



## Complete Summary

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### GUIDELINE TITLE

Fertility: assessment and treatment for people with fertility problems.

### BIBLIOGRAPHIC SOURCE(S)

National Collaborating Centre for Women's and Children's Health. Fertility: assessment and treatment for people with fertility problems. London: RCOG Press; 2004 Feb. 216 p. [1151 references]

### GUIDELINE STATUS

This is the current release of the guideline. This guideline updates the following guidelines previously released by the Royal College of Obstetricians and Gynaecologists:

- Royal College of Obstetricians and Gynaecologists. The initial investigation and management of the infertile couple. London: RCOG Press; 1998 Feb. 82 p. (Evidence-based clinical guidelines; no. 2).
- Royal College of Obstetricians and Gynaecologists. The management of infertility in secondary care. London: RCOG Press; 1998 Feb. 148 p. (Evidence-based clinical guidelines; no. 3). [677 references]
- Royal College of Obstetricians and Gynaecologists. The management of infertility in tertiary care. London: RCOG Press; 2000 Jan. 121 p. (Evidence-based clinical guidelines; no. 6).

## COMPLETE SUMMARY CONTENT

SCOPE  
 METHODOLOGY - including Rating Scheme and Cost Analysis  
 RECOMMENDATIONS  
 EVIDENCE SUPPORTING THE RECOMMENDATIONS  
 BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS  
 QUALIFYING STATEMENTS  
 IMPLEMENTATION OF THE GUIDELINE  
 INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT  
 CATEGORIES  
 IDENTIFYING INFORMATION AND AVAILABILITY  
 DISCLAIMER

## SCOPE

### DISEASE/CONDITION(S)

- Infertility

- Fertility problems

## **GUIDELINE CATEGORY**

Counseling  
Diagnosis  
Evaluation  
Management  
Treatment

## **CLINICAL SPECIALTY**

Family Practice  
Internal Medicine  
Obstetrics and Gynecology

## **INTENDED USERS**

Advanced Practice Nurses  
Health Care Providers  
Nurses  
Patients  
Physicians

## **GUIDELINE OBJECTIVE(S)**

To offer best practice advice on the care of people in the reproductive age group who perceive that they may have problems in conceiving

## **TARGET POPULATION**

Couples in the reproductive age group with fertility problems

**Note:** This guideline does not include the management of people who are outside this definition, such as the initial management of those with sexual dysfunction, couples who are using contraception (for example, where one partner has been sterilised), non-heterosexual couples, or couples outside the reproductive age range.

## **INTERVENTIONS AND PRACTICES CONSIDERED**

### **Diagnostic Investigations**

1. Semen analysis, including volume, liquefaction time, pH, sperm concentration, total sperm number, motility, vitality, white blood cells, and morphology
2. Assessment of ovulation, including serum progesterone and serum gonadotrophins (follicle-stimulating hormone and luteinising hormone)
3. Screening for *Chlamydia trachomatis*
4. Assessment of tubal damage including hysterosalpingography (HSG), hysterosalpingo-contrast-ultrasonography, and laparoscopy and dye
5. Assessment of uterine abnormalities

6. Post-coital testing of cervical mucosa

## **Treatment/Management**

### **General Management Principles**

1. Providing initial advice to people concerned about delays to conception
2. Providing information through couple-centred management
3. Describing psychological effects of fertility problems
4. Providing specialist and generalist care

### **Medical Treatment**

1. Gonadotrophin drugs, including human menopausal gonadotrophin, urinary follicle-stimulating hormone, and recombinant follicle-stimulating hormone
2. Gonadotrophin-releasing hormone agonists
3. Gonadotrophin-releasing hormone antagonists (not recommended)
4. Anti-oestrogens, including clomiphene citrate and tamoxifen
5. Androgens (not recommended)
6. Kinin-enhancing drugs (not recommended)
7. Systemic corticosteroids (not recommended)
8. Antibiotic treatment
9. Metformin
10. Growth hormone (not recommended)
11. Dopamine agonists, including bromocriptine

### **Surgical Treatment**

1. Surgical correction of epididymal blockage
2. Surgical sperm recovery
3. Laparoscopic ovarian drilling
4. Tubal microsurgery
5. Laparoscopic tubal surgery
6. Tubal catheterisation or cannulation
7. Uterine surgery
8. Surgical ablation or resection of endometriosis plus laparoscopic adhesiolysis
9. Laparoscopic cystectomy

### **Assisted Reproduction**

1. Intrauterine insemination
2. In vitro fertilisation treatment
3. Gamete intrafallopian transfer
4. Zygote intrafallopian transfer
5. Intracytoplasmic sperm injection
6. Donor insemination
7. Oocyte donation
8. Cryopreservation in cancer treatment

## **MAJOR OUTCOMES CONSIDERED**

**Primary Outcomes:**

- Live birth
- Patient satisfaction
- Anxiety/depression
- Multiple births
- Fetal abnormalities
- Ectopic pregnancy
- Ovarian hyperstimulation syndrome (OHSS)

**Secondary Outcomes:**

- Clinical pregnancy (confirmed by presence of fetal heart rate)
- Miscarriage
- Cycle cancellation
- Low birth rate
- Perinatal mortality

**Surrogate Outcomes:**

- Tubal patency
- Ovulation
- Fertilisation
- Implantation (number of gestational sacs identified by ultrasound)
- Number of embryos transferred
- Embryo quality
- Improved semen parameters
- Improved sexual function

**Other Outcomes:**

- Cost measures including cost effectiveness and quality-adjusted life years (QALY)

**METHODOLOGY****METHODS USED TO COLLECT/SELECT EVIDENCE**

Hand-searches of Published Literature (Primary Sources)  
Hand-searches of Published Literature (Secondary Sources)  
Searches of Electronic Databases

**DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE****Literature Search Strategy**

The aim of the literature review was to identify and synthesise relevant evidence within the published literature, in order to answer specific clinical questions. Searches were performed using generic and specially developed filters, relevant medical subject heading terms, and free-text terms. Details of all literature

searches are available on application to the National Collaborating Centre for Women's and Children's Health (NCC-WCH).

The National Guideline Clearinghouse database, the Turning Research into Practice database, and the Organising Medical Networked Information service on the Internet were searched for guidelines produced by other development groups. The reference lists in these guidelines were checked against the Guideline Development Group's searches to identify any missing evidence.

Searches were carried out for each topic of interest. The Cochrane Library (up to Issue 3, 2003) was searched to identify systematic reviews (with or without meta-analyses) of randomized controlled (clinical) trials (RCTs) and individual RCTs. The electronic databases MEDLINE (Ovid version for the period January 1966 to October 2003), EMBASE (Ovid version for the period between 1988 to October 2003), the Cumulative Index to Nursing and Allied Health Literature, the British Nursing Index and PsychInfo were also searched, as was the Database of Abstracts and Reviews of Effectiveness.

There was no systematic attempt to search the "grey literature" (conferences, abstracts, theses, and unpublished trials). A preliminary scrutiny of titles and abstracts was undertaken and full papers were obtained if the research question addressed the Guideline Development Group's question relevant to the topic. Following a further review of the full version of the study, articles that did not address the Group's question were excluded. Studies that did not report relevant outcomes were also excluded. Submitted evidence from stakeholders was included where the evidence was relevant to the Group's clinical question and was of equivalent or better quality than the research identified in the literature searches.

