stored material for assisted conception in an NHS setting. **[new 2013]**

1.16.1.7 When using cryopreservation to preserve fertility in people diagnosed with cancer, use sperm, embryos or oocyctes. **[new 2013]**

1.16.1.8 Offer sperm cryopreservation to men and adolescent boys who are preparing for medical treatment for cancer that is likely to make them infertile. **[new 2013]**

1.16.1.9 Use freezing in liquid nitrogen vapour as the preferred cryopreservation technique for sperm. **[new 2013]**

1.16.1.10 Offer oocyte or embryo cryopreservation as appropriate to women of reproductive age (including adolescent girls) who are preparing for medical treatment for cancer that is likely to make them infertile if:

- they are well enough to undergo ovarian stimulation and egg collection **and**
- this will not worsen their condition **and**
- enough time is available before the start of their cancer treatment. **[new 2013]**

1.16.1.11 In cryopreservation of oocytes and embryos, use vitrification instead of controlled-rate freezing if the necessary equipment and expertise is available. **[new 2013]**

1.16.1.12 Store cryopreserved material for an initial period of 10 years. **[new 2013]**

1.16.1.13 Offer continued storage of cryopreserved sperm, beyond 10 years, to men who remain at risk of significant infertility. **[new 2013]**

1.17 Long-term safety of assisted reproductive technologies for women with infertility and their children

1.17.1 Long-term health outcomes of ovulation induction and ovarian stimulation

1.17.1.1 Give people who are considering ovulation induction or ovarian stimulation up-to-date information about the long-term health outcomes of these treatments. **[new 2013]**

1.17.1.2 Inform women who are offered ovulation induction or ovarian stimulation that:

- no direct association has been found between these treatments and invasive cancer **and**
- no association has been found in the short- to medium-term between these treatments and adverse outcomes (including cancer) in children born from ovulation induction **and**
- information about long-term health outcomes in women and children is still awaited. **[new 2013]**

1.17.1.3 Limit the use of ovulation induction or ovarian stimulation agents to the lowest effective dose and duration of use. **[new 2013]**

1.17.2 Long-term health outcomes and safety of IVF

1.17.2.1 Give people who are considering IVF treatment, with or without ICSI, up-to-date information about the long-term health outcomes (including the consequences of multiple pregnancy) of these treatments. **[new 2013]**

1.17.2.2 Inform women that while the absolute risks of long-term adverse outcomes of IVF treatment, with or without ICSI, are low, a small increased risk of borderline ovarian tumours cannot be excluded. **[new 2013]**

1.17.2.3 Inform people who are considering IVF treatment that the absolute risks of long-term adverse outcomes in children born as result of IVF are low. **[new 2013]**

1.17.2.4 Limit drugs used for controlled ovarian stimulation in IVF treatment to the lowest effective dose and duration of use. **[new 2013]**

Terms used in this guideline

Expectant management

A formal approach that encourages conception through unprotected vaginal intercourse. It involves supportively offering an individual or couple information and advice about the regularity and timing of intercourse and any lifestyle changes which might improve their chances of conceiving. It does not involve active clinical or therapeutic interventions.

Full cycle

This term is used to define a full IVF treatment, which should include 1 episode of ovarian stimulation and the transfer of any resultant fresh and frozen embryo(s).

Mild male factor infertility

This term is used extensively in practice and in the literature. However, no formally recognised definition is currently available. For the purpose of this guideline it is defined as when 2 or more semen analyses have 1 or more variables below the 5th centile (as defined by the WHO, 2010). The effect on the chance of pregnancy occurring naturally through vaginal intercourse within 2 years would then be similar to people with unexplained infertility or mild endometriosis.

Natural cycle IVF

An IVF procedure in which 1 or more oocytes are collected from the ovaries during a spontaneous menstrual cycle without the use of drugs.

Putting this guideline into practice

[This section will be completed after consultation]

NICE has produced tools and resources to help you put this guideline into practice.

[Optional paragraph if issues raised] Some issues were highlighted that might need specific thought when implementing the recommendations. These were raised during the development of this guideline. They are:

- [add any issues specific to guideline here]
- [Use 'Bullet left 1 last' style for the final item in this list.]

Putting recommendations into practice can take time. How long may vary from guideline to guideline, and depends on how much change in practice or services is needed. Implementing change is most effective when aligned with local priorities.

Changes recommended for clinical practice that can be done quickly – like changes in prescribing practice – should be shared quickly. This is because healthcare professionals should use guidelines to guide their work – as is required by professional regulating bodies such as the General Medical and Nursing and Midwifery Councils.