The economic evidence presented in this guideline is not a systematic review of all the economic evidence around fertility treatment, but a review of evidence relating to specific aspects of treatment (see below). In addition to the databases listed above, the Health Economic Evaluations Database and the National Health Service (NHS) Economic Evaluations Database were searched for relevant economic studies.

The search strategies were designed to find any economic study related to infertility. Abstracts and database reviews of papers found were reviewed by the health economists and were discarded if they appeared not to contain any cost data relevant to the UK setting or did not relate to the precise topic or question being considered in the algorithm. Relevant references in the bibliographies of reviewed papers were also identified and assessed against standard criteria.

The topic had to focus on the appropriate alternatives (the appropriate clinical question) and preferably be able to be generalised to the England and Wales setting. The review of the evidence included cost-effectiveness studies, cost-consequence studies (cost of present and future costs only) and high quality systematic reviews of the evidence (see below).

## **NUMBER OF SOURCE DOCUMENTS**

Not stated

## **METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE**

Weighting According to a Rating Scheme (Scheme Given)

### **RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE**

#### **Evidence Categories**

**1a:** Evidence obtained from systematic review and meta-analysis of randomised controlled trials.

**1b:** Evidence obtained from at least one randomised controlled trial.

**2a:** Evidence obtained from at least one well-designed controlled study without randomisation.

**2b:** Evidence obtained from at least one other type of well-designed quasi-experimental study.

**3:** Evidence obtained from well-designed nonexperimental descriptive studies, such as comparative studies, correlation studies, or case studies.

**4:** Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities.

### **METHODS USED TO ANALYZE THE EVIDENCE**

Meta-Analysis  
Review of Published Meta-Analyses  
Systematic Review with Evidence Tables

### **DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE**

#### **Outcome Measures**

For this guideline, the management of fertility problems has been assessed against a variety of reproductive and pregnancy outcomes. The justification for using these outcomes is based on their relevance to women and consensus among members of the Guideline Development Group (GDG). These outcomes were also informed by the Cochrane Menstruation Disorders and Subfertility Group. The outcomes were grouped to reflect their importance to women, healthcare professionals, and the health service. Outcomes include those that were felt to be desirable (for example, a live birth) and those unwanted effects of treatment that it would be important to reduce to a minimum (for example, ectopic pregnancy or fetal abnormality). When assessing the effectiveness of a particular treatment, information about the effect of that treatment on one or more primary outcomes was sought. Where such information was not available secondary outcomes were used. If neither primary nor secondary outcomes were available, surrogate outcomes (indirect measures of effectiveness) were considered.

## **Clinical Effectiveness**

For all subject areas, evidence from the study designs least subject to bias was included. Where possible, the highest levels of evidence were used, but all papers were reviewed using established guides. Published systematic reviews or meta-analyses were used where available. For subject areas where neither was available, other appropriate experimental or observational studies were sought.

Identified articles were assessed methodologically and the best available evidence was used to form and support the recommendations. The highest level of evidence was selected for each clinical question. The retrieved evidence was graded according to the evidence-level structure shown in Table 1.1 of the original guideline document and defined above in the "Rating Scheme for the Strength of the Evidence" field.

Each clinical question dictated the highest level of evidence that could be sought. For issues of therapy or treatment the highest possible level of evidence was a meta-analysis of randomised controlled trials (RCTs) or an individual RCT.

For issues of prognosis, a cohort study was the best possible level of evidence. This equates to a grade B recommendation (defined below in the "Rating Scheme for the Strength of the Recommendations" field). However, this should not be interpreted as an inferior grade of recommendation because it represents the highest level of evidence attainable for that type of clinical question.

For diagnostic tests, test evaluation studies examining the performance of the test were used if the efficacy of the test was required, but where an evaluation of the effectiveness of the test in the management and outcome was required, evidence from RCTs or cohort studies was sought.

All retrieved articles were appraised methodologically using established guides. Where appropriate, if a systematic review, meta-analysis, or RCT existed in relation to a topic, studies of a weaker design were excluded.

The evidence was synthesised using qualitative methods. These involved summarising the content of identified papers in the form of evidence tables and agreeing brief statements that accurately reflected the relevant evidence. Quantitative synthesis (meta-analysis) was performed where appropriate. Meta-analyses based on dichotomous outcomes are presented as relative risks with 95% confidence intervals.

For the purposes of this guideline, data are presented as absolute risks, relative risks, or odds ratios where relevant (i.e., in RCTs and cohort studies). Where the data are statistically significant they are also presented as numbers needed to treat (for beneficial outcomes) or numbers need to harm (for adverse effects of treatment) if relevant.

## **METHODS USED TO FORMULATE THE RECOMMENDATIONS**

Expert Consensus (Nominal Group Technique)  
Informal Consensus

## **DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS**

The guideline was developed by a multiprofessional and lay working group (the Guideline Development Group) convened by the National Collaborating Centre for Women's and Children's Health (NCC-WCH). Membership included:

- two consumer representatives
- two gynaecologists
- an obstetrician
- an embryologist
- an andrologist
- a counsellor
- a nurse
- a General Practitioner (GP)
- a public health clinician

Staff from the NCC-WCH provided methodological support for the guideline development process, undertook systematic searches, retrieval, and appraisal of the evidence, and wrote successive drafts of the document.

### **Forming and Grading Recommendations**

The Guideline Development Group (GDG) was presented with summaries (text and evidence tables) of the best available research evidence to answer its questions. Recommendations were based on, and explicitly linked to, the evidence that supported them. Where possible, the Group worked on an informal consensus basis. Formal consensus methods (the nominal group technique) were employed when required (e.g., grading recommendations and agreeing audit criteria).

## **RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS**

### **Grading of Recommendations**

**A:** Directly based on level 1 evidence

**B:** Directly based on level 2 evidence, or extrapolated recommendation from level 1 evidence

**C:** Directly based on level 3 evidence, or extrapolated recommendation from either level 1 or 2 evidence

**D:** Directly based on level 4 evidence, or extrapolated recommendation from either level 1, 2, or 3 evidence

**Good practice point (GPP):** The view of the Guideline Development Group

## **COST ANALYSIS**

### **Aim of the Economic Analysis**

The inclusion of economic evidence in guidelines is a fairly recent phenomenon. The purpose of including economic evidence in a clinical guideline is to allow recommendations to be made not just on the clinical effectiveness of different forms of care, but also on their cost effectiveness. The aim is to produce guidance that uses scarce health service resources efficiently, that is providing the best possible care within resource constraints.

### **Cost Effectiveness of Assisted Reproduction**

The approach to presenting the economic evidence on assisted reproduction was to model the cost effectiveness of assisted reproduction under different assumptions and conditions. There were several reasons for adopting this approach. First, decision analysis is an important step towards understanding the cost effectiveness of different treatment pathways that a couple may be offered. Second, the approach allows for the synthesis of clinical effectiveness evidence, alongside the estimated costs of diagnosis and treatment and the consequences of treatment that relate to the United Kingdom (UK) setting. Third, it clearly shows where gaps exist in the published literature and research evidence.