Changes should be implemented as soon as possible, unless there is a good reason for not doing so (for example, if it would be better value for money if a package of recommendations were all implemented at once).

Different organisations may need different approaches to implementation, depending on their size and function. Sometimes individual practitioners may be able to respond to recommendations to improve their practice more quickly than large organisations.

Here are some pointers to help organisations put NICE guidelines into practice:

1. **Raise awareness** through routine communication channels, such as email or newsletters, regular meetings, internal staff briefings and other communications with all relevant partner organisations. Identify things staff can include in their own practice straight away.

2. **Identify a lead** with an interest in the topic to champion the guideline and motivate others to support its use and make service changes, and to find out any significant issues locally.

3. **Carry out a baseline assessment** against the recommendations to find out whether there are gaps in current service provision.

4. **Think about what data you need to measure improvement** and plan how you will collect it. You may want to work with other health and social care organisations and specialist groups to compare current practice with the recommendations. This may also help identify local issues that will slow or prevent implementation.

5. **Develop an action plan**, with the steps needed to put the guideline into practice, and make sure it is ready as soon as possible. Big, complex changes may take longer to implement, but some may be quick and easy to do. An action plan will help in both cases.

6. **For very big changes** include milestones and a business case, which will set out additional costs, savings and possible areas for disinvestment. A small project group could develop the action plan. The group might include the guideline champion, a senior organisational sponsor, staff involved in the associated services, finance and information professionals.

7. **Implement the action plan** with oversight from the lead and the project group. Big projects may also need project management support.

8. **Review and monitor** how well the guideline is being implemented through the project group. Share progress with those involved in making improvements, as well as relevant boards and local partners.

NICE provides a comprehensive programme of support and resources to maximise uptake and use of evidence and guidance. See our into practice pages for more information.

Also see Leng G, Moore V, Abraham S, editors (2014) Achieving high quality care – practical experience from NICE. Chichester: Wiley.

Context

It is estimated that infertility affects 1 in 7 heterosexual couples in the UK. Since the original NICE guideline on fertility published in 2004 there has been a small increase

in the prevalence of fertility problems, and a greater proportion of people now seeking help for such problems.

The main causes of infertility in the UK are (per cent figures indicate approximate prevalence):

- unexplained infertility (no identified male or female cause) (25%)
- ovulatory disorders (25%)
- tubal damage (20%)
- factors in the male causing infertility (30%)
- uterine or peritoneal disorders (10%).

In about 40% of cases disorders are found in both the man and the woman. Uterine or endometrial factors, gamete or embryo defects, and pelvic conditions such as endometriosis may also play a role.

Given the range of causes of fertility problems, the provision of appropriate investigations is critical. These investigations include semen analysis; assessment of ovulation, tubal damage and uterine abnormalities; and screening for infections such as *Chlamydia trachomatis* and susceptibility to rubella.

Once a diagnosis has been established, treatment falls into 3 main types:

- medical treatment to restore fertility (for example, the use of drugs for ovulation induction)
- surgical treatment to restore fertility (for example, laparoscopy for ablation of endometriosis)
- assisted reproduction techniques (ART) – any treatment that deals with means of conception other than vaginal intercourse. It frequently involves the handling of gametes or embryos.

More information

To find out what NICE has said on topics related to this guideline, see our web page on fertility.

Recommendations for research

In 2013, the guideline committee made the following recommendations for research. The committee's full set of research recommendations is detailed in the full guideline.

1 Expectant management before IVF

What is the optimum period of expectant management for women of different age groups before invasive treatment such as IVF is considered?

Why this is important

Where there is no known cause for infertility, expectant management increases the cumulative chances of successful conception. However, the chances of a live birth both by natural conception and by using assisted reproductive technology decline with advancing age because of a woman's decreasing ovarian reserve. The guideline currently recommends a shorter period of expectant management for women who are 36 years or older. This is a very crude cut-off. If there were better evidence it might be possible to customise the period of expectant management based on a woman's age, including longer periods of expectant management for younger women.

2 Embryo selection for single embryo transfer

Further research is needed to improve embryo selection to facilitate single embryo transfers.

Why this is important

In current IVF practice it is common to transfer more than 1 embryo in order to maximise the chance of pregnancy. As detailed in the guideline, this practice has inherent risks, especially of multiple pregnancy. Embryo selection is based on the assessment of developmental stage and morphological grading criteria in the laboratory. These features are indicative of implantation potential, though the predictive accuracy is relatively poor. However, if prediction of implantation potential could be improved, this would facilitate embryo selection for single rather than double embryo transfer.