The models developed in this guideline were based on clinical and cost effectiveness data for assisted reproduction techniques. Since robust trial data on the effectiveness of different options for assisted reproduction were not available, the models used probabilities derived from a combination of sources (see Appendix B of the original guideline document).

Key topics for the economic analysis in the guideline were determined by the Guideline Development Group (GDG) as the process of developing the guideline and reviewing the evidence evolved. The key economic questions to be considered in the guideline were:

- the cost effectiveness of in vitro fertilisation (IVF) and other forms of assisted reproduction
- the cost effectiveness of urinary versus recombinant gonadotrophins in IVF treatment
- the cost effectiveness of stimulated and unstimulated intrauterine insemination (IUI)
- a review of the current literature on the cost impact of reducing the number of embryos transferred during IVF treatment.

### **Valuing the Cost of Assisted Reproduction**

Alongside the review of the research evidence, data were gathered from other UK sources to obtain estimates of the costs for specific cost elements in each model. Historically, many of the services offered as part of an infertility diagnosis and treatment package have not been provided by the National Health Service (NHS) but rather by private clinics. However, the market prices of these services were assumed to be likely to be close to "opportunity costs" for the services. The sources of data are discussed in Appendix B of the original guideline document.

Although the value of the resources used in assisted reproduction is an important question, the overall cost effectiveness of assisted reproduction will also be determined by important differences in clinical effectiveness of assisted

reproduction techniques. The clinical and cost data that were available were not appropriate for making detailed forecasts of future expenditure on assisted reproduction. This would require a detailed costing exercise based on current and future levels of demand for the service, current capacity and future resources available. However, the data did indicate the magnitudes of costs that would be likely to be needed if specific policies were adopted. This analysis also indicates whether specific parameters (such as, the live birth rate, the number of cycles offered and the rate at which couples choose to discontinue treatment) are more important than others, and where future research effort should be directed.

### **Representation of the Consequences of Assisted Reproduction: Quality-Adjusted life years (QALY)**

Ethical and moral arguments relating to the value of live births resulting from assisted reproduction are not addressed in the economic analysis because they go beyond the issues that can be addressed in a clinical guideline. The primary outcome considered in the economic models is a live birth and not a measure of life years. There is an important debate about whether the outputs of assisted reproduction can be incorporated into a measure that can be compared with other uses of the same resources. It is not logical to try to derive a QALY measure from live births arising from IVF. It has been argued that:

"QALYs are intended to capture improvements in health among patients. They are not appropriate for placing a value on additional lives. Additional lives are not improvements in health; preventing someone's death is not the same as creating their life and it is not possible to improve the quality of life of someone who has not been conceived by conceiving them."

Another review stated that:

"Cost-utility analysis has little relevance to the management of infertility where lives are produced and not saved."

This is a valid argument, so QALYs cannot be reported in the context of assisted reproduction unless they are related only to the couple seeking treatment.

## **METHOD OF GUIDELINE VALIDATION**

External Peer Review  
Internal Peer Review

## **DESCRIPTION OF METHOD OF GUIDELINE VALIDATION**

The guideline has been developed in accordance with the National Institute for Clinical Excellence (NICE) guideline development process. This has included the opportunity for registered stakeholders to comment on the scope of the guideline, the first draft of the full and summary guidelines, and the second draft of all versions of the guideline. In addition the drafts were reviewed by an independent Guideline Review Panel established by NICE and by the NICE Executive and the Patient Involvement Unit for NICE.

The comments made by the stakeholders, peer reviewers, and the Guideline Review Panel were collated and presented anonymously for consideration by the Guideline Development Group. All comments were considered systematically by the Guideline Development Group, and the resulting actions and responses were recorded.

## RECOMMENDATIONS

### MAJOR RECOMMENDATIONS

Evidence categories (1a-4) and recommendation grades (A-D) are defined at the end of the "Major Recommendations" field.

In addition to evidence-based recommendations, the guideline development group (GDG) also identifies good practice points (GPP).

#### **Initial Advice to People Concerned about Delays in Conception**

##### ***Natural conception***

**D** - People who are concerned about their fertility should be informed that about 84% of couples in the general population will conceive within 1 year if 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 92%).

**C** - People who are concerned about their fertility should be informed that female fertility declines with age, but that the effect of age on male fertility is less clear. With regular unprotected sexual intercourse, 94% of fertile women aged 35 years, and 77% of those aged 38 years, will conceive after 3 years of trying.

##### ***Frequency and timing of sexual intercourse***

**C** - People who are concerned about their fertility should be informed that sexual intercourse every 2 to 3 days optimises the chance of pregnancy. Timing intercourse to coincide with ovulation causes stress and is not recommended.

##### ***Alcohol***

**D** - Women who are trying to become pregnant should be informed that drinking no more than one or two units of alcohol once or twice per week and avoiding episodes of intoxication reduces the risk of harming a developing fetus.

**GPP** - Men should be informed that alcohol consumption within the Department of Health's recommendations of three to four units per day for men is unlikely to affect their fertility.

**B** - Men should be informed that excessive alcohol intake is detrimental to semen quality.

### ***Smoking***

**B** - Women who smoke should be informed that this is likely to reduce their fertility.

**A** - Women who smoke should be offered referral to a smoking cessation programme to support their efforts in stopping smoking.

**B** - Women should be informed that passive smoking is likely to affect their chance of conceiving.

**GPP** - 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.

### ***Caffeinated beverages***

**B** - 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.

### ***Body weight***

**B** - Women who have a body mass index of more than 29 should be informed that they are likely to take longer to conceive.

**B** - Women who have a body mass index of more than 29 and who are not ovulating should be informed that losing weight is likely to increase their chance of conception.

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

**C** - Men who have a body mass index of more than 29 should be informed that they are likely to have reduced fertility.

**B** - Women who have a body mass index 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.

### ***Tight underwear for men***

**B** - 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.

### ***Occupation***

**B** - 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.

### ***Prescribed, over-the-counter and recreational drug use***

**B** - 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.

### ***Complementary therapy***

**GPP** - 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.

### ***Folic acid supplementation***

**A** - 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 antiepileptic medication, a higher dose of 5 mg per day is recommended.

### ***Susceptibility to rubella***

**D** - Women who are concerned about their fertility should be offered rubella susceptibility screening so that those who are susceptible to rubella can be offered rubella vaccination. Women who are susceptible to rubella should be offered rubella vaccination and advised not to become pregnant for at least 1 month following vaccination.

### ***Cervical cancer screening***

**GPP** - 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.

## **Defining Infertility, Assessment and Referral**

### ***Defining infertility***

**D** - Infertility should be defined as failure to conceive after regular unprotected sexual intercourse for 2 years in the absence of known reproductive pathology.

### ***Assessment and referral***

**GPP** - 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.

**GPP** - The environment in which investigation of fertility problems takes place should enable people to discuss sensitive issues such as sexual abuse.

**GPP** - People who have not conceived after 1 year of regular unprotected sexual intercourse should be offered further clinical investigation including semen analysis and/or assessment of ovulation.