3 Adjuvant luteal phase support treatments in IVF

Further research is needed to assess the efficacy of adjuvant luteal phase support treatments such as low-dose aspirin, heparin, prednisolone, immunoglobulins and/or fat emulsions.

Why this is important

These interventions are starting to be used in clinical practice in the absence of any RCT evidence of benefit, and even where there is RCT evidence of no benefit. Their use has potential dangers to the treated women. In cases where women are advised to continue taking the preparations until the end of the first trimester there is the additional potential for teratogenicity. Immunoglobulins are also very expensive. It is important that the clinical efficacy of these agents is formally established so that clear statements about whether they should be recommended or are contraindicated can be made.

4 Long-term safety of ovarian stimulation and ovulation induction for women

Is there an association between ovulation induction or ovarian stimulation and adverse long-term (over 20 years) effects in women in the UK?

Why this is important

Women need to be reassured that it is safe to undergo ovulation induction and ovarian stimulation and that these interventions will not lead to significant long-term health issues, especially ovarian malignancy. Both treatments are common in the management of infertile women. The use of ovarian stimulation in IVF is particularly important as IVF is the final treatment option for most causes of infertility. During the course of the review for this guideline update the GDG commented on the paucity of long-term research on the subject, despite the fact that the treatments have been established practice for over 30 years. The longest length of follow-up in the studies reviewed was 20 years, and the larger studies had shorter follow-up periods.

5 Long-term effects of IVF with or without intracytoplasmic sperm injection in children

What are the long-term (over 20 years) effects of IVF with or without ICSI in children in the UK?

Why this is important

This topic is important in informing patients, service providers and society at large about the potential long-term safety of assisted reproduction. Both IVF and ICSI involve manipulation of egg and sperm in the laboratory, with impacts on the development of the subsequent embryo. However, while the first successful live birth following IVF was over 30 years ago, there is relatively little long-term research on the subject. In the review undertaken in this guideline update, the longest length of follow-up in the studies reviewed was 20 years, and the larger studies had shorter follow-up periods.

Figures and tables to support chances of conception and embryo quality recommendations

Table 1 Cumulative probability of conceiving a clinical pregnancy by the number of menstrual cycles

Cumulative probability of conceiving a clinical pregnancy by the number of menstrual cycles attempting to conceive in different age categories (assuming vaginal intercourse occurs twice per week) (Reproduced with permission: Dunson DB, Baird DD, Colombo B [2004]. Increased infertility with age in men and women. Obstetrics and Gynecology 103: 51–6).

Age category (years)	Pregnant after 1 year (12 cycles) (%)	Pregnant after 2 years (24 cycles) (%)
19–26	92	98
27–29	87	95
30–34	86	94
35–39	82	90

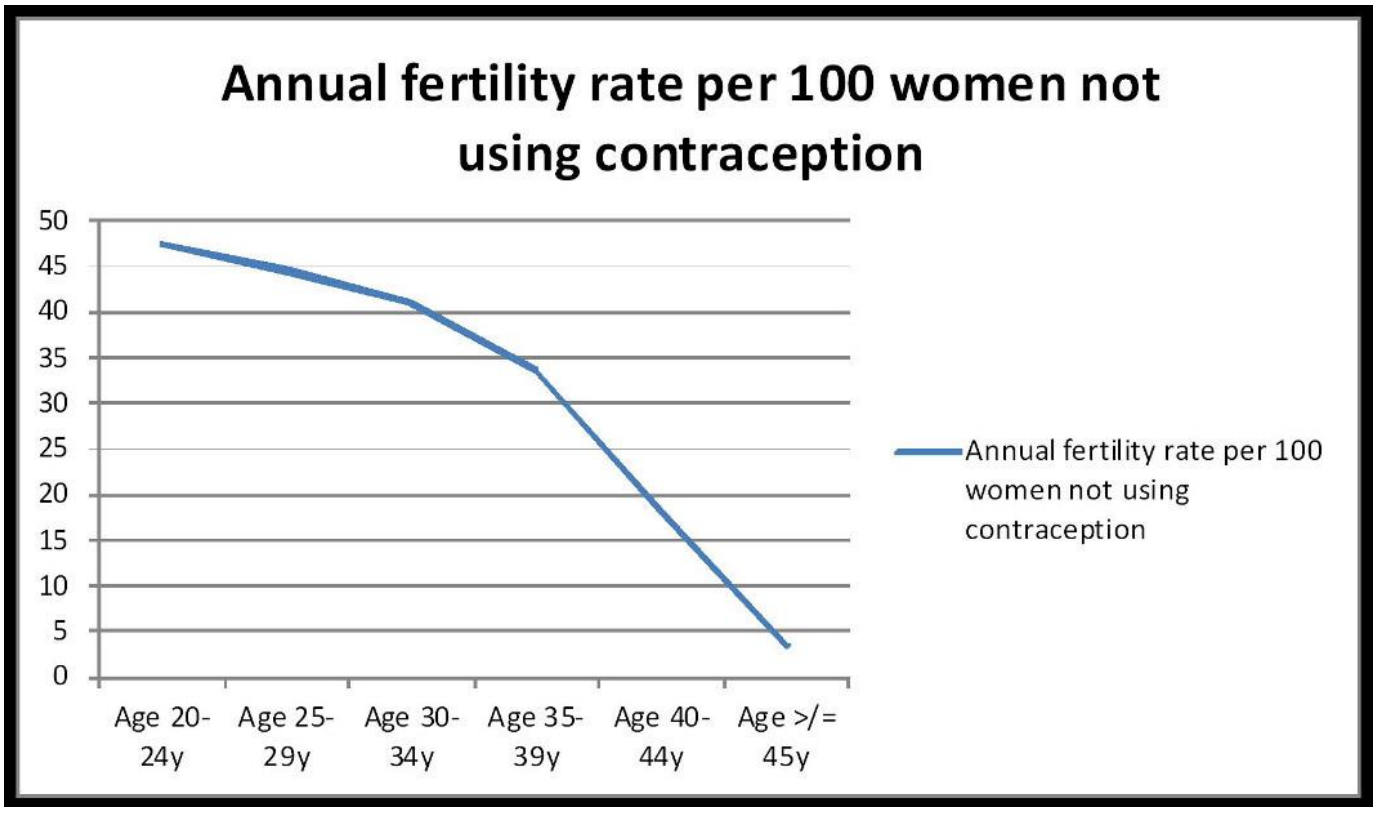
Table 2 Cumulative probability of conceiving a clinical pregnancy by the number of cycles of insemination

Cumulative probability of conceiving a clinical pregnancy by the number of cycles of insemination in different age categories and according to the method and sperm status where assisted reproduction technology is used (see the full guideline for full references).

Woman's age (years)	ICI using thawed semen (Schwartz et al. 1982)		Woman's age (years)	ICI using fresh semen (van Noord-Zaadstra, 1991)		Woman's age (years)	IUI using thawed semen (HFEA data and personal communication)	
	6 cycles	12 cycles		6 cycles	12 cycles		6 cycles	12 cycles
<30	50%	70%	<31	58%	76%	-	-	-
30–34	43%	62%	31–35	50%	71%	<35	63%	86%
>34	33%	54%	>35	39%	55%	35–39	50%	75%
Key: ICI = intracervical insemination; IUI = intrauterine insemination								

Figure 1 The effect of maternal age on the average rate of pregnancy

Calculated on the basis of studies in 10 different populations that did not use contraceptives (Heffner 2004[11], based on 2 reviews by Menken et al. 1986 and Anderson et al. 2000).



[11] Adapted from Heffner LJ (2004). Advanced maternal age – how old is too old? New England Journal of Medicine 351: 1927–9.

Figure 2 IVF success in terms of live births per 100 embryo transfers

The vertical axis shows embryo transfers; the horizontal axis shows age of woman (based on all 52,996 embryo transfers using the woman's own eggs undertaken in the UK between 1 October 2007 and 30 June 2009) [HFEA, personal communication] (note: small numbers of women aged under 24 years in the HFEA database).