**GPP** - Where there is a history of predisposing factors (such as amenorrhoea, oligomenorrhoea, pelvic inflammatory disease, or undescended testes), or where a woman is aged 35 years or over, earlier investigation should be offered.

**GPP** - Where there is a known reason for infertility (such as prior treatment for cancer), early specialist referral should be offered.

**GPP** - People who are concerned about their fertility and who are known to have chronic viral infections such as hepatitis B, hepatitis C, or human immunodeficiency virus (HIV) should be referred to centres that have appropriate expertise and facilities to provide safe risk-reduction investigation and treatment.

## **Principles of Care**

### ***Information giving and couple-centred management***

**C** - Couples who experience problems in conceiving should be seen together because both partners are affected by decisions surrounding investigation and treatment.

**C** - 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.

**GPP** - 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.

### ***Psychological effects of fertility problems***

**C** - Couples 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 fertility problems.

**GPP** - People who experience fertility problems should be informed that they may find it helpful to contact a fertility support group.

**C** - 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.

**GPP** - Counselling should be offered before, during, and after investigation and treatment, irrespective of the outcome of these procedures.

**GPP** - Counselling should be provided by someone who is not directly involved in the management of the couple's fertility problems.

### ***Specialist and generalist care***

**D** - 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 patient satisfaction.

## **Investigation of Fertility Problems and Management Strategies**

### ***Semen analysis***

**GPP** - The results of semen analysis conducted as part of an initial assessment should be compared to the following World Health Organization reference values:

- Volume: 2.0 ml or more
- Liquefaction time: within 60 minutes
- pH: 7.2 or more
- Sperm concentration: 20 million spermatozoa per mL or more
- Total sperm number: 40 million spermatozoa per ejaculate or more
- Motility: 50% or more motile (grades a\* and b\*\*) or 25% or more with progressive motility (grade a) within 60 minutes of ejaculation

\* Grade a: rapid progressive motility (sperm moving swiftly, usually in a straight line).

\*\* Grade b: slow or sluggish progressive motility (sperm may be less linear in their progression).

- Vitality: 75% or more live
- White blood cells: fewer than 1 million per mL
- Morphology: 15% or 30%\*\*\*

\*\*\* Currently being reassessed by the World Health Organization. In the interim, the proportion of normal forms accepted by laboratories in the United Kingdom (UK) is either the earlier World Health Organization lower limit of 30% or 15% based on strict morphological criteria.

**GPP** - Screening for antisperm antibodies should not be offered because there is no evidence of effective treatment to improve fertility.

**B** - If the result of the first semen analysis is abnormal, a repeat confirmatory test should be offered.

**GPP** - 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.

### **Assessing ovulation**

**B** - 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.

**B** - Women with regular menstrual cycles and more than 1 year's infertility can be offered a blood test to measure serum progesterone in the midluteal phase of their cycle (day 21 of a 28-day cycle) to confirm ovulation.

**GPP** - Women with prolonged irregular menstrual cycles should be offered a blood test to measure serum progesterone. Depending on the timing of menstrual periods, this test may need to be conducted later in the cycle (for example day 28 of a 35-day cycle) and repeated weekly thereafter until the next menstrual cycle starts.

**B** - The use of basal body temperature charts to confirm ovulation does not reliably predict ovulation and is not recommended.

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

**C** - 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.

**C** - Tests of ovarian reserve currently have limited sensitivity and specificity in predicting fertility. However, women who have high levels of gonadotrophins should be informed that they are likely to have reduced fertility.

**C** - Women should be informed that the value of assessing ovarian reserve using Inhibin B is uncertain and is therefore not recommended.

**C** - 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.

**B** - 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.

### **Screening for *Chlamydia trachomatis***

**B** - Before undergoing uterine instrumentation, women should be offered screening for *Chlamydia trachomatis* using an appropriately sensitive technique.

**C** - 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.

**GPP** - Prophylactic antibiotics should be considered before uterine instrumentation if screening has not been carried out.

### ***Assessing tubal damage***

**B** - 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.

**A** - 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.

**B** - 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.

### ***Assessing uterine abnormalities***

**B** - 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.

### ***Postcoital testing of cervical mucus***

**A** - The routine use of postcoital testing of cervical mucus in the investigation of fertility problems is not recommended because it has no predictive value on pregnancy rate.

## **Medical and Surgical Management of Male Factor Fertility Problems**

### ***Medical management***

**B** - Men with hypogonadotropic hypogonadism should be offered gonadotrophin drugs, because these are effective in improving fertility.

**A** - Men with idiopathic semen abnormalities should not be offered antioestrogens, gonadotrophins, androgens, bromocriptine, or kinin-enhancing drugs, because they have not been shown to be effective.

**A** - Men should be informed that the significance of antisperm antibodies is unclear and the effectiveness of systemic corticosteroids is uncertain.

**A** - Men with leukocytes 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.

### ***Surgical management***

**C** - 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 in vitro fertilisation.

**A** - Men should not be offered surgery for varicoceles as a form of fertility treatment because it does not improve pregnancy rates.

### ***Management of ejaculatory failure***

**C** - 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.

### **Ovulation Induction**

#### ***Antioestrogens***

**A** - Women with World Health Organization Group II ovulation disorders (hypothalamic pituitary dysfunction) such as polycystic ovary syndrome should be offered treatment with clomiphene citrate (or tamoxifen) as the first line of treatment for up to 12 months because it is likely to induce ovulation.

**B** - Women should be informed of the risk of multiple pregnancies associated with both clomiphene citrate and tamoxifen.

**A** - Women with unexplained fertility problems should be informed that clomiphene citrate treatment increases the chance of pregnancy, but that this needs to be balanced by the possible risks of treatment, especially multiple pregnancy.

**GPP** - Women undergoing treatment with clomiphene citrate should be offered ultrasound monitoring during at least the first cycle of treatment to ensure that they receive a dose that minimises the risk of multiple pregnancy.

#### ***Metformin***

**A** - Anovulatory women with polycystic ovary syndrome who have not responded to clomiphene citrate and who have a body mass index of more than 25 should be offered metformin combined with clomiphene citrate because this increases ovulation and pregnancy rates.

**GPP** - Women prescribed metformin should be informed of the side effects associated with its use (such as nausea, vomiting, and other gastrointestinal disturbances).

**\*Note:** Metformin is not currently licensed for the treatment of ovulatory disorders in the United Kingdom.

### ***Ovarian drilling***

**A** - Women with polycystic ovary syndrome who have not responded to clomiphene citrate should be offered laparoscopic ovarian drilling because it is as effective as gonadotrophin treatment and is not associated with an increased risk of multiple pregnancy.

### ***Gonadotrophin use in ovulation induction therapy for ovulatory disorders***

**A** - Women with World Health Organization Group II ovulation disorders such as polycystic ovary syndrome who do not ovulate with clomiphene citrate (or tamoxifen) can be offered treatment with gonadotrophins. Human menopausal gonadotrophin, urinary follicle-stimulating hormone, and recombinant follicle-stimulating hormone are equally effective in achieving pregnancy and consideration should be given to minimising cost when prescribing.

**A** - Women with World Health Organization Group II ovulation disorders such as polycystic ovary syndrome who ovulate with clomiphene citrate but have not become pregnant after 6 months of treatment should be offered clomiphene citrate-stimulated intrauterine insemination.

### ***Gonadotrophin use during in vitro fertilisation treatment***

**A** - Human menopausal gonadotrophin, urinary follicle-stimulating hormone, and recombinant follicle-stimulating hormone are equally effective in achieving a live birth when used following pituitary down-regulation as part of in vitro fertilisation treatment. Consideration should be given to minimising cost when prescribing.

### ***Gonadotrophin-releasing hormone analogues in ovulation induction therapy***

**A** - 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.

### ***Gonadotrophin-releasing hormone analogues during in vitro fertilisation treatment***

**A** - For pituitary down-regulation as part of in vitro fertilisation treatment, using gonadotrophin-releasing hormone agonist in addition to gonadotrophin stimulation facilitates cycle control and results in higher pregnancy rates than the use of gonadotrophins alone. The routine use of gonadotrophin-releasing hormone agonist in long protocols during in vitro fertilisation is therefore recommended.

**A** - The use of gonadotrophin-releasing hormone antagonists is associated with reduced pregnancy rates and is therefore not recommended outside a research context.

### ***Growth hormone as an adjunct to ovulation induction therapy***

**A** – 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 clomiphene citrate is not recommended because it does not improve pregnancy rates.

### ***Pulsatile gonadotrophin-releasing hormone***

**B** – Women with World Health Organization Group I ovulation disorders (hypothalamic pituitary failure, characterized by hypothalamic amenorrhoea or hypogonadotropic hypogonadism) should be offered pulsatile administration of gonadotrophin-releasing hormone or gonadotrophins with luteinising hormone activity because these are effective in inducing ovulation.

**A** – The effectiveness of pulsatile gonadotrophin-releasing hormone in women with clomiphene citrate-resistant polycystic ovary syndrome is uncertain and is therefore not recommended outside a research context.

### ***Dopamine agonists***

**A** – 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.

### ***Monitoring ovulation induction during gonadotrophin therapy***

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

**C** – Ovarian ultrasound monitoring to measure follicular size and number should be an integral part of patient management during gonadotrophin therapy to reduce the risk of multiple pregnancy and ovarian hyperstimulation.

### ***Other risks and side effects associated with ovulation induction agents***

**C** – Women who are offered ovulation induction should be informed that a possible association between ovulation induction therapy and ovarian cancer remains uncertain. Practitioners should confine the use of ovulation induction agents to the lowest effective dose and duration of use.

### ***Tubal and Uterine Surgery***

#### ***Tubal microsurgery and laparoscopic tubal surgery***

**D** – 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.

### ***Tubal catheterisation or cannulation***

**B** – 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.

### ***Uterine surgery***

**C** – 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.

## **Medical and Surgical Management of Endometriosis**

### ***Medical management (ovarian suppression)***

**A** – Medical treatment of minimal and mild endometriosis does not enhance fertility in subfertile women and should not be offered.

### ***Surgical ablation***

**A** – 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.

**A** – Women with ovarian endometriomas should be offered laparoscopic cystectomy because this improves the chance of pregnancy.

**B** – Women with moderate or severe endometriosis should be offered surgical treatment because it improves the chance of pregnancy.

**A** – Postoperative medical treatment does not improve pregnancy rates in women with moderate to severe endometriosis and is not recommended.

### **Intrauterine Insemination**

**A** – Couples with mild male factor fertility problems, unexplained fertility problems, or minimal to mild endometriosis should be offered up to six cycles of intrauterine insemination because this increases the chance of pregnancy.

**A** – Where intrauterine insemination is used to manage male factor fertility problems, ovarian stimulation should not be offered because it is no more clinically effective than unstimulated intrauterine insemination and it carries a risk of multiple pregnancy.

**A** – Where intrauterine insemination is used to manage unexplained fertility problems, both stimulated and unstimulated intrauterine insemination are more effective than no treatment. However, ovarian stimulation should not be offered, even though it is associated with higher pregnancy rates than unstimulated intrauterine insemination, because it carries a risk of multiple pregnancy.

**A** – Where intrauterine insemination is used to manage minimal or mild endometriosis, couples should be informed that ovarian stimulation increases pregnancy rates compared with no treatment, but that the effectiveness of unstimulated intrauterine insemination is uncertain.

**A** – Where intrauterine insemination is undertaken, single rather than double insemination should be offered.

**A** – Where intrauterine insemination is used to manage unexplained fertility problems, fallopian sperm perfusion for insemination (a large-volume solution, 4 mL) should be offered because it improves pregnancy rates compared with standard insemination techniques.

## **Factors Affecting the Outcome of In Vitro Fertilisation Treatment**

### ***Surgery for hydrosalpinges before in vitro fertilisation treatment***

**A** – Women with hydrosalpinges should be offered salpingectomy, preferably by laparoscopy, before in vitro fertilisation treatment because this improves the chance of a live birth.

### ***Female age***

**C** – Women should be informed that the chance of a live birth following in vitro fertilisation treatment varies with female age and that the optimal female age range for in vitro fertilisation treatment is 23–39 years. Chances of a live birth per treatment cycle are:

- greater than 20% for women aged 23–35 years
- 15% for women aged 36–38 years
- 10% for women aged 39 years
- 6% for women aged 40 years or older.

The effectiveness of in vitro fertilisation treatment in women younger than 23 years is uncertain because very few women in this age range have in vitro fertilisation treatment.

### ***Number of embryos to be transferred and multiple pregnancy***

**C** – Couples should be informed that the chance of multiple pregnancy following in vitro fertilisation treatment depends on the number of embryos transferred per cycle of treatment. To balance the chance of a live birth and the risk of multiple pregnancy and its consequences, no more than two embryos should be transferred during any one cycle of in vitro fertilisation treatment.

### ***Number of previous treatment cycles***

**C** – Couples should be informed that the chance of a live birth following in vitro fertilisation treatment is consistent for the first three cycles of treatment, but that the effectiveness after three cycles is less certain.

### ***Pregnancy history***

**C** – Women should be informed that in vitro fertilization treatment is more effective in women who have previously been pregnant and/or had a live birth.

### ***Alcohol, smoking and caffeine consumption***

**C** – Couples should be informed that the consumption of more than one unit of alcohol per day reduces the effectiveness of assisted reproduction procedures, including in vitro fertilisation treatment.

**C** – Couples should be informed that maternal and paternal smoking can adversely affect the success rates of assisted reproduction procedures, including in vitro fertilization treatment.

**C** – Couples should be informed that caffeine consumption has adverse effects on the success rates of assisted reproduction procedures, including in vitro fertilisation treatment.

### ***Body weight***

**B** – Women should be informed that female body mass index should ideally be in the range 19–30 before commencing assisted reproduction, and that a female body mass index outside this range is likely to reduce the success of assisted reproduction procedures.

### ***Clinical effectiveness and referral for in vitro fertilisation treatment***

**GPP** - Couples in which the woman is aged 23–39 years at the time of treatment and who have an identified cause for their fertility problems (such as azoospermia or bilateral tubal occlusion) or who have infertility of at least 3 years' duration should be offered up to three stimulated cycles of in vitro fertilisation treatment.

**GPP** - Embryos not transferred during a stimulated in vitro fertilisation treatment cycle may be suitable for freezing. If two or more embryos are frozen, then they should be transferred before the next stimulated treatment cycle because this will minimise ovulation induction and egg collection, both of which carry risks for the woman and use more resources.

### ***Gamete intrafallopian transfer and zygote intrafallopian transfer***

**A** – There is insufficient evidence to recommend the use of gamete intrafallopian transfer or zygote intrafallopian transfer in preference to in vitro fertilisation in couples with unexplained fertility problems or male factor fertility problems.

## **Procedures Used during In Vitro Fertilisation Treatment**

### ***Medical assessment and screening***

**B** - People undergoing in vitro fertilisation treatment should be offered screening for HIV, hepatitis B virus, and hepatitis C virus; people found to test positive should be managed and counselled appropriately.

### ***Management of couples with viral infections***

**D** - In considering the decision to provide fertility treatment for couples with HIV, hepatitis B, or hepatitis C infections, the implications of these infections for potential children should be taken into account.

### ***Ovulation induction during in vitro fertilisation treatment***

**A** - Natural cycle in vitro fertilisation has lower pregnancy rates per cycle of treatment than clomiphene citrate-stimulated and gonadotrophin-stimulated in vitro fertilisation and is therefore not recommended, except in the rare circumstances where gonadotrophin use is contraindicated.

**B** - For women who have regular ovulatory cycles, the likelihood of a live birth after replacement of frozen-thawed embryos is similar whether the embryos are replaced during natural or stimulated cycles.

**A** - The use of adjuvant growth hormone with gonadotrophins during in vitro fertilisation cycles does not improve pregnancy rates and is therefore not recommended.

### ***Oocyte maturation – human chorionic gonadotrophin***

**A** - Couples should be informed that, in effecting oocyte maturation, recombinant human chorionic gonadotrophin achieves similar results to urinary human chorionic gonadotrophin in terms of pregnancy rates and incidence of ovarian hyperstimulation syndrome. Consideration should be given to minimising cost when prescribing.

### ***Monitoring of stimulated cycles***

**C** - Ultrasound monitoring of ovarian response should form an integral part of the in vitro fertilisation treatment cycle.

**A** - Monitoring oestrogen levels during ovulation induction as part of in vitro fertilisation treatment is not recommended as a means of improving in vitro fertilisation treatment success rates because it does not give additional information with regard to live birth rates or pregnancy rates compared with ultrasound monitoring.

### ***Ovarian hyperstimulation syndrome***

**GPP** - Clinics providing ovarian stimulation with gonadotrophins should have protocols in place for preventing, diagnosing, and managing ovarian hyperstimulation syndrome.

**A** - Women who have a significant risk of developing ovarian hyperstimulation syndrome should not be offered oocyte maturation (or luteal support) using human chorionic gonadotrophin.

### ***Oocyte retrieval***

**A** - Women undergoing transvaginal retrieval of oocytes should be offered conscious sedation because it is a safe and acceptable method of providing analgesia.

**D** - The safe practice of administering sedative drugs published by the Academy of Medical Royal Colleges should be followed.

**A** - Women who have developed at least three 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.

### ***Assisted hatching***

**A** - Assisted hatching is not recommended because it has not been shown to improve pregnancy rates.

### ***Embryo transfer techniques***

**A** - Women undergoing in vitro fertilisation treatment should be offered ultrasound-guided embryo transfer because this improves pregnancy rates.

**B** - Embryo transfers on day 2 or 3 and day 5 or 6 appear to be equally effective in terms of increased pregnancy and live birth rates per cycle started.

**B** - 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.

**A** - Women should be informed that bed rest of more than 20 minutes' duration following embryo transfer does not improve the outcome of in vitro fertilisation treatment.

### ***Luteal support***

**A** - Women who are undergoing in vitro fertilization treatment using gonadotrophin-releasing hormone agonists for pituitary down-regulation should be informed that luteal support using human chorionic gonadotrophin or progesterone improves pregnancy rates.

**A** - The routine use of human chorionic gonadotrophin for luteal support is not recommended because of the increased likelihood of ovarian hyperstimulation syndrome.

### ***Intracytoplasmic Sperm Injection***

### ***Indications for intracytoplasmic sperm injection***

**B** - The recognised indications for treatment by intracytoplasmic sperm injection include:

- Severe deficits in semen quality
- Obstructive azoospermia
- Non-obstructive azoospermia.

In addition, treatment by intracytoplasmic sperm injection should be considered for couples in whom a previous in vitro fertilisation treatment cycle has resulted in failed or very poor fertilisation.

### ***Genetic issues and counselling***

**C** - Before considering treatment by intracytoplasmic sperm injection, couples should undergo appropriate investigations, both to establish a diagnosis and to enable informed discussion about the implications of treatment.

**B** - Before treatment by intracytoplasmic sperm injection, consideration should be given to relevant genetic issues.

**B** - Where a specific genetic defect associated with male infertility is known or suspected, couples should be offered appropriate genetic counselling and testing.

**B** - Where the indication for intracytoplasmic sperm injection is a severe deficit of semen quality or non-obstructive azoospermia, the man's karyotype should be established.

**GPP** - Men who are undergoing karyotype testing should be offered genetic counselling regarding the genetic abnormalities that may be detected.

**C** - Testing for Y chromosome microdeletions should not be regarded as a routine investigation before intracytoplasmic sperm injection. 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.

### ***Intracytoplasmic sperm injection versus in vitro fertilisation***

**A** - Couples should be informed that intracytoplasmic sperm injection improves fertilisation rates compared to in vitro fertilisation alone, but once fertilisation is achieved the pregnancy rate is no better than with in vitro fertilisation.

### ***Sperm recovery***

**C** - Surgical sperm recovery before intracytoplasmic sperm injection may be performed using several different techniques depending on the pathology and wishes of the patient. In all cases, facilities for cryopreservation of spermatozoa should be available.

## **Donor Insemination**

### ***Indications for donor insemination***

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

- Obstructive azoospermia
- Non-obstructive azoospermia
- Infectious disease in the male partner (such as HIV)
- Severe rhesus isoimmunisation
- Severe deficits in semen quality in couples who do not wish to undergo intracytoplasmic sperm injection

Donor insemination should also be considered in certain cases where there is a high risk of transmitting a genetic disorder to the offspring.

### ***Information and counselling***

**C** - Couples should be offered information about the relative merits of intracytoplasmic sperm injection and donor insemination in a context that allows equal access to both treatment options.

**C** - 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.

### ***Screening of sperm donors***

**C** - Units undertaking semen donor recruitment and the cryopreservation of donor spermatozoa for treatment purposes should follow the current guidelines issued by the British Andrology Society describing the selection and screening of donors.

**GPP** - All potential semen donors should be offered counseling 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.

### ***Assessment of female partner***

**C** - Before starting treatment by donor insemination 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.

**GPP** - Women with no risk factors in their history should be offered tubal assessment after three cycles if treatment has been unsuccessful.

### ***Intrauterine insemination versus intracervical insemination***

**A** - Couples using donor sperm should be offered intrauterine insemination in preference to intracervical insemination because it improves pregnancy rates.

### ***Unstimulated versus stimulated donor insemination***

**GPP** - Women who are ovulating regularly should be offered a minimum of six cycles of donor insemination without ovarian stimulation to reduce the risk of multiple pregnancy and its consequences.

### ***Timing of donor insemination***

**C** - Couples should be informed that timing of insemination using either urinary luteinising hormone or basal body temperature changes is equally effective in donor cycles. However, using urinary luteinising hormone detection reduces the number of clinic visits per cycle.

### ***Maximum number of cycles***

**GPP** - Couples should be offered other treatment options after six unsuccessful cycles of donor insemination.

## **Oocyte Donation**

### ***Indications for oocyte donation***

**C** - 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 in vitro fertilisation 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.

### ***Screening of oocyte donors***

**D** - Before donation is undertaken, oocyte donors should be screened for both infectious and genetic diseases in accordance with guidance issued by the Human Fertilisation and Embryology Authority.

### ***Oocyte donation and egg sharing***

**C** - Oocyte donors should be offered information regarding the potential risks of ovarian stimulation and oocyte collection. The section above titled "Other risks and side effects associated with ovulation induction agents" refers to risks and side effects associated with ovarian stimulation.

**GPP** - 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.

**GPP** - All people considering participation in an egg-sharing scheme should be counselled about its particular implications.

### **Applications of Cryopreservation in Cancer Treatment**

**D** - Before commencing chemotherapy or radiotherapy likely to affect fertility, or management of post-treatment fertility problems, the procedures recommended by the Royal College of Physicians and the Royal College of Radiologists should be followed.

**B** - Men and adolescent boys preparing for medical treatment that is likely to make them infertile should be offered semen cryostorage because the effectiveness of this procedure has been established.

**C** - Local protocols should exist to ensure that health professionals are aware of the value of semen cryostorage in these circumstances, so that they deal with the situation sensitively and effectively.

**C** - Women preparing for medical treatment that is likely to make them infertile should be offered oocyte or embryo cryostorage as appropriate if they are well enough to undergo ovarian stimulation and egg collection, provided that this will not worsen their condition and that sufficient time is available.

**D** - Women preparing for medical treatment that is likely to make them infertile should be informed that oocyte cryostorage has very limited success, and that cryopreservation of ovarian tissue is still in an early stage of development.

**GPP** - People preparing for medical treatment that is likely to make them infertile should be offered counselling from someone who is independent of the treatment unit to help them cope with the stress and the potential physical and psychological implications for themselves, their partners, and any potential children resulting from cryostorage of gametes and/or embryos.

**GPP** - Where cryostorage of gametes and/or embryos is to be undertaken because of medical treatment that is likely to make people infertile, this should occur before such treatment begins.

### **Follow-up of Children Born as a Result of Assisted Reproduction**

**C** - Couples contemplating assisted reproduction should be given up-to-date information about the health of children born as a result of assisted reproduction. Current research is broadly reassuring about the health and welfare of children born as a result of assisted reproduction.

### **Definitions**

#### **Evidence Categories**

**1a:** Evidence obtained from systematic review and meta-analysis of randomised controlled trials

**1b:** Evidence obtained from at least one randomised controlled trial

**2a:** Evidence obtained from at least one well-designed controlled study without randomisation

**2b:** Evidence obtained from at least one other type of well-designed quasi-experimental study.

**3:** Evidence obtained from well-designed nonexperimental descriptive studies, such as comparative studies, correlation studies, or case studies

**4:** Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities

### **Grading of Recommendations**

**A:** Directly based on level 1 evidence

**B:** Directly based on level 2 evidence, or extrapolated recommendation from level 1 evidence

**C:** Directly based on level 3 evidence, or extrapolated recommendation from either level 1 or level 2 evidence

**D:** Directly based on level 4 evidence, or extrapolated recommendation from either level 1, 2, or 3 evidence

**Good practice point (GPP):** The view of the Guideline Development Group

### **CLINICAL ALGORITHM(S)**

Clinical algorithms are provided for the assessment and treatment for people with fertility problems, clinical investigation of fertility problems and management strategies, and management options associated with in vitro fertilisation treatment and other forms of assisted reproduction.

## **EVIDENCE SUPPORTING THE RECOMMENDATIONS**

### **TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS**

The type of supporting evidence is identified and graded for each recommendation (see "Major Recommendations").

## **BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS**

### **POTENTIAL BENEFITS**

Appropriate assessment and treatment of fertility problems

## POTENTIAL HARMS

- Women who are offered ovulation induction should be informed that a possible association between ovulation induction therapy and ovarian cancer remains uncertain. Practitioners should confine the use of ovulation induction agents to the lowest effective dose and duration of use.
- 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.
- There is a risk of multiple pregnancies associated with both clomiphene and tamoxifen. Multiple gestations are high-risk pregnancies associated with higher obstetric complications, perinatal, neonatal and infant mortality, as well as significant financial and psychological consequences. However, assisted reproduction multiple pregnancies do not appear to be at any more risk of poor obstetric and neonatal outcomes than those conceived spontaneously. Recent surveys have suggested that multiple pregnancies may not be viewed as an adverse outcome by women with fertility problems.
- The theoretical risk of transmitting prion disease, however unlikely, must always be considered when medicinal products are derived from or contain materials of human or bovine origin. In the case of gonadotrophins, such theoretical risks could arise from the human source material used to manufacture urinary-derived products or from bovine reagents used in the manufacture of recombinant products. However, there is no evidence of transmission of prion disease by any gonadotrophin.
- Gonadotrophins can cause symptoms of the menopause such as hot flushes.
- Metformin has side effects, which can include nausea, vomiting and other digestive symptoms.

## QUALIFYING STATEMENTS

### QUALIFYING STATEMENTS

- The guideline does not address primary prevention of fertility or the management of pregnancies resulting from fertility treatment (for example, the management of multiple births). It is also beyond the scope of this guideline to address the effective management and treatment of conditions or comorbidities that are not directly related to the treatment of subfertility, such as endometriosis or sexual dysfunction.
- Infertility is defined as failure to conceive after frequent unprotected sexual intercourse for one to two years in couples in the reproductive age group. This guideline does not include the management of people who are outside this definition, such as the initial management of sexual dysfunction, couples who are using contraception (for example, where one partner has been sterilised), non-heterosexual couples, or couples outside the reproductive age range. If the problem persists despite appropriate treatment then their management is within the remit of the guideline. Embryo donation and surrogacy are outside the remit.
- The guideline does not include preimplantation genetic diagnosis.
- The guideline does not address laboratory standards or service configuration that may impact on the quality of care. It also does not include assessment of social criteria that might be relevant to access for fertility services funded by

the National Health Service for example whether there are any existing children in the family.

## IMPLEMENTATION OF THE GUIDELINE

### DESCRIPTION OF IMPLEMENTATION STRATEGY

#### Implementation in the National Health Service

##### **Resource implications**

Information on the cost impact of this guideline is available on the National Institute for Clinical Excellence (NICE) website and includes a template for local health communities to use (<http://www.nice.org.uk/page.aspx?o=202212>). In light of this information, local health communities should review their existing practice for assessment and treatment for people with fertility problems against this guideline as they develop their Local Delivery Plans. The review should consider the resources required to implement the recommendations, the people and processes involved, and the timeline over which full implementation is envisaged. It is in the interests of people with fertility problems and their partners that the implementation timeline is as rapid as possible.

##### **In general**

Relevant local clinical guidelines, care pathways, and protocols should be reviewed in the light of this guidance and revised accordingly. The following guidance is referred to in the recommendations of the original guideline document.

Academy of Medical Royal Colleges (2001) Implementing and ensuring safe sedation for healthcare procedures in adults: report of an Intercollegiate Working Party chaired by the Royal College of Anaesthetists (see [www.aomrc.org.uk](http://www.aomrc.org.uk)).

British Andrology Society (1999). British Andrology Society guidelines for the screening of semen donors for donor insemination. *Human Reproduction* 14, 1823–26 (see [www.britishandrology.org.uk](http://www.britishandrology.org.uk)).

Human Fertilisation and Embryology Authority (2004). Code of Practice, 6th edition (see [www.hfea.gov.uk](http://www.hfea.gov.uk)).

Royal College of Physicians and Royal College of Radiologists (1998). Management of gonadal toxicity resulting from the treatment of adult cancer: report of a working party of the Joint Council for Clinical Oncology. Joint Council for Clinical Oncology (see [www.rcplondon.ac.uk](http://www.rcplondon.ac.uk)).

##### **Audit**

Suggested audit criteria are listed in the original guideline document. These can be used as the basis for local clinical audit, at the discretion of those in practice.

#### Key Priorities for Implementation

The following recommendations have been identified as priorities for implementation.

### **Screening for *Chlamydia trachomatis***

- Before undergoing uterine instrumentation women should be offered screening for *Chlamydia trachomatis* using an appropriately sensitive technique.

### **Assessing tubal damage**

- 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.

### **Intrauterine insemination**

- Couples with mild male factor fertility problems, unexplained fertility problems, or minimal to mild endometriosis should be offered up to six cycles of intrauterine insemination because this increases the chance of pregnancy.

### **In vitro fertilisation treatment**

- Couples in which the woman is aged 23–39 years at the time of treatment and who have an identified cause for their fertility problems (such as azoospermia or bilateral tubal occlusion) or who have infertility of at least 3 years' duration should be offered up to three stimulated cycles of in vitro fertilization treatment.
- Human menopausal gonadotrophin, urinary follicle-stimulating hormone, and recombinant follicle-stimulating hormone are equally effective in achieving a live birth when used following pituitary down-regulation as part of in vitro fertilization treatment. Consideration should be given to minimizing cost when prescribing.
- Couples should be informed that the chance of multiple pregnancy following in vitro fertilisation treatment depends on the number of embryos transferred per cycle of treatment. To balance the chance of a live birth and the risk of multiple pregnancy and its consequences, no more than two embryos should be transferred during any one cycle of in vitro fertilisation treatment.
- Embryos not transferred during a stimulated in vitro fertilisation treatment cycle may be suitable for freezing. If two or more embryos are frozen then they should be transferred before the next stimulated treatment cycle because this will minimise ovulation induction and egg collection, both of which carry risks for the woman and use more resources.

## **IMPLEMENTATION TOOLS**

Clinical Algorithm  
Patient Resources

For information about [availability](#), see the "Availability of Companion Documents" and "Patient Resources" fields below.

## INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

### IOM CARE NEED

Getting Better

### IOM DOMAIN

Effectiveness  
Patient-centeredness

## IDENTIFYING INFORMATION AND AVAILABILITY

### BIBLIOGRAPHIC SOURCE(S)

National Collaborating Centre for Women's and Children's Health. Fertility: assessment and treatment for people with fertility problems. London: RCOG Press; 2004 Feb. 216 p. [1151 references]

### ADAPTATION

Not applicable: The guideline was not adapted from another source.

### DATE RELEASED

2004 Feb

### GUIDELINE DEVELOPER(S)

National Collaborating Centre for Women's and Children's Health - National Government Agency [Non-U.S.]

### SOURCE(S) OF FUNDING

National Institute for Clinical Excellence

### GUIDELINE COMMITTEE

Not stated

### COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

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## **FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST**

All Guideline Development Group members' interests were recorded in a standard form that covered consultancies, fee-paid work, share-holdings, fellowships, and healthcare industry in accordance with guidance from the National Institute for Clinical Excellence (NICE).

## **GUIDELINE STATUS**

This is the current release of the guideline. This guideline updates the following guidelines previously released by the Royal College of Obstetricians and Gynaecologists:

- Royal College of Obstetricians and Gynaecologists. The initial investigation and management of the infertile couple. London: RCOG Press; 1998 Feb. 82 p. (Evidence-based clinical guidelines; no. 2).
- Royal College of Obstetricians and Gynaecologists. The management of infertility in secondary care. London: RCOG Press; 1998 Feb. 148 p. (Evidence-based clinical guidelines; no. 3). [677 references]
- Royal College of Obstetricians and Gynaecologists. The management of infertility in tertiary care. London: RCOG Press; 2000 Jan. 121 p. (Evidence-based clinical guidelines; no. 6).

## **GUIDELINE AVAILABILITY**

Electronic copies: Available in Portable Document Format (PDF) from the [Royal College of Obstetricians and Gynaecologists \(RCOG\) Web site](#).

Print copies: Available from the National Collaborating Centre for Women's and Children's Health (NCC-WCH), 27 Sussex Place, Regent's Park, London NW1 4RG

## **AVAILABILITY OF COMPANION DOCUMENTS**

The following are available:

- National Collaborating Centre for Women's and Children's Health. Fertility: assessment and treatment for people with fertility problems. Evidence tables. 2004 Feb. 115 p. Available from the [Royal College of Obstetricians and Gynaecologists \(RCOG\) Web site](#).

- National Collaborating Centre for Women's and Children's Health. Fertility: assessment and treatment for people with fertility problems. Summary. 2004 Feb. 45 p. Available from the [Royal College of Obstetricians and Gynaecologists \(RCOG\) Web site](#).
- National Collaborating Centre for Women's and Children's Health. Fertility: assessment and treatment for people with fertility problems. Clinical practice algorithm. 2004 Feb. 3 p. Available from the [Royal College of Obstetricians and Gynaecologists \(RCOG\) Web site](#).

Print copies: Available from the National Collaborating Centre for Women's and Children's Health (NCC-WCH), 27 Sussex Place, Regent's Park, London NW1 4RG

## **PATIENT RESOURCES**

The following is available:

- Assessment and treatment for people with fertility problems. Understanding NICE guidance – information for people with fertility problems, their partners, and the public. 2004 Feb. 75 p. Available from the [Royal College of Obstetricians and Gynaecologists \(RCOG\) Web site](#).

Print copies: Available from the National Collaborating Centre for Women's and Children's Health (NCC-WCH), 27 Sussex Place, Regent's Park, London NW1 4RG

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

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