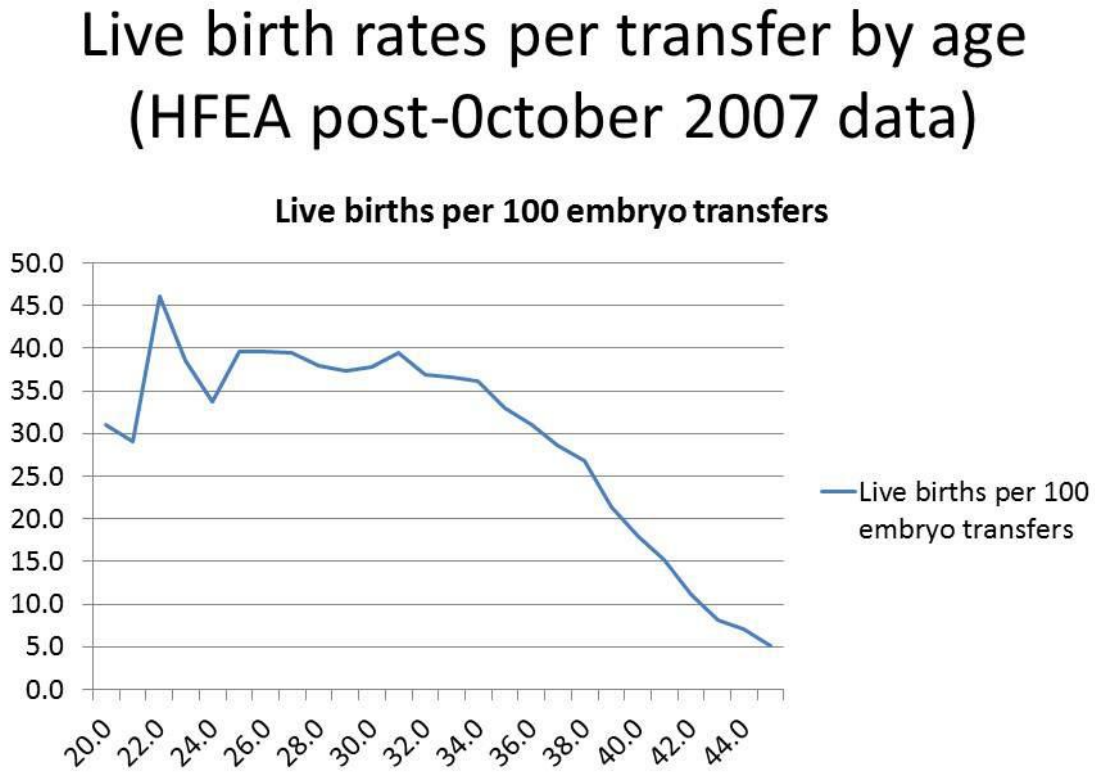


Figure 3 UK NEQAS embryo morphology scheme

UK NEQAS
Reproductive Science

Embryo Morphology Scheme

Cleavage stage embryo grading system

Blastomere Number		
Blastomere Size	4 =	Regular, even division
	3 =	<20% difference (blastomere diameter)
	2 =	20-50% difference
	1 =	>50% difference *Hardarson et al 2001*
Fragmentation	4 =	10% fragmentation by volume
	3 =	10-20%
	2 =	20-50%
	1 =	>50% *van Royen et al 2003*

Blastocyst grading system

Expansion Status	6 =	Hatched blastocyst; the blastocyst has evacuated the ZP.
	5 =	Hatching blastocyst; trophectoderm has started to herniate through the ZP.
	4 =	Expanded blastocyst: blastocoele volume now larger than that of the early embryo, ZP very thin.
	3 =	Full blastocyst; blastocoele completely fills the embryo.
	2 =	Blastocyst; blastocoele more than half the volume of the embryo, some expansion in overall size, ZP beginning to thin.
	1 =	Early blastocyst; blastocoele less than half the volume of the embryo, little or no expansion in overall size, *zona pellucida* (ZP) still thick.
ICM Grading	5 =	ICM prominent, easily discernible and consisting of many cells, cells compacted and tightly adhered together.
	4 =	Cells less compacted so larger in size, cells loosely adhered together; some individual cells may be visible.
	3 =	Very few cells visible; either compacted or loose, may be difficult to completely distinguish from trophectoderm.
	2 =	Cells of the ICM appear degenerate or necrotic.
	1 =	No ICM cells discernible in any focal plane.
Trophectoderm	3 =	Many small identical cells forming a continuous trophectoderm layer.
	2 =	Fewer larger cells; may not form a completely continuous layer.
	1 =	Sparse cells; may be very large, very flat or appear degenerate.

(Modified for UK NEQAS Embryo Morphology Scheme 2010 from Cutting et al, Elective Single Embryo Transfer: Guidelines for Practice. British Fertility Society and Association of clinical Embryologists. Human Fertility, September 2008; 11(3): 131–146)

Update information

May 2016

In 1 recommendation the evidence has been reviewed and no change made to the recommended action. This recommendation is marked as **[2016].**

Recommendations that are shaded in grey are marked as follows:

- **[new 2013]** if the evidence was reviewed and the recommendation was updated or added in 2013
- **[2013]** if the evidence was reviewed in 2013 but no changes were made to the recommendation
- **[2004, amended 2013]** if the evidence has not been updated and reviewed since 2004, but a small amendment was made to the recommendation in 2013
- **[2004]** if the evidence has not been updated and reviewed since 2004.

See also the original NICE guideline and supporting documents.

ISBN: