Fertility Guideline:

Assessment and Treatment for

People with Fertility Problems

National Collaborating Centre for

Women's and Children's Health

Commissioned by the

National Institute for

Clinical Excellence

Second draft for consultation

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Abbreviations and glossary of terms

Abbreviations (to be completed)

BMI	Body mass index
CBAVD	Congenital bilateral absence of vas deferens
FIVNAT	French national in vitro organisation
FSH	Follicle-stimulating hormone
GDG	Guideline Development Group
GIFT	Gamete intrafallopian transfer
GnRH	Gonadotrophin-releasing hormone
GP	General Practitioner
GPP	Good Practice Point
GRP	Guideline Review Panel
HFEA	Human Fertilisation and Embryology Authority
HIV	Human immunodeficiency virus
hCG	Human chorionic gonadotrophin
hMG	Human menopausal gonadotrophin
HSG	Hysterosalpingography
HyCoSy	Hysterosalpingo-contrast-sonogaphy
ICSI	Intracytoplasmic sperm injection

IUI	Intra-uterine insemination
IVF	In vitro fertilisation
LH	Luteinising hormone
LSHTM	London School of Hygiene and Tropical Medicine
MESA	Microsurgical epididymal sperm aspiration
NCC-WCH	National Collaborating Centre for Women's and Children's Health
NICE	National Institute for Clinical Excellence
NHS	National Health Service
NNT	Number needed to treat
OHSS	Ovarian hyperstimulation syndrome
OR	Odds ratio
PCOS	Polycystic ovary syndrome
PCT	Primary Care Trust
PESA	Percutaneous epididymal sperm aspiration
PROST	Pronucleate stage tubal transfer
QALY	Quality-adjusted life year
RCOG	Royal College of Obstetricians and Gynaecologists
RCT	Randomised controlled (clinical) trial
RR	Relative risk (or risk ratio)
TEFNA	Testicular fine needle aspiration
TESA	Testicular sperm aspiration
TESE	Testicular sperm extraction

WHO	World Health Organization
ZIFT	Zygote intrafallopian transfer

Glossary of terms (to be completed)

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Peer reviewers and stakeholder organisations (to be completed)

Chairman's preface

Clinical guidelines commissioned by the National Institute for Clinical Excellence are intended to define clinical standards for the National Health Service in England and Wales. This guideline was developed by a Guideline Development Group convened by the National Collaborating Centre for Women's and Children's Health and is based on the best quality evidence available. Drafts of the guideline were prepared by the Guideline Development Group and evolved by consultation with registered stakeholder organisations and peer reviewers.The final guideline represents an evidence-based guide to clinical and cost-effective standards of practice in a clinically credible framework, but is not intended to be a text book on fertility problems.

Having defined what the guideline does, it is important to explain what it does not do. It is not the responsibility of the guideline developers to define service configuration for the delivery of the defined standards, nor a timetable for implementation. These aspects are the responsibility of National Service Frameworks in clinical fields where such frameworks exist.

Each guideline has a clearly defined scope which is developed in consultation with stakeholder organisations. For this guideline, the scope specified that the guideline recommendations would include optimal lower and upper age ranges for IVF treatment, the number of cycles of IVF treatment to be offered, and the maximum number of embryos to be transferred in any one cycle of IVF treatment. The scope also specified that the guideline would not consider a number of issues, including primary prevention of infertility, the management of pregnancies resulting from treatment, and the management of other health conditions discovered incidentally during investigation. The guideline does not address pre-implantation genetic diagnosis, laboratory standards, or social criteria that might be relevant to access for fertility services funded by the National Health Service. These might include whether there are any existing children in the family, same sex couples or single women, and couples with previous sterilisation.

In evaluating evidence relating to the investigation and treatment of fertility problems it has been very valuable to build on the work of the three previous clinical guidelines covering primary, secondary and tertiary care for infertility, which were produced by the Royal College of Obstetricians and Gynaecologists. In seeking the best quality evidence, the Guideline Development Group has been very conscious of the many areas of fertility practice where robust evidence based on randomised controlled trials is not available. In many of these areas we have made recommendations for future research and drawn on less robust evidence to form clinical practice recommendations; this is reflected in the strength of the clinical recommendations. Patient representatives and those who treat fertility problems recognise that this is a landmark guideline in terms of the future direction of National Health Service provision of fertility services, particularly assisted reproduction. In achieving this I would like to thank all the members of the Guideline Development Group, those who provided comments on the drafts, and especially the team at the National Collaborating Centre for Women's and Children's Health whose contribution in support of the guideline has been considerable.

David Barlow

Chairman of the Guideline Development Group

Chapter 1 Introduction

1.1 Aim of the guideline

Clinical guidelines have been defined as 'systematically developed statements which assist clinicians and patients in making decisions about appropriate treatment for specific conditions'. This guideline has been developed with the following aims:

- to offer advice on best practice on the care of people in the reproductive age group who perceive problems in conceiving;
- to address optimal lower and upper age ranges for treatment; and
- to offer advice on the management of people with a known condition or reason for their fertility problems, such as prior treatment for cancer or a genetic condition.

Infertility affects one in seven couples in the United Kingdom. It appears that there has been no major change in the prevalence of fertility problems, but that more people now seek help for such problems than did so previously. A typical Primary Care Trust (PCT), Health Board or Strategic Health Authority may expect to see around 230 new consultant referrals (couples) per 250 000 population per year. National Health Service (NHS) funding for investigation of fertility problems is generally available, but there is wide variation in access to NHS-funded treatment and management between centres. This is particularly true in relation to assisted reproduction techniques, such as in vitro fertilisation (IVF), where NHS-funded services are currently very limited or do not exist.

Patient dissatisfaction with clinical services has been expressed. Fertility problems can cause considerable psychological stress to people, and counselling is an important aspect of management. There is increasing concern about multiple births resulting from fertility treatment, particularly the triplet birth rate in England and Wales.

In the United Kingdom, nearly 30% of infertility cases are unexplained. The rest are caused by ovulatory failures (27%), tubal damage (14%), endometriosis (5%), low sperm count or quality (19%) and other factors (5%).[1;2] The presence of disorders in both the man and the woman has been reported to occur in about 39% of cases.[3]

There are three main types of fertility treatment: medical treatment (for example, use of drugs for ovulation induction), surgical treatment (for example, laparoscopy for ablation of endometriosis); and assisted reproduction. Assisted reproduction relates to all treatments that deal with means of conception other than normal coitus. It frequently involves the handling of gametes or embryos and includes one or more of the following: ovarian stimulation; oocyte collection; sperm preparation; IVF;* embryo transfer;* intra-uterine insemination (IUI); donor insemination;* intracytoplasmic sperm injection (ICSI);* gamete intrafallopian transfer (GIFT); pronucleate stage tubal transfer (PROST);* cryopreservation* and other related procedures.[4] Those procedures which involve the handling of embryos or donated gametes (indicated by * above) are regulated by the Human Fertilisation and Embryology Authority (HFEA).

Between 1998 and 2000, the Royal College of Obstetricians and Gynaecologists (RCOG) published three guidelines on the management of infertility that covered, respectively, initial investigation and management, management in secondary care, and management in tertiary care. The aim of the guidelines was to improve and develop the provision of services. It appears that the guidelines have had some impact on clinical practice, but little or no effect on the provision and availability of services.

This guideline is based on the three RCOG guidelines that cover the management of infertility, taking into account a new review of the research evidence.

1.2 Who has developed the guideline?

The guideline was developed by a multi-professional and lay working group (the Guideline Development Group; GDG) 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); and
- 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.

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

1.3 For whom is the guideline intended?

This guideline is of relevance to those who work in or use the NHS in England and Wales:

- professional groups who share in caring for couples seeking advice and treatment for fertility problems, such as gynaecologists, andrologists, general practitioners and nurses;
- those with responsibilities for commissioning and planning fertility services in PCTs and Health Commission Wales; and
- couples seeking advice and treatment for possible infertility.

1.4 Areas outside the remit of the guideline

The guideline does not address:

- the primary prevention of infertility;
- the management of pregnancies after fertility treatment (for example, the management of multiple births);
- the management and treatment of conditions found during the investigation of subfertility that are not directly related to the problem;
- the reversal of sterilisation;
- co-morbidities (except where they relate to the treatment of subfertility);
- pre-implantation genetic diagnosis;
- sexual dysfunction;
- social issues related to fertility treatment (including social eligibility criteria); or
- non-heterosexual intercourse.

1.5 Guideline methodology

The guideline was commissioned by NICE and developed in accordance with the guideline development process outlined in The Guideline Development Process – Information for National Collaborating Centres and Guideline Development Groups, which is available from the NICE website (**http://www.nice.org.uk**).

1.5.1 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 NCC-WCH.

The National Guidelines 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 our searches to identify any missing evidence.

Searches were carried out for each topic of interest. The Cochrane Library (up to Issue 1 2003) was searched to identify systematic reviews (with or without meta-analyses) of randomised controlled (clinical) trials (RCTs), and individual RCTs. The electronic databases MEDLINE (Ovid version for the period January 1966 to April 2003), EMBASE (Ovid version for the period between 1988 to April 2003), the Cumulative Index to Nursing and Allied Health Literature, the British Nursing Index and PsychInfo were also searched. The Database of Abstracts and Reviews of Effectiveness was searched.

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 GDG's question relevant to the topic. Following a critical review of the full version of the study, articles not relevant to the subject in 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 GDG's clinical question and was either better or equivalent in quality to 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 relatig to specific aspects of treatment (see Section 1.5.3). In addition to the databases listed above the Health Economic Evaluations Database and the 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/or 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 United Kindom 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 generalisable 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 Section 1.5.3).

1.5.2 Clinical effectiveness

For all the 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 (see below). 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 the table below:

Hierarchy of evidence

Ia	systematic review and meta-analysis of randomised controlled trials
Ib	at least one randomised controlled trial
IIa	at least one well-designed controlled study without randomisation
IIb	at least one other type of well-designed quasi-experimental study
III	well-designed non-experimental descriptive studies, such as comparative studies, correlation studies or case studies
IV	expert committee reports or opinions and/or clinical experience of respected authorities

The clinical question dictates the highest level of evidence that should be sought. For issues of therapy or treatment the highest level of evidence is a meta-analysis of RCTs or an individual RCT.

For issues of prognosis, a cohort study is the best level of evidence available. The best possible level of evidence would equate to a grade B recommendation. This should not be interpreted as an inferior grade of recommendation, as 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 not included.

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 if appropriate.

For the purposes of this guideline, data are presented as absolute risks, relative risks (RRs) or odds ratios (ORs) where relevant (i.e. in RCTs and cohort studies). Where the data are statistically significant they are also presented as numbers needed to treat (NNTs) if relevant.

1.5.3 Health economics

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 the 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 IVF was to model the cost-effectiveness of IVF under different assumptions and conditions. This approach has been adopted for a number of reasons. 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 UK setting. Third, it clearly shows where gaps exist in the published literature and research evidence.

Two recent systematic reviews of economic evaluations of infertility treatment have been undertaken.[5;6] The most recent review[5] identified 2 547 studies. From these, 30 economic evaluations, 22 cost studies and 5 economic benefit studies met the selection criteria and were reported. This was a high quality systematic review with a transparent methodology and the results were summarised in tables showing the synthesis of cost and clinical effectiveness data where available. The authors reported a high level of variability in the cost, largely due to the variation in definitions of cost and whether costs associated with the consequences of assisted reproduction or wider social costs (to other services, or to patients and their families) were incorporated.

The earlier review[6] was undertaken to complement the RCOG clinical guidelines for infertility services in the United Kingdom. A high proportion of studies were not relevant to the United Kingdom setting and did not reflect the true cost of treatment in the United Kingdom.[6]

The model developed in this guideline was 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 A).

Key topics for the economic analysis in the guideline were determined by the 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 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 IUI; and
- a review of the current literature on the 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 United Kingdom 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 NHS, but rather by private businesses. However, the market prices of these services were assumed to be likely to be close to an 'opportunity cost' for these services. The sources of data are discussed in Appendix A.

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 effectiveness of assisted reproduction techniques. The data that were available were not appropriate for making detailed forecasts of future spend 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

There is an important debate about whether the outputs of assisted reproduction can be incorporated into a measure than can be compared with other uses of the same resources. It is not logical to try to derive a quality-adjusted life year (QALY) measure from live births arising from IVF. It has been argued that:[7]

"QALYs are intended to capture improvements in health amongst 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 states that[8]

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

We believe this that this argument is valid and that QALYs cannot be reported in the context of assisted reproduction (unless they are related only to the couple seeking treatment). However, data on healthy live births can be translated into life years (by simple multiplication), and so these values are reported for completeness.

1.5.4 Forming and grading recommendations

The GDG was presented with the 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 GDG worked on an informal consensus basis. Formal consensus methods (modified Delphi

techniques or nominal group technique) were employed if required (e.g. grading recommendations and agreeing audit criteria).

The strength of evidence corresponding to each level of recommendation is shown below. The grading of recommendations follows that outlined in the Health Technology Assessment 'How to develop cost conscious guidelines'.[9]

A	Directly based on level I evidence
B	Directly based on level II evidence or extrapolated recommendation from level I evidence
C	Directly based on level III evidence or extrapolated recommendation from either level I or II evidence
D	Directly based on level IV evidence or extrapolated recommendation from either level I, II or III evidence
Good practice point (GPP)	The view of the Guideline Development Group
NICE Technology Appraisal	Recommendation taken from a NICE Technology Appraisal

Summary results are presented in the guideline text. More detailed results and other data are presented in the relevant evidence tables.

1.5.5 External review [note that this version is the second consultation draft]

The guideline has been developed in accordance with the 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 first draft was reviewed by nominated individuals with an interest in fertility problems and an independent Guideline Review Panel (GRP) established by NICE.

The comments made by the stakeholders, peer reviewers and the GRP were collated and presented anonymously for consideration by the GDG. All comments were considered systematically by the GDG and the resulting actions and responses were recorded.

Chapter 2 Summary

2.1 Summary of recommendations

Chapter 3 Human reproduction and fertility

3.1 Defining infertility and criteria for referral

Couples should be informed that most (84%) will conceive within a year if they do not use contraception and have regular sexual intercourse. Of those who do not conceive in the first year half will do so in the second year (cumulative pregnancy rate 92%). [D]

For the purposes of investigation, infertility should be defined as failure to conceive after regular unprotected sexual intercourse for 2 years in the absence of any reproductive pathology. [D]

Where there is a history of predisposing factors (such as oligomenorrhoea, amenorrhoea, pelvic inflammatory disease or undescended testes) investigation should begin immediately after presentation, which could be after only 1 year of trying to conceive or even earlier in some circumstances. [GPP]

Where there is a known condition or reason for infertility (such as prior treatment for cancer, HIV or a genetic condition) treatment should begin immediately after presentation. [GPP]

Chapter 4 Principles of care

4.1 Information giving and couple-centred management

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

When a diagnosis of infertility has been established, this information should be conveyed to couples sensitively and tactfully. [GPP]

Couples 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. [C]

Information regarding care and treatment options should be made available in forms that are appropriate for non-English speaking couples (for example, through an interpreter), and for people with disabilities. [GPP]

Couples with fertility problems should be informed that they may find it helpful to contact a patient support group. [GPP]

4.2 Counselling

Couples who experience problems with fertility should be offered counselling because infertility itself, and the management and treatment of infertility, can cause psychological stress. [C]

Counselling should be offered before, during and after treatment, irrespective of the outcome of treatment. [GPP]

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

4.3 Specialist and generalist care

Couples who experience problems with fertility 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. [D]

Chapter 5 General advice

5.1 Timing and frequency of sexual intercourse

Couples should be informed that sexual intercourse at least every 2 to 3 days optimises the chance of pregnancy. [C]

5.2 Alcohol

Couples should be informed that alcohol consumption within the Department of Health's recommendations of 2–3 units per day for women and 3–4 units per day for men is unlikely to affect natural fertility. [GPP]

Couples should be informed that excessive alcohol intake can be detrimental to semen quality. [B]

Couples should be informed that consumption of alcohol may reduce the effectiveness of assisted reproduction procedures, including in vitro fertilisation treatment. [C]

5.3 Smoking

Women who smoke should be informed that this may reduce their fertility. [B]

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

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. [GPP]

Couples should be informed that smoking can adversely affect the success rates of assisted reproduction procedures, including in vitro fertilisation treatment. [C]

Couples should be informed that passive smoking may affect their chance of achieving a pregnancy. [B]

5.4 Caffeinated beverages

Couples should be informed that there is no consistent evidence of an association between consumption of caffeinated beverages (tea, coffee and colas) and problems with fertility. [B]

5.5 Body weight

Women who have a body mass index of more than 29 should be informed that they may 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 chances of conception. Participation in a group programme involving exercise and dietary advice leads to more pregnancies than weight loss advice alone. [A]

Men with a body mass index of more than 29 should be informed that a link between weight reduction and fertility is unproven, but that weight loss may improve their general health. [GPP]

Couples should be informed that a high female body mass index may reduce the success of assisted reproduction procedures. [B]

Couples should be informed that a high female body mass index may adversely affect pregnancy outcomes. [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 restoring body weight may improve their chances of conception. [B]

Couples should be informed that a low female body mass index may reduce the success of assisted reproduction procedures. [B]

5.6 Tight underwear for men

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- or tight-fitting underwear has any effect on fertility. [B]

5.7 Occupation

Some occupations can reduce male or female fertility and therefore a specific enquiry about these should be made to each partner and appropriate advice should be offered. [B]

5.8 Stress

Couples should be informed that psychological stress may reduce fertility in women, but that the effect of stress on men is less clear. Stress in the male and/or female partner may reduce libido and affect the couple's relationship. [B]

5.9 Prescribed, over the counter and recreational drug use

A number of prescription, over the counter and recreational drugs may interfere with male and female fertility, and therefore a specific enquiry about these should be made to each partner and appropriate advice should be offered. [B]

5.10 Complementary therapy

If asked, couples should be informed that complementary treatments for infertility have not been properly evaluated and that further research is needed in these areas before such interventions can be recommended. [GPP]

Chapter 6 Preconceptional advice

6.1 Folic acid supplementation

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 400 micrograms per day. For women who have previously had an infant with a neural tube defect or who are receiving anti-epileptic medication, a higher dose of 5 milligrams per day is recommended. [A]

6.2 Susceptibility to rubella

To prevent rubella infection in pregnancy and to reduce the risk of having a baby with a congenital birth defect, rubella immunity screening should be

offered. Women who are susceptible to rubella should be offered rubella vaccination 1 month before they intend to become pregnant. [GPP]

6.3 Cervical cancer screening

To avoid delay in fertility treatment a specific enquiry about the timing and result of the most recent cervical smear test should be made. Cervical screening should be offered in accordance with the national cervical screening programme guidance. [GPP]

Chapter 7 Initial assessment

7.1 Semen analysis

As part of the initial assessment a semen analysis should be offered. This should be performed in accordance with the World Health Organization methods. [GPP]

If the result of the first semen analysis is abnormal, a repeat confirmatory test should be offered. Ideally this second sample should be collected 3 months after the initial analysis. [B]

7.2 Assessing ovulation

Women who experience problems in conceiving should be asked about the frequency and regularity of their menstrual cycles. Women with regular menstrual cycles should be informed that they are likely to be ovulating. [B]

To confirm ovulation, women may be offered a blood test to measure serum progesterone in the mid-luteal phase of their cycle. The use of basal body temperature charts to confirm ovulation is not recommended. [B]

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

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 may have reduced fertility and are likely to experience early menopause. [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 infertility 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 reserved for women with symptoms of an ovulatory disorder and thyroid disease. [C]

Women who have ovulatory disorder, galactorrhoea or pituitary tumour should be offered a blood test to measure serum prolactin. Women who are asymptomatic should not be offered this test. [C]

An endometrial biopsy to evaluate the luteal phase is not recommended as part of the investigation of infertile couples because there is no evidence that medical treatment of luteal phase defect improves pregnancy rates. [B]

7.3 Screening for Chlamydia trachomatis

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

If positive, women and their sexual partners should be referred for appropriate management with treatment and contact tracing. [C]

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

7.4 Assessing tubal damage

Women who are not known to have co-morbidities (such as pelvic inflammatory disease, previous ectopic pregnancy or endometriosis) should be offered hysterosalpingography [B] or hysterosalpingo-contrast-ultrasonography [A] to screen for tubal occlusion because they are reliable tests for ruling out tubal occlusion, and they are less invasive and make more efficient use of resources than laparoscopy.

Women who are thought to have co-morbidities should be offered a laparoscopy and dye so that tubal and other pelvic pathology can be assessed at the same time. [B]

7.5 Assessing uterine abnormalities

Women should not be offered hysteroscopy by itself as part of the initial investigation unless clinically indicated. There is conflicting evidence linking the treatment of uterine abnormalities with enhanced fertility. [B]

7.6 Post-coital testing of cervical mucus

The routine use of post-coital testing of cervical mucus in infertility investigations is not recommended because it has no predictive value on pregnancy rate. [A]

Chapter 8 Strategies for management of fertility problems

8.1 Ovulatory disorders

Both pulsatile administration of gonadotrophin-releasing hormone and gonadotrophins with leuteinising hormone activity are effective in inducing ovulation in women with irregular ovulation and who have low gonadotrophins and low oestrogen (WHO Group I ovulation disorders). [B]

Women with an ovulatory disorder due to hyperprolactinaemia should be offered treatment with dopamine agonists such as bromocriptine. Consideration should be given to safety for use in pregnancy and cost when prescribing. [A]

8.2 Fertility problems associated with uterine abnormalities

For women with amenorrhoea who are found to have intra-uterine adhesions, hysteroscopic adhesiolysis may restore menstruation and improve the chance of pregnancy. [C]

8.3 Unexplained fertility problems

Danazol is not effective in treating couples with unexplained infertility and should not be offered. [A]

Bromocriptine is not effective in treating couples with unexplained infertility and should not be offered. [B]

Fallopian sperm perfusion with ovarian stimulation is an alternative to intra-uterine insemination with ovarian stimulation in patients with unexplained infertility. [A]

Chapter 9 Ovulation induction agents

9.1 Anti-oestrogens

Women with WHO Group II ovulation disorders such as polycystic ovary syndrome should be offered treatment with either clomifene citrate or tamoxifen for up to 12 months because both are effective treatments. [A]

Women should be informed of the risk of multiple pregnancies associated with both clomifene citrate and tamoxifen. [B]

Women with unexplained fertility problems may have higher pregnancy rates if they take clomifene citrate, but this needs to be balanced by the possible risks of treatment, especially multiple pregnancy. [A]

9.2 Metformin

In anovulatory women with polycystic ovary syndrome who have not responded to clomifene citrate and who have a high body mass index,

metformin combined with clomifene citrate may be effective in enhancing the success of ovulation and pregnancy rates. [A]

Women prescribed metformin should be informed of the side effects associated with the use of metformin. [GPP]

9.3 Ovarian drilling

Women with polycystic ovary syndrome who have not responded to clomifene citrate may be offered laparoscopic ovarian drilling because it is as effective as gonadotrophin treatment and is not associated with a risk of multiple pregnancy. [A]

9.4 Gonadotrophin use in ovulation induction therapy for ovulatory disorders

Women with WHO group II ovulation disorders such as polycystic ovary syndrome who do not respond to treatment with anti-oestrogens or who have not become pregnant after 12 months of treatment with anti-oestrogens should 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 cost when prescribing. [A]

9.5 Gonadotrophin use during in vitro fertilisation treatment

Human menopausal gonadotrophin and recombinant follicle-stimulating hormone are both effective in improving pregnancy rates when used following down-regulation with gonadotrophin-releasing hormone agonist. [A]

For ovarian stimulation during in vitro fertilisation treatment urinary-derived gonadotrophins and recombinant follicle-stimulating hormone are equally effective when used with pituitary down-regulation. Consideration should be given to cost when prescribing. [A]

9.6 Gonadotrophin-releasing hormone analogues in ovulation induction therapy

Women with polycystic ovary syndrome who have not responded to clomifene treatment should not be offered treatment with gonadotrophin-releasing hormone agonist concomitantly with gonadotrophins because this does not improve pregnancy rates, but may be associated with an increased risk of ovarian hyperstimulation. [A]

9.7 Gonadotrophin-releasing hormone analogues during in vitro fertilisation treatment

For pituitary down-regulation as part of in vitro fertilisation treatment, using gonadotrophin-releasing 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 agonist in long protocols during in vitro fertilisation is therefore recommended. [A]

The use of gonadotrophin-releasing hormone antagonists may allow for shorter treatment cycles and lower doses of gonadotrophin, but their use is associated with reduced pregnancy rates and is therefore not recommended as a first line of treatment. [A]

9.8 Growth hormone as an adjunct to ovulation induction therapy

There is no role for the use of adjuvant growth hormone treatment with gonadotrophin-releasing hormone agonist/human menopausal gonadotrophin in ovulation induction in women with polycystic ovary syndrome who are resistant to clomifene citrate. [A]

9.9 Pulsatile gonadotrophin-releasing hormone

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

9.10 Monitoring ovulation induction

Couples who are offered ovulation induction 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 to reduce the risk of multiple pregnancy and ovarian hyperstimulation. [C]

9.11 Other risks and side effects associated with ovulation induction agents

Couples should be informed that the evidence for an association between ovarian cancer and ovulation induction therapy is unclear. [C]

Chapter 10 Tubal surgery

10.1 Tubal microsurgery and laparoscopic tubal surgery

The effectiveness of tubal surgery is uncertain, but it may be effective for women who have mild tubal disease. [C]

10.2 Selective salpingography and catheterisation

Selective salpingography plus tubal catheterisation or hysteroscopic tubal cannulation may be considered for patients with proximal tubal obstruction to improve the chance of pregnancy. [B]

Chapter 11 Management of fertility problems associated with endometriosis

11.1 Medical management (ovarian suppression)

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

11.2 Surgical ablation

Women with minimal and mild endometriosis who undergo laparoscopy should be offered surgical ablation or resection of endometriosis because this improves the chance of pregnancy. [A]

Women with ovarian endometrioma should be offered laparoscopic cystectomy because this improves the chance of pregnancy. [A]

Surgical treatment of moderate and severe endometriosis may improve fertility and should be offered. [B]

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

Chapter 12 Management of male factor fertility problems

12.1 Hypogonadotrophic hypogonadism

Use of gonadotrophin drugs can be effective in improving fertility in men with hypogonadotrophic hypogonadism. [B]

12.2 Primary testicular failure

Men undergoing treatment such as chemotherapy or radiotherapy should be offered the opportunity to cryopreserve their semen. [D]

12.3 Obstructive azoospermia

For men with obstructive azoospermia, surgical correction of epididymal blockage may restore patency of the duct and improve fertility. Surgical correction may be considered as an alternative to surgical sperm recovery and in vitro fertilisation. [C]

12.4 Immunological factors

Couples should be informed that the significance of antisperm antibodies is unclear and the effectiveness of systemic corticosteroids is uncertain. [A]

12.5 Varicoceles

Men should not be offered surgery for varicocele as a form of fertility treatment because it does not improve pregnancy rates. [A]

12.6 Leukocytospermia

Men with white cells in semen should not be offered antibiotic treatment unless there is an identified infection because there is no evidence that this improves pregnancy rates. [A]

12.7 Treatment for idiopathic semen abnormalities

Couples should be informed that anti-oestrogens, gonadotrophins, androgens, bromocriptine and kinin-enhancing drugs have not been shown to be effective in the treatment of men with idiopathic semen abnormalities. [A]

Chapter 13 Intra-uterine insemination

13.1 Intra-uterine insemination for the management of male infertility

Couples with male factor infertility where the man's semen is of appropriate quality should be offered three cycles of intra-uterine insemination because this increases the chance of pregnancy. [A]

Where intra-uterine insemination is used to manage male factor infertility, unstimulated and stimulated cycles are equally effective [A], but because stimulated cycles carry a risk of multiple pregnancy stimulated cycles are not recommended. [C]

13.2 Intra-uterine insemination for the management of unexplained infertility

Couples with unexplained fertility problems should be offered three cycles of intra-uterine insemination because it improves pregnancy rates. [A]

Where intra-uterine insemination is used to manage unexplained fertility problems, couples should be informed that stimulated intra-uterine insemination improves pregnancy rates, but is associated with an increased risk of multiple pregnancy compared to unstimulated intra-uterine insemination. [A]

Where gonadotrophin-stimulated intra-uterine insemination is used to manage unexplained fertility problems, a low dose follicle-stimulating hormone regimen may reduce the incidence of ovarian hyperstimulation syndrome. [A]

13.3 Intra-uterine insemination for the management of endometriosis

Women with minimal and mild endometriosis should be offered three cycles of intra-uterine insemination with ovarian stimulation because this is more

effective in increasing pregnancy rates than either no treatment or intra-uterine insemination alone in subfertile women. [A]

Couples should be informed of the risks of intra-uterine insemination (such as multiple pregnancy and ovarian hyperstimulation) and the response to treatment should be monitored with ultrasound scans. [GPP]

13.4 Single vs double intra-uterine insemination

Where intra-uterine insemination is used to manage fertility problems, single rather than double insemination should be used. [A]

Chapter 14 In vitro fertilisation

14.1 Effectiveness of in vitro fertilisation

Women who have hydrosalpinges and who are having in vitro fertilisation should be offered laparoscopic salpingectomy because it improves the chance of a live birth. [A]

14.2 Factors that affect the outcome of in vitro fertilisation treatment

Couples should be informed that the chance of a live birth following in vitro fertilisation treatment decreases with the woman's age. Women aged 23–35 years have more than a 20% chance of a live birth per treatment cycle. However, those aged 36–38 years have a 15% chance, those aged 39 years have a 10% chance, and those aged 40 years and older have a 6% chance. The effectiveness of in vitro fertilisation treatment where the woman is younger than 23 years of age is uncertain because very few women have in vitro fertilisation treatment in this age range. [C]

Couples should be informed that the optimal woman's age range for in vitro fertilisation treatment is 23–39 years, inclusive. [GPP]

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. Balancing the chance of 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. [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. [C]

In vitro fertilisation treatment should consist of a maximum of three complete 'fresh' treatment cycles (that is, ovarian stimulation and an attempt at egg collection) to achieve a live birth. Embryos not transferred in a fresh treatment

cycle may be suitable for freezing. If two or more embryos are suitable for freezing then they should be transferred before the next fresh treatment cycle because this will minimise ovarian stimulation and egg collection, both of which carry risks for the woman and use more resources. [GPP]

Couples who meet the following criteria should be offered in vitro fertilisation treatment: [GPP]

- **either**
  - **the woman is within the optimal age range for in vitro fertilisation (that is, the woman is aged 23–39 years) and**
  - **there is an appropriately diagnosed cause of infertility of any duration, or unexplained infertility of at least 3 years' duration (including mild endometriosis and mild semen abnormality);**
- **or**
  - **the woman is younger than 23 years of age and**
  - **there is an absolute indication for in vitro fertilisation treatment (for example, tubal blockage, very poor semen quality, or prior treatment for cancer).**

14.3 Gamete intrafallopian transfer and zygote intrafallopian transfer

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

Chapter 15 Conduct of in vitro fertilisation

15.1 Medical assessment and screening

To prevent transmission between patients and their gametes patients undergoing in vitro fertilisation treatment should be offered screening for HIV, hepatitis B virus and hepatitis C virus, and those found to be positive should be treated appropriately. [B]

15.2 Ovulation induction

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

The use of adjuvant growth hormone with gonadotrophin during in vitro fertilisation cycles does not improve pregnancy rates and is therefore not recommended. [A]

15.4 Oocyte maturation — human chorionic gonadotrophin

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. [A]

Recombinant human chorionic gonadotrophin is as effective as urinary human chorionic gonadotrophin for oocyte maturation. [A]

15.5 Monitoring of stimulated cycles

Ultrasound monitoring of ovarian response should form an integral part of the in vitro treatment cycle. [C]

Monitoring oestrogen levels during ovulation induction is not recommended because it does not give additional information compared to ultrasound monitoring. [A]

15.6 Ovarian hyperstimulation syndrome

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

Prophylactic albumin treatment may be of benefit but more research on timing and dose is required. [B]

Women who have a significant risk of developing ovarian hyperstimulation syndrome should not be offered human chorionic gonadotrophin. [A]

15.7 Oocyte retrieval

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

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

Follicle flushing is not associated with improvements in pregnancy rates or numbers of oocytes retrieved, and it increases the duration of the procedure and associated pain. It is therefore not recommended. [A]

15.8 Sperm recovery

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 made available. [C]

15.9 Assisted hatching

Assisted hatching should not be offered because it has not been shown to be effective in increasing pregnancy rates. [A]

15.10 Embryo transfer techniques

The use of ultrasound during embryo transfer appears to increase pregnancy rates and is therefore recommended. [A]

Day 2/3 transfers and day 5/6 transfers 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. [B]

Couples 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. [A]

15.11 Luteal support

Couples who are undergoing in vitro fertilisation treatment using gonadotrophin-releasing hormone agonists for pituitary down-regulation should be offered luteal support using human chorionic gonadotrophin or progesterone because they improve pregnancy rates. [A]

Chapter 16 Intracytoplasmic sperm injection

16.1 Indications for intracytoplasmic sperm injection

The recognised indications for treatment by intracytoplasmic sperm injection include:

- **severe deficits in semen quality in the male partner**
- **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. [B]

16.2 Information for couples

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. [C]

Independent counselling should be offered to couples considering intracytoplasmic sperm injection. [GPP]

16.3 Genetic issues and counselling

Before treatment by intracytoplasmic sperm injection consideration should be given to relevant genetic issues. [B]

Where a specific gene 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. [B]

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. [C]

16.4 Ejaculatory failure before intracytoplasmic sperm injection

The cause of ejaculatory failure should be diagnosed, and a range of treatment options should be offered, bearing in mind that it may be possible to restore fertility without the need for invasive methods of sperm retrieval or the use of assisted reproduction. [C]

Treatment options for ejaculatory failure should include drug therapy and surgical recovery of sperm from the vas deferens. [B]

16.5 Intracytoplasmic sperm injection vs in vitro fertilisation

Couples with 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. [A]

Chapter 17 Donor insemination

17.1 Indications for donor insemination

Recognised indications for donor insemination include:

- **severe deficits in semen quality in the male partner**
- **obstructive azoospermia**
- **non-obstructive azoospermia**
- **genetic or infectious disease in the male partner**
- **severe rhesus isoimmunisation. [B]**

17.2 Information and counselling

It is important that any discussion with a couple about the relative merits of intracytoplasmic sperm injection and donor insemination takes place in a context that allows equal access to both treatment options, and that the couple has the opportunity for independent counselling regarding all the physical and psychological implications of treatment for themselves and the potential child. [C]

17.3 Screening of sperm donors

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. [C]

All potential semen donors should be offered independent counselling regarding the implications for themselves and any potential children resulting from donated or undonated semen. [GPP]

17.4 Assessment of the female partner

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. [C]

Women with no risk history should be offered tubal assessment within the first six cycles of unsuccessful treatment. [GPP]

17.5 Intra-uterine insemination vs intra-cervical insemination

Couples should be offered intra-uterine insemination in preference to intra-cervical insemination because it improves pregnancy rates. [C]

17.6 Unstimulated vs stimulated donor insemination

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. [GPP]

17.7 Timing of donor insemination

Couples should be informed that insemination may be timed using either measurement of urinary luteinising hormone or basal body temperature changes because there is no difference in the effectiveness of these methods. [A]

However, luteinising hormone surge detection may be beneficial in terms of clinic organisation and costs. [C]

17.8 Maximum number of cycles

Couples should be offered other treatment options after six to nine unsuccessful cycles of donor insemination. [GPP]

Chapter 18 Oocyte donation

18.1 Indications for oocyte donation and counselling

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. [C]

18.2 Screening of oocyte donors

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. [D]

18.3 Oocyte donation and egg sharing

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

Oocyte recipients and donors should be offered independent counselling regarding the physical and psychological implications of treatment for themselves and children resulting from donated and undonated oocytes. [GPP]

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

18.4 Oocyte donation in older women

Women who are considering using donated oocytes beyond the age of natural menopause should be offered information regarding the welfare of potential offspring and the risks of pregnancy and labour (including risks associated with multiple pregnancy) in older women before starting such treatment. [C]

Women who are considering using donated oocytes beyond the age of natural menopause should be offered independent counselling regarding the physical and psychological implications of such treatment. [GPP]

Chapter 19 Cryopreservation

19.1 Information about cryopreservation in cancer treatment

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. [D]

Men undergoing medical treatment that is likely to make them infertile should be offered information about semen cryostorage because the effectiveness of this procedure has been established. [B]

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 quickly and effectively. [C]

Men undergoing medical treatment that is likely to make them infertile should be offered independent counselling to help them cope with the stress and the potential physical and psychological implications for themselves, their partners and any potential children resulting from semen cryostorage. [GPP]

19.2 Cryopreservation of supernumerary embryos

Cryopreservation of supernumerary embryos allows multiple embryo transfers from a single egg collection and improves the chances of a live birth. [B]

Embryo cryopreservation should be discussed with all couples considering assisted reproduction and should be offered if sufficient embryos of suitable quality for cryopreservation are available. [C]

19.3 Natural vs artificial replacement cycles

In women who have regular ovulatory cycles, the likelihood of live birth after replacement of frozen-thawed embryos is similar whether natural or artificial replacement cycles are used. [B]

Chapter 20 Follow-up of children born as a result of assisted reproduction

20.1 Risk of cancer

Couples contemplating assisted reproduction should be given up-to-date information about the health of resulting children. [C]

2.2 Future research recommendations

Further research is needed to ascertain the value of fertiloscopy and falloposcopy in the investigation of couples with fertility problems.

The role of pelvic ultrasound in women who are not suspected to have pelvic pathology requires further evaluation.

Randomised controlled trials to evaluate any benefits of surgical treatment of leiomyomas on improving the chance of live birth are needed.

Further research to evaluate any benefit on live birth rates of surgical resection of uterine septum in women with infertility is needed.

Further randomised controlled trials are needed to evaluate the potentially therapeutic effects of tubal flushing with water soluble media.

Further research is needed to evaluate the effect of ovarian drilling on the formation of adhesions.

Further research is needed to compare the clinical effectiveness (incuding patient satisfaction) and the cost-effectiveness of the gonadotrophin-releasing hormone agonists and antagonists during in vitro fertilisation treatment.

Further research is needed to assess the long-term health effects of ovulation induction agents on women who have undergone ovulation induction therapy for their fertility problems.

Further evaluation of the effectiveness of tubal surgery for women compared with no treatment and other treatment options is needed.

Randomised controlled trials to evaluate the benefit of treatment of varicocele in men with abnormal semen quality on improving fertility are needed.

Research is needed to define national semen quality criteria for intra-uterine insemination and intracytoplasmic sperm injection to be effective in the management of male infertility.

Research is needed to determine the relative effectiveness of oral (anti-oestrogen) and injectable (gonadotrophin) drugs in stimulated intra-uterine insemination in couples with unexplained fertility problems.

Research is needed to determine the relative effectiveness of intra-uterine insemination and in vitro fertilisation in couples with unexplained fertility problems.

For women who have hydrosalpinges the effectiveness of draining of hydrosalpinges or performing salpingostomy on improving live birth rate during in vitro fertilisation needs further evaluation.

Further randomised controlled trials evaluating the effectiveness of in vitro fertilisation in comparison against no treatment are needed for different durations and causes of fertility problems.

Further research is needed to evaluate the clinical effectiveness of single embryo transfers.

Further research is needed to evaluate the effect of general anaesthesia on oocyte retrieval and outcome of IVF treatment.

Randomised controlled trials are needed to evaluate the possible benefits of assisted hatching in certain subgroups, such as women aged older than 38 years.

Further research into the effect of cleavage (day 2/3) and blastocyst (day 5/6) stage methods of embryo transfer on live birth rates is needed.

Type of catheter may affect pregnancy rates but further research is needed.

Further research is needed to compare the effectiveness (incuding patient satisfaction) of different drugs and routes of administration for luteal support during in vitro fertilisation using agonist cycles.

Long-term longitudinal follow-up of children resulting from assisted reproduction is important, and such follow-up should be co-ordinated on a national basis.

2.3 Algorithm

[Included as a separate file for consultation]

Chapter 3 Human reproduction and fertility

3.1 Defining infertility and criteria for referral

Infertility has been defined as failure to conceive after unprotected sexual intercourse for 1 or 2 years.[1;3;10-32] The prevalence of infertility in European countries is around 14%, affecting one in seven couples.[1;3;12;15;16;20-24;27;29;31;33;34] Infertility can be primary, in couples who have never conceived, or secondary, in couples who have previously conceived.

The United Nations defines reproductive health as 'a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity in all matters relating to the reproductive system and to its functions and processes'.[35] [evidence level IV] Infertility should, therefore, be considered to be a disease process worthy of investigation and treatment.

In the general population (which includes people with fertility problems), it is estimated that 84% of women would conceive within 1 year of regular unprotected sexual intercourse. This rises cumulatively to 92% after 2 years and 93% after 3 years.[36;37] Diagnosis based on a failure to conceive within 1 year can exaggerate the risk of infertility, since about 50% of women who do not conceive in the first year are likely to do so in the second year.

Fertility may be measured as conception rate per menstrual cycle. This is known as fecundability. It is well-recognised that natural fertility declines with age,[38] but reliable data on fecundability rates of specific age groups in fertile populations is limited. The decline with age in rates of conception is significant after 30 years of age and marked after age 35 years.[39;40] However, this decline at specific ages should be interpreted with caution as it is based on women receiving artificial donor insemination and fecundability is higher in fertile women having natural intercourse than in fertile women receiving donor insemination.[39;41]

Data from historical populations estimated the average prevalence of infertility to be 5.5%, 9.4% and 19.7%, respectively at ages 25–29 years, 30–34 years and 35–39 years.[42]

Other important factors that can influence conception rates in the general population are male fertility and coital frequency. Statistical estimates suggest that fecundability rises sharply with frequency of intercourse.[43] With regular intercourse, 93.8% and 77% of fertile women aged 35 years and 38 years conceive after 3 years of trying [40;44] The effect of age on male fertility is less clear.[45] [evidence level III]

It is recognised that some people who are not having regular unprotected sexual intercourse may benefit from fertility services. Such people should not be excluded from investigation if they experience problems with fertility.

Recommendations:

Couples should be informed that most (84%) will conceive within a year if they do not use contraception and have regular sexual intercourse. Of those who do not conceive in the first year half will do so in the second year (cumulative pregnancy rate 92%). [D]

For the purposes of investigation, infertility should be defined as failure to conceive after regular unprotected sexual intercourse for 2 years in the absence of any reproductive pathology. [D]

Where there is a history of predisposing factors (such as oligomenorrhoea, amenorrhoea, pelvic inflammatory disease or undescended testes) investigation should begin immediately after presentation, which could be after only 1 year of trying to conceive or even earlier in some circumstances. [GPP]

Where there is a known condition or reason for infertility (such as prior treatment for cancer, HIV or a genetic condition) treatment should begin immediately after presentation. [GPP]

3.2 Natural conception

The process of human reproduction begins with the deposition of spermatozoa, during sexual intercourse, into the vagina. The spermatozoa migrate through the cervix and uterine cavity to the fallopian tubes where they meet the egg and fertilisation takes place. The embryo then travels back down the fallopian tube and enters the uterine cavity where implantation takes place.

This process is complex and reliant on the chance of satisfactory ovulation and transport of viable sperm and ova in the reproductive tract. It is influenced by endocrine control, timing and frequency of sexual intercourse and the general health status of the couple. The length of a menstrual cycle varies between 26 days and 36 days. Ovulation usually takes place 12–16 days before the start of the next period. For a woman with a 28-day menstrual cycle (the first day of menstruation being day 1), ovulation takes place around day 14. After ovulation, the egg usually lives for up to 24 hours. After ejaculation, sperm can survive for up to 7 days in the genital tract and sometimes even longer (see Section 5.1).[46]

3.3 Outcome measures

For this guideline the management of infertility has been assessed against a variety of reproductive and pregnancy outcomes. The justification for using these outcomes is based on their relevance to patients, and consensus among members of the GDG. These outcomes were also informed by the Cochrane Menstruation Disorders and Subfertility Group. The outcomes were grouped to reflect their importance to patients, health care 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 which 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.

Primary outcomes considered in the guideline include:

- live birth;
- patient satisfaction;
- anxiety/depression;
- multiple births;
- fetal abnormalities;
- ectopic pregnancy; and
- ovarian hyperstimulation syndrome (OHSS).

Secondary outcomes considered in the guideline include:

- clinical pregnancy (confirmed by presence of fetal heart rate);
- miscarriage;
- cycle cancellation;
- low birth weight; and

- perinatal mortality.

Surrogate outcomes considered in the guideline include:

- tubal patency;
- ovulation;
- fertilisation;
- implantation (number of gestational sacs identified by ultrasound);
- number of embryos transferred;
- embryo quality;
- improved semen parameters; and
- improved sexual function.

Chapter 4 Principles of care

4.1 Information giving and couple-centred management

The management of couples with fertility problems requires tact and sensitivity from all health professionals involved in their care, in particular when conveying a diagnosis of infertility. Verbal information should be supported by written evidence-based guidance sensitive to the needs of individual patients.[47] A clear protocol that sets out the purpose of investigation the proposed care plan should be designed.

Seeking infertility treatment concerns both partners. One study reported that couples were seen together in only 35% of clinics. [48] Women were more satisfied when seen with their partners at their infertility consultation.[49;50] There was strong agreement among GPs that couples should be seen together as part of infertility management.[51] Both the World Health Organization (WHO) and the HFEA strongly suggest that couples should be seen together.{8665, 7807} [evidence level IV]

Couples want more information about their conditions, their treatment and outcomes.[52] Low levels of satisfaction about information given to infertility patients at consultation have been reported in patients' surveys.[50;53-57] [evidence level III] Verbal as well as written information can improve understanding.[58] [evidence level IIb] Patients have reported that videos and booklets of information about the practical and psychological aspects of IVF improved knowledge and passage through the IVF cycle.[59] [evidence level III] For assisted reproduction, the HFEA Code of Practice stipulates that 'people seeking treatment should be given oral explanations supported by relevant written material and should be encouraged to ask for further information'.{7807} [evidence level IV]

Information and advice given in a manner that is culturally sensitive to the individuals concerned may improve acceptability of infertility management and care.[60-62] [evidence level III]

Information leaflets about various aspects of assisted reproduction are available from the HFEA.[63-73]

Couples with fertility problems may find it helpful to contact a patient support group (see Section 4.2).

Recommendations:

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

When a diagnosis of infertility has been established, this information should be conveyed to couples sensitively and tactfully. [GPP]

Couples 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. [C]

Information regarding care and treatment options should be made available in forms that are appropriate for non-English speaking couples (for example, through an interpreter), and for people with disabilities. [GPP]

Couples with fertility problems should be informed that they may find it helpful to contact a patient support group. [GPP]

4.2 Counselling

The relationship between stress and fertility problems is complex. Despite years of research, it has not been possible to determine whether psychological stress is a cause or an effect of infertility.[74] [evidence level III]

Infertility is regarded as the most upsetting and difficult life experience for some women,[75;76] with a sub-population of patients reporting elevated levels of emotional distress.[75;77-83] However, the association between infertility and anxiety and depression is not consistent. Some studies report increased anxiety and depression [84;85] and others do not.[86] In one study, the psychological symptoms of anxiety and depression associated with infertility were found to be similar to those associated with other serious medical conditions such as heart disease, cancer, hypertension and infection with human immunodeficiency virus (HIV).[87] Psychiatric morbidity was reported to be positively associated with the experience of infertility and the number of treatment cycles, affecting more women than men.[85] [evidence level III]

The psychological state of couples undergoing IVF may vary at different stages of treatment, the most stressful stages being waiting for the outcome of treatment and finding out that IVF has been unsuccessful.[88] A study in Sweden reported that almost 50% of women said they needed professional help and support to deal with their anxiety and problems in their marital relationship 2 years after tubal reconstructive surgery.[89] [evidence level III]

Most patients felt that access to a support group and counselling would be beneficial.[55;83;90;91] Some felt that psychological support should be available at all stages of

infertility treatment and investigation.[59] A recent unpublished survey[91] found that very few GPs offered counselling or identified methods of support, but two-thirds of couples attending an infertility clinic would accept psychological assistance if offered.[83] [evidence level III] In another study, 70% of patients said they would request counselling if it were available free of charge.[57] [evidence level III] Despite this, overall uptake of counselling is low at between 18–25%.[55;59;92;92] It has been suggested that less distressed patients may not wish to receive counselling, and some may cope well with support from their spouses and family.[93] Two-thirds of patients undergoing IVF treatment reported reading newspaper/magazine articles and watching television programmes about the psychological aspects of infertility even though few participated in a support group or sought counselling before treatment.[94] This suggests that, for some patients, information about local and national support groups and booklets on the psychological aspects of treatment, in addition to medical information, may be beneficial. [evidence level III]

Two RCTs showed that group psychological interventions such as cognitive behavioural therapy and support prevent distress{6994, 7249} and improve pregnancy rates (55% in a cognitive behavioural therapy group vs 54% in a support group vs 20% in a routine care group){7249} in women with less than 2 years' duration of infertility. [evidence level Ib] An RCT that evaluated the use of information and information combined with counselling for couples undergoing IVF treatment showed no significant differences between the two groups in terms of psychological symptoms and satisfaction.[95] [evidence level 1b]

The impact of stress should be acknowledged in the initial visit with continued offers of counselling before, during after treatment irrespective of the outcome of the treatment. The emotional consequences of anxiety and stress can be reduced by adequate provision of clear information about all aspects of investigations and treatment, involving each partner as an integral part of the management plan.

Counselling involves a professional relationship between a qualified counsellor and a patient, who may be an individual, a couple or a group of people. This relationship is contained within a formal counselling contract agreed and understood by both parties. The

counsellor has no other relationship with the client. Nurses, doctors and scientists in infertility clinics offer support and emotional help to couples as part of their professional role, but it is necessary to recognise this as using counselling skills within an existing role.[96]

Counselling cannot be imposed, but access should be offered.{7807} In considering the counselling needs of their patients, health professionals need to take account of evidence that suggests that couples may deny experiencing difficulties in their relationship, which may prevent them seeking help.[97] In addition, fertility patients have been described as very vulnerable.[98] This may lead them to be overly compliant with suggestions made by their clinical team, for example, going ahead with treatments despite having reservations or simply requiring more time to reflect on all the implications.[98] [evidence level III]

The HFEA Code of Practice{7807} identifies three distinct types of counselling, all of which should be clearly distinguished from information exchange:

- implication counselling aims to enable the client to understand the implications of proposed treatments and consequent actions for themselves, their families, and for any children born as a result of treatment;
- support counselling aims to give emotional support at times of particular stress, for example, when there is a failure to achieve a pregnancy;
- therapeutic counselling aims to help people cope with the consequences of infertility and treatment, to resolve problems which these may cause, and to adjust their expectations so that they can cope with the outcome of treatment whatever that may be.

The HFEA Code of Practice states that people seeking licensed treatment or consenting to the use or storage of embryos, or the donation or storage of gametes, must be given ‘a suitable opportunity to receive proper counselling about the implications of taking the proposed steps’ before they consent.{7807} [evidence level IV]

Counsellors should have professional counselling qualifications and the ability to work in accordance with the HFE Act. They should abide by a professional code of practice, such as the Ethical Framework for Good Practice in Counselling and Psychotherapy used by the British Association for Counselling and Psychotherapy, with a commitment to regular supervision.

If there is need for genetic counselling an appropriate referral should be made to a qualified genetic counsellor. Genetic counsellors should have recognised training, either through a Masters Programme in Genetic Counselling or a nursing qualification with additional relevant academic qualifications.

Recommendations:
Couples who experience problems with fertility should be offered counselling because infertility itself, and the management and treatment of infertility, can cause psychological stress. [C]

Counselling should be offered before, during and after treatment, irrespective of the outcome of treatment. [GPP]

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

4.3 Specialist and generalist care

The impact of specialist care on infertility management as compared with non-specialist care has not been evaluated. In studies reviewing care of patients by specialists and generalists across many conditions (including cancer, heart disease and psychiatric illness) specialists were reported to be more knowledgeable about their area of expertise

and quicker to adopt new and effective treatment than generalists, resulting in improved patient satisfaction, patterns of care and clinical outcomes.[99-101] [evidence level IIb–III] Training and expertise was reported to be a possible reason for patients achieving higher pregnancy rates after tubal surgery carried out by specialists rather than by general gynaecologists.[102] [evidence level III]

Patients seeking fertility treatment appeared to be more satisfied with services provided in a specialist clinic than those provided in a general gynaecological clinic.[50] [evidence level III] Patients were dissatisfied with attending an infertility clinic which shared a waiting room with users of antenatal classes or was situated where parent craft classes took place.[91]

A systematic review recommended that the management of fertility services should be carried out in specialist units with access to a wider range of skills than a general hospital because this is expected to improve the efficiency and effectiveness of treatment.[2] [evidence level IV]

Recommendations:

Couples who experience problems with fertility 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. [D]

Chapter 5 General advice

The first consultation should include an assessment of the perceived fertility problem. This should include a detailed enquiry about the medical, surgical, sexual and contraceptive history of the couple and a general physical examination to detect abnormalities, including measurement of height and weight to calculate body mass index (BMI) It is important to explain the concept of a realistic expectation of the chance of pregnancy in general populations. It may be necessary to describe the primary aspects of conception leading to the birth of a healthy baby. Human reproduction is a matter of chance, influenced by the subtle balance of sperm formation, ovulation, sexual intercourse, transport of gametes, fertilisation, embryo movement through the fallopian tubes, implantation and intra-uterine development of the fetus. Failure at any of these stages can prevent a pregnancy.

In order to identify contributory factors which may be avoided or which may need treatment a detailed history taking is needed. Advice and information need to be couple-specific (see Chapter 3).

5.1 Timing and frequency of sexual intercourse

It has been observed that most pregnancies can be attributed to sexual intercourse during a 6-day period ending on the day of ovulation,[103;104] with the highest estimated conception rates associated with intercourse 2 days before ovulation.[105] [evidence level III]

We found no evidence that using basal body temperature or urinary luteinising hormone (LH) kits to time intercourse improves the chance of conception.{4917,6416,5033,5853,6413,7566} [evidence level IIb] Timed intercourse has been found to be an emotionally stressful intervention in the initial evaluation of infertility.[106] [evidence level III] However, for the small proportion of couples who find it

difficult to have frequent sexual intercourse, the prediction of ovulation using LH kits can be useful.

Daily intercourse results in the highest probability of conception, but is not the only factor influencing conception,[43] considering the viability of the egg and its short survival time. [evidence level III] Ejaculation eight times per week tends to reduce sperm parameters,[107-110] but not the fertility potential of the men.[107] The best sperm motility was found in semen emission every 3 to 4 days on average.[107] [evidence level IIb] Coitus every 2 to 3 days is likely to maximise the overall chance of natural conception, as spermatozoa survive in the female reproductive tract for up to 7 days after insemination.[46;110] [evidence level III]

Recommendation:
Couples should be informed that sexual intercourse at least every 2 to 3 days optimises the chance of pregnancy. [C]

5.2 Alcohol

There is inconsistent evidence about the impact of alcohol intake on female fertility.{5993, 5356, 7461, 7143, 3964, 7229} [evidence level IIb] The current recommended guidelines for safe drinking limits for women are 2 to 3 units per day.[111] Excessive alcohol consumption is harmful to the fetus[112] and the NICE Antenatal Care guideline recommended that pregnant women should be careful about alcohol consumption and limit this to no more than one unit per day.

Excessive alcohol consumption can be detrimental to semen quality, but the effect is reversible and there is no evidence of a causal association between moderate alcohol consumption and poor semen quality.[113-116] [evidence level IIb] The current recommended guidelines on safe drinking limits for men are 3 to 4 units per day.[111]

Maternal and paternal alcohol consumption up to 1 year before assisted reproduction have been associated with a significant decreases in the success rates of IVF and GIFT.[117] [evidence level III]

Recommendation:
Couples should be informed that alcohol consumption within the Department of Health's recommendations of 2–3 units per day for women and 3–4 units per day for men is unlikely to affect natural fertility. [GPP]

Couples should be informed that excessive alcohol intake can be detrimental to semen quality. [B]

Couples should be informed that consumption of alcohol may reduce the effectiveness of assisted reproduction procedures, including in vitro fertilisation treatment. [C]

5.3 Smoking

There is a significant association between smoking and reduced fertility among female smokers.[118;119] [evidence level IIb] There is an association in men between smoking and reduced semen parameters.[114;120-124] [evidence level IIb] However, the relationship between the male partner's smoking habits and fertility is uncertain. It has been reported that male and female smoking exposure are associated with delayed conception in the couple.[125;126] [evidence level IIb]

For infertile women, basic information about the impact of smoking on fertility or a scripted 3–5 minute intervention with booklets specific to the woman's 'stage-of-change' smoking continuum, along with exhaled carbon monoxide monitoring, were highly effective in stopping smoking, but not in improving pregnancy rates.[127] [evidence level 1b] We found

no studies which investigated the effect of the use of nicotine replacement therapy on infertility.

Maternal and paternal smoking before assisted reproduction have been associated with significant decreases in the success rates of IVF and GIFT.[128;129]{6971}[130] [evidence level III]

Recommendations:
Women who smoke should be informed that this may reduce their fertility. [B]

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

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. [GPP]

Couples should be informed that smoking can adversely affect the success rates of assisted reproduction procedures, including in vitro fertilisation treatment. [C]

Couples should be informed that passive smoking may affect their chance of achieving a pregnancy. [B]

5.4 Caffeinated beverages

Caffeine is present in coffee, tea and colas. The association between caffeine and female infertility is inconsistent.{5961, 7701, 7705, 7131, 7335, 7231, 7407, 7710, 4941, 7133, 7699, 7409, 3964} [evidence level IIb] We did not find any studies reporting the effect of

caffeine on pregnancy rates, nor studies which investigated the effect of decaffeinated beverages on fertility.

We found one study addressing the question of caffeine intake and male fertility. This study showed no evidence of an association between caffeine intake and poor semen parameters.[114] [evidence level IIb]

Recommendation:
Couples should be informed that there is no consistent evidence of an association between consumption of caffeinated beverages (tea, coffee and colas) and problems with fertility. [B]

5.5 Body weight

5.5.1 Obesity

BMI is a measure of body fat calculated from an individual's weight and height (kg/m^2). The internationally accepted range for BMI is from < 18.5 kg/m^2 (underweight) to 30 kg/m^2 or over (obese).[131] Fertile women with BMI over 30 kg/m^2 take longer to conceive, compared with women with lower BMI, even after adjusting for other factors such as menstrual irregularity.{7218, 7277, 6896} [evidence level IIb] For infertile anovulatory women with BMI of over 29 kg/m^2, there is evidence that a supervised weight loss programme or a group programme including exercise, dietary advice and support helps to reduce weight,[132;133] resume ovulation[132] and improve pregnancy rates.[133] [evidence level Ib] It has also been reported that a weight loss programme may improve ovulation and pregnancy outcomes in obese infertile women for all forms of fertility treatment including ovulation induction, IUI and IVF treatment.[134;135] [evidence level IIb]

Obesity (BMI 25.8 to 30.8 kg/m^2) has been shown to be a risk factor for spontaneous abortion in women after IVF or ICSI.[136] [evidence level IIb] Obesity is also associated with lower pregnancy rates after IVF when compared with women with a BMI of 25 kg/m^2 or under.[137] [evidence level IIb] Extremes of BMI (over 25 kg/m^2 or under 20 kg/m^2) have been associated with negative effects on IVF parameters leading to decreased chances of pregnancy.[138] [evidence level IIb]

An increased risk of miscarriage has been reported in moderately obese women (BMI 25 to 27.9 kg/m^2) with polycystic ovary syndrome (PCOS; see Section 8.1) undergoing ovulation induction.[139] [evidence level IIb] High BMI in women can adversely affect other pregnancy outcomes. *(Refer to Antenatal Care Guideline.)*

We did not find any studies which assessed the relationship between obesity and sperm functions in men. The association between high BMI and abnormal endocrine parameters in men is not clear.[140-144] Weight reduction may normalise endocrine status, but the effect of this on fertility has not been established.[140;141] [evidence level IIb] Obesity may have a deleterious effect on erectile function in men with existing vascular risk factors such as heart disease and diabetes.[145] [evidence level IIb]

Recommendations:

Women who have a body mass index of more than 29 should be informed that they may 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 chances of conception. Participation in a group programme involving exercise and dietary advice leads to more pregnancies than weight loss advice alone. [A]

Men with a body mass index of more than 29 should be informed that a link between weight reduction and fertility is unproven, but that weight loss may improve their general health. [GPP]

Couples should be informed that a high female body mass index may reduce the success of assisted reproduction procedures. [B]

Couples should be informed that a high female body mass index may adversely affect pregnancy outcomes. [B]

5.5.2 Low body weight

Low body weight is recognised as an important cause of hypo-oestrogenic amenorrhea. It is important that the subgroup who have anorexia nervosa are detected and managed appropriately. Many women with hypo-oestrogenic amenorrhea associated with low body weight do not wish to conceive, and the management priority for these women will lie outside the scope of this guideline.

In women, weight loss of over 15% of ideal body weight is associated with menstrual dysfunction, and secondary amenorrhoea when over 30% of body fat is lost.[146] Restoration of body weight may help to resume ovulation and restore fertility.[147;148] [evidence level IIb]

Extremes of BMI (over 25 kg/m^2 or under 20 kg/m^2) have been associated with negative effects on IVF parameters leading to decreased chances of pregnancy.[138] [evidence level IIb]

An increased risk of preterm delivery has been associated with women who are underweight, and ovulation induction in such women has been associated with a higher incidence of babies who were small for gestational age.[149] [evidence level IIb] *(Refer to Antenatal Care Guideline.)*

Recommendations:

Women who have a body mass index of less than 19 and who have irregular menstruation or are not menstruating should be advised that restoring body weight may improve their chances of conception. [B]

Couples should be informed that a low female body mass index may reduce the success of assisted reproduction procedures. [B]

5.6 Tight underwear for men

Increased scrotal temperature is closely associated with reduced semen quality in healthy populations.[150-152] [evidence level III] Important determinants of testicular temperature such as a sedentary work position and occupational heat exposure have been associated with abnormal sperm quality (see Section 5.7).[152;153] [evidence level III] There is some evidence that, in a fertile population, wearing tight-fitting underwear can impair semen quality.[154] [evidence level Ib] However, the effect of impaired semen quality on pregnancy rates has not been established. A cohort study of 97 men with subfertility showed that there was no difference in scrotal temperatures and semen parameters between a group wearing boxer shorts and a group wearing briefs.[155] [evidence level IIb]

Recommendation:
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- or tight-fitting underwear has any effect on fertility. [B]

5.7 Occupation

More than 104 000 chemical and physical agents have been identified in the workplace, but the effects on reproduction of at least 95% of them have not been assessed, partly because of the fast rate of introduction of these agents into industry.[156] The following tables summarise the main occupational agents implicated in the reduction of human

fertility.[157-163] [evidence level IIb–III] The lists of agents presented in the tables are not exhaustive.

Occupational agents	Occupational groups	Effects on male fertility
Physical		
Shift work/long working hours	Shift workers	No association[164;165]
Heat (increase in scrotal temperature)	Welders, bakers, drivers	Abnormal sperm parameters[153]
X-ray	Radiotherapists	Azoospermia, reduced sperm count, may be reversible[166;167]
Non-ionising radiation: electromagnetic fields	Metal workers	Inconsistent association[138;168;169]
Vibrations	Engine drivers, diggers	Oligozoospermia, asthenozoospermia[170]
Chemical		
Dibromochloropropane (pesticide)	Agricultural workers	Oligozoospermia and azoospermia, reversible in most cases[171-174], reduced fertilisation rate[175]
Ethylene dibromide (pesticide)		Abnormal sperm parameters[161]
Carbaryl (pesticide)		No association[176]
Polychlorinated biphenyls	Agricultural workers	Abnormal sperm parameters[177;178]
Lead, cadmium, manganese	Metal workers, smelters, battery factory workers	Reduced fertility, mainly affecting female partners[179-184], no association[185]
Mercury	Dental amalgam	No association[186;187]

Acetone, carbon disulphide, glycol ethers (solvents)	Chemists, laboratory workers, painters	Abnormal sperm parameters[188;189], reduced fecundability[190], oligospermia {Welch 1989}
Toluene, styrene (solvents)	Plastic and printing industry	No association[191;192]
Anaesthetic gases	Dentists, anaesthetists	No association[193;194]

Occupational agents	Occupational groups	Effects on female fertility
Physical		
Shift work/intense physical work load/long working hours	Hospital workers	Reduced fecundability[195;196], prolonged TTP[164;165], no association[165]
Ionising radiation	Nuclear industry workers	Non-significant association[197].
VDUs	Office workers	No association,[198] increased risk of infertility[199]
Chemical		
Pesticides	Agricultural workers	Inconsistent in TTP[200]
Lead	Smelters	No association at low levels[201], prolonged TTP[202]
Mercury, cadmium		prolonged TTP[202]
Antineoplastics (chemotherapy drugs)	Nurses, pharmacists	Increased self-reported infertility[203]
Antibiotics		Small risk of prolonged TTP[204]
Nitrous oxide	Anesthetists, theatre nurses dental assistants	Reduced fecundability[195;205;206]
Chloroform, benzene		No association[193]
Mercury vapour	Lamp factory workers	No clear association[207], reduced fecundability[208]
Solvents		Infertility[199]
Formaldehyde	Wood workers	Reduced fecundability[209]

Evidence suggestive of a harmful effect on the human reproductive system has been recognised for specific agents, such as heat, X-rays, metals and pesticides, whereas for many other agents the association is only suspected and needs further evaluation.

Recommendation:
Some occupations can reduce male or female fertility and therefore a specific enquiry about these should be made to each partner and appropriate advice should be offered. [B]

5.8 Stress

Assessment of stress can be difficult due to variations in the individual response to stress. There may be an association between job and psychological stress and a lower probability of conception in women.[210-212] [evidence level IIb] Any association between stress and poor semen quality in men is less clear.[213;214] [evidence level IIb] Although it is not possible to isolate the factors causing stress from the stress of being infertile, there is evidence that counselling helps to reduce stress in couples undergoing infertility treatment (see Section 4.3). Psychological stress may also affect the couple's relationship and libido, which may impact upon their chance of conception.

Recommendation:
Couples should be informed that psychological stress may reduce fertility in women, but that the effect of stress on men is less clear. Stress in the male and/or female partner may reduce libido and affect the couple's relationship. [B]

5.9 Prescribed, over the counter and recreational drug use

A number of prescribed, over the counter and recreational drugs may interfere with male or female fertility. However, the potential benefits and risks of certain medications need to be weighed and medical advice sought in order to determine the appropriate course for individual patients.

Prescribed drug use

There is evidence that nonsteroidal anti-inflammatory drugs inhibit ovulation.[215;216] [evidence level Ib] Immunosuppressive and anti-inflammatory drugs for rheumatic diseases may affect conception.[217] [evidence level III] In a case-control study, women who had ever used thyroid replacement hormones, anti-depressants, tranquilisers or asthma medication were reported to have elevated risks of anovulatory infertility.[218] [evidence level IIb] Chemotherapy treatment with cytotoxic drugs can induce ovarian failure at different rates for various types of malignancies and treatment regimens.[219;220] [evidence level IIb]

Medication such as cimetidine and sulphasalazine and long term-daily use of some antibiotics and androgen injections can affect semen quality and cause oligozoospermia.[221-223] The effect is generally reversible after 3 months following withdrawal of medication. Use of beta-blockers and psychotropic drugs may lead to impotence.[224] Chemotherapy treatment can induce azoospermia, which is permanent in most cases.[225] [evidence level III]

The effect of anti-psoriatic treatment for arthritis with methotrexate on male infertility is unclear.[226] [evidence level III]

Recreational drug use

The use of recreational drugs and/or drugs of abuse such as marijuana and cocaine can adversely affect ovulatory and tubal function.[227] The use of drugs such as anabolic steroids and cocaine can adversely affect semen quality.[228-230] [evidence level IIb–III] Overall, use of these recreational drugs diminishes the fertility potential of the couple.

However, the effect of such drug use on pregnancy rates has not been established. [evidence level III]

Recommendation:

A number of prescription, over the counter and recreational drugs may interfere with male and female fertility, and therefore a specific enquiry about these should be made to each partner and appropriate advice should be offered. [B]

5.10 Complementary therapy

We found four RCTs that evaluated the effects of various substances on sperm quality,[231;232] ovulation and pregnancy rates.{7631, 7511} The RCTs were generally of poor design, and the efficacy of the substances investigated needs further evaluation.{7551, 7631, 7511} There is some evidence that selenium may improve sperm quality in men with impaired sperm motility.[232] [evidence level Ib] However, a positive effect on pregnancy rates has not been established.

An increase in pregnancy rates was observed in a preliminary trial assessing the effect of intercessory prayer on patients undergoing IVF tretament. However, there is no biological mechanism to explain such an effect.[233]

We did not find any RCTs evaluating the effectiveness of complementary therapies on pregnancy rates, nor any RCTs that showed that complementary therapy is harmful.

Recommendation:

If asked, couples should be informed that complementary treatments for infertility have not been properly evaluated and that further research is needed in these areas before such interventions can be recommended. [GPP]

Chapter 6 Preconceptional advice

6.1 Folic acid supplementation

A systematic review of four RCTs showed that periconceptional folate supplementation reduced the incidence of neural rube defects (anencephaly and spina bifida) in children (RR 0.28, 95% CI 0.13 to 0.58). Multivitamins alone were not associated with prevention of neural tube defects and did not produce additional preventative effects when given in combination with folate.[234] [evidence level Ia] An Expert Advisory Group to the Department of Health recommends a dose of 400 micrograms per day, and an increase to 5 mg per day for women who have previously had an infant with neural tube defects and women who are receiving anti-epileptic drugs.[235] [evidence level IV] The British National Formulary recommends that women on anti-epileptic drugs wishing to become pregnant should be referred to an appropriate specialist to discuss the risk of teratogenecity.[236] [evidence level IV]

Recommendation:
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 400 micrograms per day. For women who have previously had an infant with a neural tube defect or who are receiving anti-epileptic medication, a higher dose of 5 milligrams per day is recommended. [A]

6.2 Susceptibility to rubella

Rubella infection during pregnancy is associated with a significant teratogenic risk to the fetus, resulting in multiple congenital abnormalities.[237] [evidence level IIb] The introduction of the rubella vaccine has resulted in a decrease of rubella infections and infants with congenital rubella syndrome. The reported proportion of infertile women who were rubella

susceptible ranged from 2% to 12%.{6759, 6764, 6761, 6758} [evidence level III] The rubella vaccine is a live attenuated virus, thus when vaccination is given pregnancy should be deferred for 1 month.

Recommendation:

To prevent rubella infection in pregnancy and to reduce the risk of having a baby with a congenital birth defect, rubella immunity screening should be offered. Women who are susceptible to rubella should be offered rubella vaccination 1 month before they intend to become pregnant. [GPP]

6.3 Cervical cancer screening

The reported proportion of infertile women with abnormal cervical smears ranged from 5% to 13%.[238;239] [evidence level III] As part of the national screening programme, women between the age of 20 years and 64 years are offered cervical screening every 3 years or 5 years depending on their age [240] Abnormal cervical cytology that is overlooked may lead to increased delay in fertility treatment[238] because treatment of cervical intraepithelial neoplasia is more complicated during pregnancy.

Recommendation:

To avoid delay in fertility treatment a specific enquiry about the timing and result of the most recent cervical smear test should be made. Cervical screening should be offered in accordance with the national cervical screening programme guidance. [GPP]

Chapter 7 Initial assessment

7.1 Semen analysis

The WHO semen values are based on populations of fertile men and are described as 'reference' values rather than 'normal' values.{7808} [evidence level IV] In the detection of male factor infertility basic semen analysis using WHO criteria is a relatively sensitive test (sensitivity of 89.6%) but it has poor specificity. Analysis of repeat semen samples provides greater specificity in identifying semen abnormalities; a single-sample analysis will falsely identify about 10% of men as abnormal, but repeating the test reduces this to 2%.[241] [evidence level IIb]

There may also be considerable variation in semen measurements within individuals over time.[108;109] This has prompted the suggestion that two{7808} or three semen samples[109] are needed in order to establish a reliable semen profile. However the WHO criteria provide a sensitive test (that is, the test is likely to identify most 'true' abnormalities) so that if the semen analysis is normal there is no need for a repeat analysis. It has also been suggested that a repeat semen analysis should be performed only if the result of the first analysis is abnormal.[242] The optimal time for the second sample is at least 3 months after the initial sample to allow for the cycle of spermatogenesis. However, this delay may cause anxiety and the timing should take into consideration the preferences of the couple. When azoospermia is found on the initial semen analysis the test should be repeated within 2–4 weeks. If the second test is normal the semen analysis can be regarded as normal and no further testing is needed.

Men who have two abnormal semen analyses may need further, more detailed, semen assessment. The tests should be interpreted within the clinical context and circumstances of the couple. If azoospermia is confirmed, this should be explained sensitively to the patient, who should be referred for early specialist advice in order to minimise anxiety.

The WHO includes assessment for the presence of auto-immune antisperm antibodies as a standard part of semen analysis.{7808} [evidence level IV] This is performed using either an immunobead test or a mixed antiglobulin reaction test. However, opinion differs on the use and reliability of these tests.[243;244]

Sperm function tests vary in their ability to detect defects in the complex processes leading to fertilisation, and are of limited use from a practical point of view.[30;245] [evidence level IV]

WHO reference values for semen analysis, 1999

Volume	2.0 ml or more
Liquefaction time	within 60 minutes
pH	7.2 or more
Sperm concentration	20 million spermatozoa per millilitre or more
Total sperm number	40 million spermatozoa per ejaculate or more
Motility	50% or more motile (grades a + b) or
	25% or more with progressive motility (grade a) within 60 minutes of ejaculation
Morphology	15% or 30%*
Vitality	75% or more live
White blood cells	fewer than 1 million per millilitre

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

The WHO semen values are based on ‘reference’ values rather than ‘normal’ values.{7808} [evidence level IV] The reliability of these values, especially sperm

concentration, in predicting the chance of conception has been questioned.[246] [evidence level III]

Recommendations:

As part of the initial assessment a semen analysis should be offered. This should be performed in accordance with the World Health Organization methods. [GPP]

If the result of the first semen analysis is abnormal, a repeat confirmatory test should be offered. Ideally this second sample should be collected 3 months after the initial analysis. [B]

7.2 Assessing ovulation

Regular menstrual cycles in the range 26 to 36 days are usually indicative of ovulation.[247] A review of patient-monitored basal body temperature charts showed that they are not reliable enough to detect ovulation.{4917, 6416, 5033, 5853, 6413, 7566} Urinary LH kits used by couples can suggest ovulation is imminent. Ovulation can be confirmed retrospectively by measurement of serum progesterone in mid-luteal phase, approximately on day 21 of a 28-day cycle. For women with irregular cycles this test may need to be performed later in the cycle (e.g. day 28 of a 35-day cycle) or repeated weekly until the next menstrual cycle starts. Values range from 16 to 28 nmol/l as the lowest limit indicative of ovulation.[30;248-250] [evidence level IIb]

(See Section 5.1 for timing and frequency of sexual intercourse.)

(See Section 17.7 for timing of donor insemination.)

Recommendation:

Women who experience problems in conceiving should be asked about the frequency and regularity of their menstrual cycles. Women with regular menstrual cycles should be informed that they are likely to be ovulating. [B]

To confirm ovulation, women may be offered a blood test to measure serum progesterone in the mid-luteal phase of their cycle. The use of basal body temperature charts to confirm ovulation is not recommended. [B]

7.2.1 Ovulation disorders

Anovulation and oligo-ovulation are ovulatory disorders and are estimated to cause 21% of female infertility.[1] The WHO classifies ovulation disorders into three groups.[26]

Group I: Low gonadotrophins and low oestrogen (hypothalamic amenorrhoea, hypogonadotrophic hypogonadism). This accounts for about 10% of ovulatory disorders.

Group II: Gonadotrophin disorder and normal oestrogen (predominantly PCOS). This accounts for about 85% of ovulatory disorders.

Group III: High gonadotrophin and low oestrogen (premature ovarian failure). This accounts for about 4–5% of ovulatory disorders.

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

7.2.2 Assessing ovarian reserve

Female fecundability is related to the total number of primordial follicles remaining within the ovaries (referred to as ovarian reserve), which declines with age.[251] It would be valuable if reliable estimates of ovarian reserve were possible in the management of women above the age of 35 years, before embarking on fertility therapy such as ovulation induction and IVF.[252;253] [evidence level III–IV]

Indirect measurements using endocrine markers, such as day-3 basal serum follicle-stimulating hormone (FSH) and clomifene citrate challenge test, correlate well with the probability of conception in populations. These include women in the infertility population,[254;255] women undergoing complex ovulation induction, and women participating in assisted reproductive technology cycles.[256-259]

When ovarian screening was carried out in woman aged over 35 years, women of any age with unexplained infertility, and women with one ovary or a poor response to human menopausal gonadotrophin (hMG), one in six women was found to have an abnormal test result.[260] [evidence level III]

An elevated basal day-3 FSH is correlated with diminished ovarian reserve in women aged over 35 years, and is associated with poor pregnancy rates after treatment of ovulation induction (6% vs 42%) and assisted reproduction (2.7%),[256;261] and high rates of pregnancy loss (71.4%), regardless of age,[261] when compared with women with normal ovarian reserve. [evidence level IIb–II]

A cohort study of 344 women undergoing IVF following pituitary desensitisation showed that basal FSH is a better predictor of cycle cancellation rates and of the number of oocytes collected than age, but age and not basal FSH was independently associated with pregnancy rate.[262] Another cohort study of 1045 cycles of women undergoing IVF showed

that the combined use of age and basal FSH significantly improved the predictive power of number of oocytes collected, fertilised and embryos transferred. However, age was an independent predictor of pregnancy rate (area under the receiver operating-characteristic curve 0.617 with age alone vs 0.545 with FSH alone, p = 0.002). Increasing age, but not basal FSH, was associated significantly with reduced implantation rate and pregnancy rate. Women aged 40 years or over have the poorest pregnancy outcomes when compared with those aged under aged 35 years, and those aged 35–39 years.[263] [evidence level IIb]

A cohort study of 547 women showed that those with poor response to ovarian stimulation and raised basal FSH were more likely to have poor reproductive performance and have a higher risk of early menopause when compared with normal responders.[264] [evidence level IIb]

It has been reported that direct measures of ovarian function such as Inhibin B correlate inversely with age and FSH levels,[265] and that Inhibin B levels are reduced in women with diminished ovarian reserve.[266] However, the role of Inhibin B in predicting pregnancy outcome is unclear[267;268] and need further evaluation.

None of these markers was found to reflect accurately ovarian reserve in a recent study which compared follicle numbers in ovarian histology of 22 parous women who undertook the tests before oophorectomy, but the clomifene citrate challenge test was more accurate according to receiver operator characteristic analysis compared with basal FSH and gonadotrophin-releasing hormone agonist stimulation tests.[269]

It has been reported that pregnancy rates decline significantly as day-3 FSH rises above 15 mIU/ml. Very few pregnancies were reported when FSH exceeded 25 mIU/ml.[257] [evidence level III] However, interpretation of basal FSH is subject to great inter-laboratory variation. There appear to be marked differences in ‘normal’ ranges of values of the FSH

assay. It is important for each laboratory to define its own normal range of laboratory assays.[270] [evidence level IV]

Tests of ovarian reserve do not currently have the necessary sensitivity or specificity for general application.[253]

Recommendation:
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 may have reduced fertility and are likely to experience early menopause. [C]

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

7.2.3 Thyroid function tests

Thyroid dysfunction can lead to menstrual and ovulatory disorder, associated with infertility.[271;272] It has been common practice to screen women with infertility for thyroid dysfunction using thyroid function tests, whether or not symptoms of thyroid disease are present.

Asymptomatic hypothyroidism occurs in up to 7% of the general population.[273] Abnormal thyroid function test measurements have been reported in 1.3% to 5.1% of infertile women.[274-278] [evidence level III] It has been estimated that subclinical hypothyroidism occurs in 0.88% to 11.3% of women with ovulation disorders.[275;276] [evidence level III]

Recommendation:

Women with possible infertility 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 reserved for women with symptoms of an ovulatory disorder and thyroid disease. [C]

7.2.4 Prolactin measurement

Hyperprolactinaemic amenorrhoea is associated with infertility. The incidence of raised prolactin in infertile but ovulatory women ranges from 3.8% to 11.5%.[277;279;280] [evidence level III] There is no significant association between prolactin, progesterone levels and cumulative conception rates in ovulatory women.[281] [evidence level III] Estimation of prolactin levels should be reserved for women with symptoms of an ovulatory disorder, galactorrhoea or pituitary tumour.

Recommendation:
Women who have ovulatory disorder, galactorrhoea or pituitary tumour should be offered a blood test to measure serum prolactin. Women who are asymptomatic should not be offered this test. [C]

7.2.5 Endometrial biopsy

Luteal phase defect has been defined as either a defect of progesterone secretion by the corpus luteum or a defect in endometrial response to hormonal stimulation, resulting in an inadequate endometrium for blastocyst implantation and subsequent pregnancy.[282] The defect is estimated to affect 3% to 20% of the infertile population, and 23% to 60% of women with recurrent abortions.[283]

The lack of consensus about the diagnosis and treatment of luteal phase defect has questioned the role of luteal phase defect as a cause of infertility.[284;285] The benefit of

treatment for luteal phase defect on pregnancy rates has not been established.[286;287] [evidence level Ib–III]

Traditionally, luteal phase defect is diagnosed by a timed endometrial biopsy based on a standard set of criteria,[288] repeated on at least two occasions. [evidence level IIb] It has been suggested that diagnosis of luteal phase defect based on histological dating of endometrial biopsy could be a chance event.[287]

Recommendation:
An endometrial biopsy to evaluate the luteal phase is not recommended as part of the investigation of infertile couples because there is no evidence that medical treatment of luteal phase defect improves pregnancy rates. [B]

7.3 Screening for Chlamydia trachomatis

Chlamydia trachomatis is present in 10.9% of the sexually active population aged 19 years or less.[289] It is a major cause of pelvic inflammatory disease, leading to chronic abdominal pain, ectopic pregnancy and tubal factor infertility.[290;291] Asymptomatic chlamydial infection may go unrecognised and untreated. Although the prevalence of chlamydia among subfertile women in the United Kingdom is only 1.9%,[292] uterine instrumentation carried out routinely as part of the normal infertility investigation may reactivate or introduce upper tract dissemination of endocervical chlamydial infection, resulting in iatrogenic pelvic inflammatory disease. [evidence level IIb]

Clinical pelvic infection following hysterosalpingography (HSG) has been reported in up to 4% of cases and in 10% of patients with tubal disease.[293] [evidence level III] Prophylactic antibiotics are effective in reducing this and should be considered.[292;294] [evidence level III] Both doxycycline and azithromycin are effective prophylaxis and treatment for chlamydia.[295] [evidence level Ib]

There is evidence that screening for and treating cervical chlamydial infection can reduce the incidence of pelvic inflammatory disease in women at increased risk of chlamydia.[296] [evidence level Ib] The Chief Medical Officer's Expert Advisory Group on Chlamydia has called for action to reduce the prevalence and morbidity of chlamydial infection. [evidence level IV] It recommends that consideration be given to screening couples attending fertility clinics and women undergoing procedures requiring instrumentation of the uterus.[297] [evidence level III] Women who are found to have chlamydial infection should be treated for the infection before proceeding.

DNA techniques such as polymerase chain reaction and ligase chain reaction for analysis of cervical and urine specimens are highly sensitive and specific for diagnosing chlamydial infection.[298-300] [evidence level IIb]

Chlamydial infection has been implicated in male infertility[301] and it may cause epididymitis and obstruction. If chlamydial infection is detected in the female partner, male partners should be notified and treated to limit re-infection and the potential need for retreatment.

The Chief Medical Officer's Expert Advisory Group on Chlamydia advises referral to genitourinary medicine clinics so that sexual partners can be traced and treated if either partner is found to have chlamydial infection.[297] [evidence level III]

Recommendations:

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

If positive, women and their sexual partners should be referred for appropriate management with treatment and contact tracing. [C]

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

7.4 Assessing tubal damage

An ideal (or 'gold standard') test would correctly identify all women with tubal disease (i.e. be a sensitive test) such that a negative test would rule out disease in all those without disease. It would also be specific (i.e. the test would be positive only in women with the disease).

Hysterosalpingography compared with laparoscopy and dye

HSG and laparoscopy with dye are the two most widely used methods to test for tubal pathology. Among women whose tubes were found to be patent (unobstructed) using HSG, 18% were found to have tubal obstruction or peritubal adhesions using laparoscopy, and a further 34% were found to have endometriosis and/or fibroids.[302] However, the detection and treatment of pathology missed by HSG did not increase live birth rates.[302]

The diagnostic accuracy of HSG has been compared with that of laparoscopy and dye in a systematic review of 20 studies that distinguished between tubal obstruction and peritubal adhesions.[303] However, only three studies involved judgement of laparoscopy without knowledge of HSG results. Meta-analysis based on these three studies gave pooled estimates of sensitivity and specificity for HSG as a test for tubal obstruction of 0.65 (95% CI 0.50 – 0.78) and 0.83 (95% CI 0.77 – 0.88), respectively.[303] [evidence level IIb] Given that tubal damage accounts for 14% of fertility problems,[1] these estimates imply that when HSG suggests the presence of tubal obstruction this will be confirmed by laparoscopy in only 38% of women. Thus, HSG is a not a reliable indicator of tubal occlusion. However,

when HSG suggests that the tubes are patent, this will be confirmed at laparoscopy in 94% of women, and so HSG is a reliable indicator of tubal patency.

Results from another review[247] suggest that HSG could be used as a screening test for couples with no history of pelvic infection, and if abnormal, confirmatory laparoscopy would follow.[304] [evidence level IIb] Considerable interobserver variability in interpretation of HSGs has been reported, depending on the type of pathology being assessed.[305;306] Women with possible co-morbidity such as pelvic and tubal diseases may need a laparoscopic assessment.

The choice of laparoscopy as a gold standard in the diagnosis of tubal pathology has been questioned in a cohort study that formed part of the Canadian Infertility Treatment Evaluation Study.[307] [evidence level III] This study compared the prognostic significance of HSG and laparoscopy using adjusted fecundity rate ratios, which express the probability of spontaneous pregnancy per unit time for women with a particular feature, relative to those without that feature. One-sided occlusion detected using HSG was found to decrease spontaneous pregnancy rates slightly compared to the absence of tubal occlusion at HSG (fecundity rate ratio 0.80), and two-sided occlusion at HSG decreased spontaneous pregnancy rates further (fecundity rate ratio 0.49).[307] [evidence level III] However, occlusion detected using laparoscopy was associated with even lower spontaneous pregnancy rates (fecundity rate ratio 0.51 for one-sided occlusion and 0.15 for two-sided occlusion).[307] [evidence level III] Thus, tubal pathology detected at laparoscopy has a stronger effect on future fertility than that detected at HSG.

A meta-analysis of 23 test evaluation studies found that the discriminative capacity of chlamydial antibody testing, using ELISA, immunofluorescence or microimmunofluorescence is comparable to that of HSG in the diagnosis of tubal pathology.[308] [evidence level IIb] Elevated titres of chlamydial antibodies in women were significantly associated with tubal disease.[309] The titre of chlamydia antibodies has also been reported to be more accurate in predicting severe tubal pathology than unspecified tuboperitoneal abnormalities.[310] However, it has been reported that the negative predictive

value for pelvic pathology from the use of clinical features in addition to the chlamydial antibody titre is not significantly higher than that from the chlamydial antibody titre alone at 53%; this may not justify the avoidance of a diagnostic and confirmatory laparoscopy.[311]

A cohort study found that chlamydial antibody levels are quantitatively related to severity and extent of tubal pelvic damage. An elevated chlamydial antibody titre result is significantly associated with poor live birth rates, but not pregnancy rates.[312] [evidence level IIb] However, the chance of conception with or without tubal surgery is related to the degree of damage found at laparoscopy, with the chlamydial antibody titre adding no further diagnostic value.[313] [evidence level IIb]

Hysterosalpingo-contrast-sonography compared with laparoscopy and dye or hysterosalpingography

Evaluative studies of hysterosalpingo-contrast-sonogaphy (HyCoSy) showed good statistical comparability and concordance with HSG and laparoscopy combined with dye.[314] [evidence level Ib] HyCoSy is well-tolerated and can be a suitable alternative outpatient procedure.[315] [evidence level Ib] HyCoSy using contrast agent Infoson appears to be more efficient than saline solution in detecting tubal obstruction.[316] [evidence level Ib]

Fertiloscopy and falloposcopy

Fertiloscopy is defined as the combination in one investigation of transvaginal hydropelviscopy, dye test, optional salpingoscopy and hysteroscopy performed under local anaesthesia or neuroleptanalgesia.[317] It offers a complete informative status of the uterus, tubes, ovary and the peritoneum in one procedure.

Diagnostic fertiloscopy has also been used to identify tubal pathology as an alternative to laparoscopy.[317] [evidence level III]

Procedures such as ovarian drilling in the treatment of PCOS can be performed via operative fertiloscopy,[318] which also allows salpingoscopy-microsalpingoscopy to be performed, detecting tubal abnormality irrespective of normal afertiloscopy.[319] Minor bowel[320] and rectal injuries[317] following fertiloscopy have been reported. [evidence level III]

Whether fertiloscopy can replace HSG and laparoscopy needs further prospective evaluation, taking into consideration the learning curve requirement.

Falloposcopy is defined as transvaginal microendoscopy of the fallopian tubes. It allows direct visualisation of the entire fallopian tube lumen[321] and it can be more accurate in diagnosing real unexplained or real tubal infertility, with spontaneous pregnancy rates significantly higher in patients with normal tubes (27.6%) defined by falloscopy than in patients with mild or severe endotubal lesions (11.5% to 0%).[322] In another study, the management plan was changed in 90% of patients following falloposcopy, and 24% conceived naturally[323] [evidence level III] However, technical problems limit the use of falloposcopy in routine clinical practice.[324;325]

Recommendations:

Women who are not known to have co-morbidities (such as pelvic inflammatory disease, previous ectopic pregnancy or endometriosis) should be offered hysterosalpingography [B] or hysterosalpingo-contrast-ultrasonography [A] to screen for tubal occlusion because they are reliable tests for ruling out tubal occlusion, and they are less invasive and make more efficient use of resources than laparoscopy.

Women who are thought to have co-morbidities should be offered a laparoscopy and dye so that tubal and other pelvic pathology can be assessed at the same time. [B]

Research recommendation:

Further research is needed to ascertain the value of fertiloscopy and falloposcopy in the investigation of couples with fertility problems.

7.5 Assessing uterine abnormalities

Uterine abnormalities such as adhesions, polyps, submucous leiomyomata and septae may be associated with infertility, and are estimated to be a factor in 10% to 15% of couples seeking treatment.[326] Compared with HSG, hysteroscopy is recognised as the 'gold standard' test for identifying uterine abnormalities as it allows direct visualisation of the uterine cavity.[327] [evidence level IIb]

Opinions differ as to whether hysteroscopy should be considered as a routine investigation in addition to HSG and laparoscopy and dye in the infertile couple. A causal relationship between leiomyoma and infertility has not been established.[328] [evidence level IIb] In patients undergoing assisted reproduction, the presence of uterine leiomyoma is associated with a reduced chance of clinical pregnancy or delivery.[329;330] [evidence level IIb–III] However, the effectiveness of surgical treatment of uterine abnormalities to enhance pregnancy rates is not established.

7.5.1 Ultrasound of the pelvis

Compared with bimanual pelvic examination, transvaginal ultrasound enables pelvic anatomy to be identified with increase accuracy and reliability and can be used in the evaluation of pelvic pathology, such as endometriosis, endometrioma, cysts, polyp, leiomyoma, adnexal and ovarian abnormality.[331-333] [evidence level IIb–III]

The diagnostic criteria for polycystic ovaries and PCOS, in which ultrasonic parameters have an important role, have been evolving over many years, and have recently been clarified in an international consensus statement (see Section 8.1).

Recommendation:
Women should not be offered hysteroscopy by itself as part of the initial investigation unless clinically indicated. There is conflicting evidence linking the treatment of uterine abnormalities with enhanced fertility. [B]

Research recommendation:

The role of pelvic ultrasound in women who are not suspected to have pelvic pathology requires further evaluation.

7.6 Post-coital testing of cervical mucus

The value of post-coital testing of cervical mucus for the presence of motile sperm is controversial and is a subject of continuous debate.[334-339]

It has been reported that the post-coital test is an effective predictor of conception where defined female causes of infertility are absent and duration of infertility is less than 3 years.[340] [evidence level III] However, a systematic review of 11 observational studies (n=3093 women) showed that the post-coital test has poor predictive power of fertility and lacks validity.{7419} [evidence level III] One RCT (n=444) compared cumulative pregnancy rates between couples offered a post-coital test vs couples who were not offered this test as part of their infertility investigation. No significant differences were shown in their respective cumulative pregnancy rates (49%, 95% CI 42% to 55% in the intervention group vs 48%, 95% CI 42% to 55% in the control group). There is evidence that the postcoital test can lead to more tests and treatments.[341] [evidence level Ib]

The post-coital test may be of value in the diagnosis of sexual dysfunction and ejaculatory problems. It has been suggested that results of post-coital testing may have little influence on treatment strategy in the light of the widespread use of assisted reproduction techniques (for example, IUI and IVF) for fertility problems associated with sperm-cervical mucus interaction. In addition, the lack of a reliable sperm function test may render post-coital testing unnecessary.[338] [evidence level IV]

Recommendation:

The routine use of post-coital testing of cervical mucus in infertility investigations is not recommended because it has no predictive value on pregnancy rate. [A]

Chapter 8 Strategies for management of fertility problems

The investigation of couple with fertility problems will lead to a number of possible diagnostic categories. If no cause is indentified the term unexplained infertility will be used. Each diagnostic category tends to have its own management strategy, but these strategies are based on a core of techniques that apply across many conditions. This applies particularly to the techniques involved in assisted reproduction. The diagnostic categories and management strategies are described in this chapter, and the individual techniques are described in subsequent chapters.

Male factor fertility problems

In the United Kingdom low sperm count or quality is found to be the only cause of infertility in about 20% and is a contributory factor in a further 25% of couples[1 2;342] It is estimated that in between 30% and 50% of men with poor semen quality no cause for this will be identified.[343;344]

Definitions

- Normozoospermia – normal ejaculate as defined by the WHO reference values
- Oligozoospermia – sperm concentration less than the WHO reference values
- Asthenozoospermia – less than the WHO reference values for motility
- Teratozoospermia – less than the WHO reference values for morphology
- Oligoasthenoteratozoospermia – signifies disturbance of all three variables (combinations of only two prefixes may also be used)
- Azoospermia – no spermatozoa in the ejaculate
- Aspermia – no ejaculate
- Crypotozoospermia – few spermatozoa recovered after centrifugation

Unless there is azoospermia, the predictive value of subnormal semen variables is limited. No functional test has yet been established that can unequivocally predict the fertilising capacity of spermatozoa. Sperm function tests such as computer-assisted semen analysis have not been found to be more predictive. Reliable sperm function tests are urgently required.[30;245] [evidence level IV]

The WHO specifications provide reference values on semen parameters. As there are no reliable sperm function tests, different sperm quality criteria are used by different clinics when considering allocating couples to treatments such as IUI, IVF or ICSI. There is no evidence or even consensus-based recommendations for good practice to support any particular sperm quality criteria for ICSI or other forms of assisted reproduction.

The several categories of male factor infertility are described alongside their specific treatments in Chapter 12.

Fertility problems associated with tubal disease

It is estimated that tubal factors account for 14% of the causes of subfertility in women.[1] Tubal blockage involves the proximal, mid or distal part. Proximal (uterotubal) obstruction occurs in 10–25% of women with tubal disease.[345]

Tubal disease includes tubal obstruction and pelvic adhesions due to infection, endometriosis and previous surgery. The management of tubal disease traditionally involved surgery, but IVF has become the predominant approach in recent years. The surgical approaches to management of tubal disease are discussed in Chapter 10. The management of tubal disease by IVF does not generally differ from the use of IVF for other indications (see Chapter 14).

Fertility problems associated with endometriosis

Endometriosis accounts for about 5% of female infertility.[1] It is defined as the presence of endometrial tissue occurring outside the uterine cavity and is associated with pelvic pain, dysmenorrhoea and infertility.

The diagnosis and severity of endometriosis are established by laparoscopy and biopsy using the revised American Fertility Society system,[346] which classifies the severity of endometriosis into four stages: stage I (minimal), stage II (mild), stage III (moderate); and stage IV (severe).This classification system is widely used and includes visual assessment, which is subject to inter- and intra-observer error. However, disease severity has not been shown to predict the chance of pregnancy.[347;348]

In the management of fertility problems associated with endometriosis it is widely accepted that minimal and mild endometriosis may be considered equivalent to unexplained infertility, and managed accordingly (see Section 8.5). Medical management, in the absence of pelvic pain, is no longer thought to be an appropriate strategy (see Section 11.1). Surgical management by the ablation of endometriotic lesions and the removal of endometriomas is an established approach (see Section 11.2), but many women with endometriosis of all severities choose to have IVF treatment (see Chapter 14).

8.1 Ovulatory disorders

Ovulatory disorders can be categorised as: those in which there is a failure of ovarian follicular development resulting in hypo-oestrogenic amenorrhea (WHO category I); those with hyperprolactinaemia; those in which the problem relates to anovulation (WHO category II); and those in which there is ovarian failure. Ovarian failure and its management by oocyte donation are discussed in Chapter 18.

8.1.1 WHO Group I: Low gonadotrophin and low oestrogen

Women with this problem will include those with low body weight, and restoration of body weight may help to resume ovulation and restore fertility (see Section 5.5). Most other women in this category will have ovulation induction treatment using pulsatile gonadotrophin-releasing hormone (GnRH) or gonadotrophin therapy (See Chapter 9).

Treatment for this group of women has included GnRH, a hypothalamic hormone which, if given in pulses, leads to a rise in the pituitary gonadotrophin hormones (FSH and LH). Continuous administration of GnRH results in increased gonadotrophin production. In case series studies pulsatile GnRH induces ovulation, achieving cumulative pregnancy rates of up to 82% in patients with hypogonadotrophic hypogonadism, and 95% in women with weight-related amenorrhoea after 12 cycles. The corresponding figures for live birth rates were 65% and 85% respectively.[349-351] [evidence level III]

Alternatively women can be treated with gonadotrophins. Treatment with hMG, which includes FSH and LH, was reported to be more effective in improving ovulation when compared with FSH alone.[352] [evidence level IIa] A study comparing hMG with pulsatile GnRH reported no difference in multiple gestation rates (14.8% vs 8.3%), but a lower rate of triplets in the pulsatile GnRH group.[353] [evidence level IIb]

8.1.2 Hyperprolactinaemia

Hyperprolactinaemia is an endocrine disorder caused by an increased secretion of prolactin from the pituitary gland, resulting in galactorrhoea, irregular menstruation and possible infertility. Where a diagnosis of hyperprolactinaemia is made, the management must include investigation to exclude the presence of a pituitary adenoma or extrapituitary tumours, which would require specific management before proceeding with fertility treatment. Dopamine agonists are widely used in the treatment of hyperprolactinaemia.[354] [evidence level IV] There are several newer dopamine agonists, but the effects of these on

reproductive outcomes has not been evaluated fully, and their safety in women intending to become pregnant has not been established (see Chapter 9).

Two RCTs (n=306) comparing cabergoline to bromocriptine in women with hyperprolactinaemic amenorrhoea reported that cabergoline was more effective in restoring ovulation and increased pregnancy rates (72% and 72% with cabergoline vs 52 and 48% with bromocriptine, respectively).[355;356] [evidence level Ib] However the manufacturer advises discontinuation of cabergoline at least 1 month before pregnancy.[236] [evidence level IV]

8.1.3 WHO Group II: Gonadotrophin disorder and normal oestrogen

This group of ovulation disorders predominately involves women with polycystic ovaries. Polycystic ovaries are present in about 80–90% of women with oligomenorrhoea and 30% of women with amenorrhoea.[357] About 30% of the PCOS population is of normal weight.[358] In women who have polycystic ovaries, where there are associated clinical symptoms (such as menstrual disturbance, hirsutism or acne) this is refered to as PCOS.

Over many years, the diagnostic criteria for polycystic ovaries and PCOS have been evolving, and different researchers have used differing definitions. A recent international consensus definition provides the possibility that future research will be based on a consistent definition. ***Awaiting details of international consensus definition.***

Reduction in weight and increased pregnancy rates have been reported in obese infertile women who took up lifestyle improvement programmes involving increased exercise and weight loss as compared with conventional management.[133] [evidence level Ib] (See Section 5.5).

Treatment strategies in women with PCOS include three established options. These options are: the use of oral anti-oestrogens; the use of ovarian drilling; and the use of injectable gonadotrophins. Another option is the use of oral metformin, which is not currently licensed for this indication. These treatment options are dicussed in detail in Chapter 9.

Recommendations:

Both pulsatile administration of gonadotrophin-releasing hormone and gonadotrophins with leuteinising hormone activity are effective in inducing ovulation in women with irregular ovulation and who have low gonadotrophins and low oestrogen (WHO Group I ovulation disorders). [B]

Women with an ovulatory disorder due to hyperprolactinaemia should be offered treatment with dopamine agonists such as bromocriptine. Consideration should be given to safety for use in pregnancy and cost when prescribing. [A]

8.2 Fertility problems associated with uterine abnormalities

Uterine abnormalities such as adhesions, polyps, submucous leiomyomata and septae may be associated with infertility, but their role in causing infertility is not clear.

Uterine myomas (leiomyomas)

We did not find any RCTs comparing myomectomy versus expectant management for women with leiomyomas. The incidence of myomas in women with infertility without any obvious cause of infertility is estimated to be 1–2.4%.[359;360]

A systematic review of 11 cohort studies suggests that women with submucous myoma have lower pregnancy rates compared with women with other causes for their infertility (RR 0.30, 95% CI 0.13 to 0.70). Myomectomy was not assocaiated with an increase in live

birth rate (RR 0.98, 95% CI 0.45 to 2.41), but was associated with a higher pregnancy rate (RR 1.72, 95% CI 1.13 to 2.58).[361] [evidence level IIb] Another cohort study found that women with intramural uterine fibroids had a reduced chance of pregnancy when compared with women with no fibroids following assisted reproduction (OR 0.46, 95% CI 0.24 to 0.88), having adjusting for number of embryos replaced and for age of over 40 years.[329] [evidence level IIb]

A case-control study found a lower pregnancy rate in women with myomas when compared with women without myomas (11% vs 25%). The pregnancy rate in women following myomectomy was higher than that in women with untreated myomas (42% vs 25%).[362] [evidence level IIb]

An RCT (n=109) that compared different surgical methods for undertaking myomectomy (abdominal myomectomy vs laparoscopic myomectomy) found no differences in pregnancy rates (55.9% with abdominal myomectomy vs 53.6% with laparoscopic myomectomy) or miscarriage rates (12% vs 20%) in women with large myomata. There was significantly higher incidence of post-operative fever, and a drop in haemoglobin and hospital stay in the group following abdominal myomectomy.[363] [evidence level Ib]

Septate uterus

Uterine septum is a congenital anomaly of the female reproductive tract. The incidence is not increased among women with infertility compared with other women (2–3%).[364;365] It is more common in women who have had recurrent pregnancy loss or pre-term birth.[366-368] Hysteroscopic metroplasty has not been shown to increase pregnancy rates in women with infertility who have a septate uterus.[369-372] [evidence level IIb –III]

Intra-uterine adhesions

Intra-uterine adhesions are rare, but they may result from previous uterine evacuation or surgery. They are associated with oligo-amenorrhoea. A case series (n=40) suggests that hysteroscopic adhesiolysis restored normal menstrual pattern in 81% of women of the 16

infertile women in the series, 63% (n=10) conceived and 37% (n=6) delivered a viable infant.[373] [evidence level III]

Recommendation:
For women with amenorrhoea who are found to have intra-uterine adhesions, hysteroscopic adhesiolysis may restore menstruation and improve the chance of pregnancy. [C]

Research recommendations:

Randomised controlled trials to evaluate any benefits of surgical treatment of leiomyomas on improving the chance of live birth are needed.

Further research to evaluate any benefit on live birth rates of surgical resection of uterine septum in women with infertility is needed.

8.3 Unexplained fertility problems

Unexplained (idiopathic) infertility is a diagnosis made by exclusion in couples who have not conceived and in whom standard investigations have not detected any abnormality. It accounts for about 40% of female infertility[374] and 8–28% of couple infertility.[1;3] In couples with unexplained infertility, the chance of spontaneous conception will relate to the duration of infertility (see Chapter 3). The spontaneous cumulative pregnancy rate has been estimated to lie between 33% and 60% at 3 years[375;376] and 36% at 7 years although this will be influenced by other known prognostic factors such as the age of the woman.[377;378] [evidence level IIb] [379-381] [evidence level III]

Minimal-mild endometriosis is often managed as unexplained infertility (see Sections 8.3 and Chapter 11).

Many couples who have unexplained fertility problems will have expectant management initially, and further management is essentially empirical. Anti-oestrogens (usually clomifene; see Chapter 9) and IUI (see Chapter 13) are usually used as intermediate options, with the final stage of management being IVF treatment (see Chapter 14). There is no evidence to suggest that ICSI improves pregnancy rates above those achieved with IVF in unexplained fertility problems (see Section 16.5).

Four further treatments that have been used in the management of unexplained infertility (danazol, bromocriptine, tubal flushing and fallopian sperm perfusion) are discussed below.

Danazol

A systematic review of two small RCTs assessing the effect of danazol in the treatment of unexplained infertility found no significant difference in pregnancy rates (OR 2.57, 95% CI 0.53 to 12.46) when compared with placebo.{5309} [evidence level Ia]

Bromocriptine

A systematic review of three RCTs found no improvement in pregnancy rates (OR 1.12, 95% CI 0.48 to 2.57) following treatment with bromocriptine vs placebo in couples with unexplained infertility.{5314} [evidence level Ia]

Tubal flushing

The potential therapeutic effect of diagnostic tubal patency testing has been debated for over 40 years. Tubal flushing might involve water- or oil-soluble media. Current practice usually involves water-soluble media when tubal flushing is performed at laparoscopy. A systematic review of eight RCTs showed a significant increase in pregnancy rates with tubal flushing using oil-soluble contrast media when compared with no treatment (OR 3.57, 95% CI 1.76 to 7.23). Tubal flushing with oil-soluble contrast media was associated with an increase in the odds of live birth (OR 1.49, 95% CI 1.05 to 2.11), but not pregnancy

rates (OR 1.23, 95% CI 0.95 to 1.60) when compared with tubal flushing with water-soluble media.{13192} [evidence level Ia] There were no significant differences in miscarriage, ectopic pregnancy and infection rates between tubal flushing with oil or water, or between oil plus water media vs water media only.{13192} [evidence level Ia] There were no trials assessing tubal flushing with water-soluble media versus no treatment.[382]

The potential consequences of extravasations of oil-soluble contrast media into the pelvic cavity and fallopian tubes may be associated with anaphylaxis and lipo-granuloma.

Fallopian sperm perfusion

Fallopian sperm perfusion is an insemination technique in which sperm are suspended in a large volume of solution (4ml) to allow the inseminate to be deposited not only in the uterine cavity but also to perfuse the fallopian tubes.[383]

A meta-analysis of five RCTs (number of patients in trials uncertain, 610 cycles) comparing fallopian sperm perfusion to IUI in women with various causes of infertility found that fallopian sperm perfusion improved pregnancy rates only in patients with unexplained infertility who underwent controlled ovarian stimulation with gonadotrophin/insemination protocols(OR 1.9, 95% CI 1.2 to 3).[382] [evidence level Ia] Similar results were found in a subsequent RCT (n=65, 42.4% with fallopian sperm perfusion vs 15.6% with IUI ; RR 2.72, 95% CI 1.11 to 6.66).[384] [evidence level Ib] A further RCT (n=96, 100 cycles) found that in a subgroup of patients with unexplained infertility, there was no significant benefit of fallopian sperm perfusion over IUI following ovulation stimulation in clinical pregnancy rate (21.4% with fallopian sperm perfusion vs 25% with IUI).[385] [evidence level Ib]

One RCT compared IUI with 1ml sperm suspension, fallopian sperm perfusion with 4ml sperm suspension and fallopian sperm perfusion using a system to ensure good cervical sealing (FAST). It found no significant differences between fallopian sperm perfusion with 4ml sperm suspension and fallopian sperm perfusion using the FAST system in terms of

pregnancy outcomes, but there were significant benefits with these two interventions when compared with IUI with 1ml sperm suspension in pregnancy rates (40% vs 18%). There were, however, no significant differences between the three interventions in terms of miscarriage, multiple pregnancy and OHSS rates.[386] [evidence level Ib]

Side effects of fallopian sperm perfusion were addressed in two trials,[384;386] but no complications were reported.

Recommendations:

Danazol is not effective in treating couples with unexplained infertility and should not be offered. [A]

Bromocriptine is not effective in treating couples with unexplained infertility and should not be offered. [B]

Fallopian sperm perfusion with ovarian stimulation is an alternative to intra-uterine insemination with ovarian stimulation in patients with unexplained infertility. [A]

Research recommendation:

Further randomised controlled trials are needed to evaluate the potentially therapeutic effects of tubal flushing with water soluble media.

Chapter 9 Ovulation induction agents

There are several approaches to ovulation induction therapy for the management of women with ovulatory disorders, and the drugs used in ovulation induction therapy also form the basis of superovulation therapy as used in IUI and IVF treatment. Issues common to the drugs across both ovulation induction therapy, IUI and IVF are discussed in this chapter, and issues more specific to IUI and IVF are discussed in Chapters 13 and 14, respectively.

9.1 Anti-oestrogens

Clomifene citrate and tamoxifen are anti-oestrogens. Tamoxifen has similar structure and properties to clomifene citrate. They induce gonadotrophin release by occupying the oestrogen receptors in the hypothalamus, thereby interfering with the normal feedback mechanisms.

Anti-oestrogens in women with ovulatory disorders

A systematic review of four cross-over RCTs that compared clomiphene citrate with placebo in patients with amenorrhoea/oligo-menorrhoea, including PCOS found that all doses of clomifene citrate were associated with increased pregnancy rates per treatment cycle (OR 3.41, 95% CI 4.23 to 9.48) and with increased ovulation (OR 4.6, 95% CI 2.84 to 7.45).{5315} [evidence level 1a] These RCTs involved women with a variety of ovulatory disorders, including some who had low oestrogens and would not be expected to benefit from anti-oestrogen treatment, so this may be an under-estimate of the effectiveness in women with PCOS.

Clomifene citrate and tamoxifen have been shown to have similar effects on pregnancy rate (22% with tamoxifen vs 15% with clomifene citrate; RR 1.45, 95% CI 0.58 to 3.63) and ovulation (44% with tamoxifen vs 45% with clomifene citrate) in anovulatory women with

infertility.[387] [evidence level Ib] Similar results were found in three other studies, including a quasi-randomised study.[388-390] [evidence level Ib]

One RCT showed that tamoxifen/clomifene citrate combination therapy did not improve pregnancy rate per cycle (8.6% with tamoxifen/clomifene citrate vs 4.8%with clomifene citrate; RR 1.80, 95% CI 0.20 to 16.21).[391] [evidence level Ib]

About 70% of anovulatory patients ovulate in response to clomifene citrate treatment,[392;393] and they do so at a dose of 50–100 mg,[394] the maximum dose being 250 mg. Anovulatory patients who do not ovulate while receiving the 150 mg dose of clomifene citrate are considered to be resistant to the drug.[395] In anovulatory women, there is a significant association between clomifene citrate treatment failure and increased BMI (BMI > 27.2 kg/m^2 or > 30.6 kg/m^2).[396;397] [evidence level IIb] A weight loss programme may improve ovulation and pregnancy outcomes in obese infertile women for all forms of fertility treatment including ovulation induction, IUI and IVF (see Section 5.5).[134;135] [evidence level IIb] Advice on weight reduction may improve response to clomifene citrate treatment, as a modest weight reduction of 5% of initial body weight can result in improvement in endocrine and ovulatory function of obese women with PCOS.[398] Lifestyle modification may improve insulin sensitivity and restore ovulation in women with PCOS.[399] [evidence level IIb]

Although the British National Formulary recommends a maximum of six cycles of clomifene citrate,[236] this relates to the number of cycles in one course of treatment. In clinical practice, many women will require more than one course of treatment, and this will result in administration of more than six cycles of clomifene citrate.

There may be benefit in receiving clomifene citrate in up to 12 cycles as cumulative pregnancy rates continue to rise after six treatment cycles before reaching a plateau, comparable to that of the normal fertile population, by cycle 12[396;400] [evidence level IIb] However, use of clomifene for 12 or more cycles has been associated with an increased

risk of ovarian cancer in one study (RR 11.1, 95% CI 1.5 to 82.3).[401] [evidence level III] It would be appropriate to consider alternative treatments after 12 cycles of poor results from clomifene citrate.

Clomifene citrate in unexplained fertility problems

Seven RCTs were found. Six of these studies were included in a systematic review.{5311} [evidence level Ia] The seventh trial was excluded from the systematic review because it used alternation rather than randomisation to allocate treatment. Allocation based on laternation may be predictable and this could bias the findings. In patients with unexplained infertility, clomifene citrate treatment compared with no treatment increased clinical pregnancy rates per patient (OR 2.37, 95% CI 1.22 to 4.62) and per treatment cycle (OR 2.5, 95% CI 1.35 to 4.62).{5311} The RCTs identified by the review were generally of poor quality and underpowered, and so this small treatment effect could be offset by one further medium-sized trial if one becomes available. The trial excluded from this review showed a decrease in pregnancy rate per patient and per cycle in the clomifene citrate group compared with the no treatment group.[402]

Recommendations:

Women with WHO Group II ovulation disorders such as polycystic ovary syndrome should be offered treatment with either clomifene citrate or tamoxifen for up to 12 months because both are effective treatments. [A]

Women should be informed of the risk of multiple pregnancies associated with both clomifene citrate and tamoxifen. [B]

Women with unexplained fertility problems may have higher pregnancy rates if they take clomifene citrate, but this needs to be balanced by the possible risks of treatment, especially multiple pregnancy. [A]

9.2 Metformin

Metformin is an oral biguanide insulin-sensitising agent widely used for the treatment of type 2 diabetes. Two systematic reviews have evaluated the use of metformin alone or in combination with clomifene citrate. The more recent review includes 15 RCTs and is used here.[403] The earlier review is of poorer quality and includes 12 RCTs and a number of observational studies.{12654} The inclusion criteria for the reviews were similar, but two RCTs in the earlier review were excluded from the later review. In women with clomifene resistant PCOS and a mean BMI above 25 kg/m^2 , metformin had no significant effect as a single agent in clinical pregnancy rate when compared with placebo, but a significant increase was shown when combined with clomifene citrate vs clomifene citrate alone (OR 4.88; 95% CI 2.46 to 9.67). Metformin can induce ovulation either as a single agent when compared with placebo (OR 3.88; 95% CI 2.25 to 6.69), or in combination with clomifene citrate compared with clomifene citrate alone (OR 4.41; 95% CI 2.37 to 8.22). Sensitivity analysis supported the stability of these results. There were significant adverse side effects such as nausea and vomiting and gastrointestinal disturbances with the use of metformin.[403] [evidence level Ia] Metformin can also be used as an adjuvant to general lifestyle improvements (see Sections 5.5 and 9.1).

A descriptive review also suggested that ovulation rates were higher with the use of clomifene after metformin pre-treatment or cotreatment when compared with placebo and clomifene. Metformin treatment of patients with clomifene citrate-resistant PCOS undergoing IVF significantly improved clinical pregnancy rates.[404] [evidence level Ib–IIb]

Metformin is not currently licensed for use in the management of PCOS.

Recommendations:

In anovulatory women with polycystic ovary syndrome who have not responded to clomifene citrate and who have a high body mass index, metformin combined with

clomifene citrate may be effective in enhancing the success of ovulation and pregnancy rates. [A]

Women prescribed metformin should be informed of the side effects associated with the use of metformin. [GPP]

9.3 Ovarian drilling

Surgical methods of ovulation induction for women with clomifene citrate-resistant PCOS include laparoscopic ovarian drilling with diathermy. This technique is designed to create several surface lesions of the ovary, which may help to correct endocrine abnormalities and trigger ovulation.

A systematic review of four RCTs found no significant differences between laparoscopic ovarian drilling after 6–12 months follow up and 3–6 cycles of ovulation induction with gonadotrophins in cumulative pregnancy rate (OR 1.42; 95% CI 0.84 to 2.42) or miscarriage rate (OR 0.61; 95% CI 0.17 to 2.16) in women with clomifene citrate-resistant PCOS.{5151} [evidence level Ia] Multiple pregnancy rates were considerably reduced in those women who conceived following laparoscopic drilling (OR 0.16; 95% CI 0.03 to 0.98). There was insufficient evidence to support any one surgical technique over another relating to adhesion formation.{5151} [evidence level Ia]

One RCT showed a significant difference between the use of a fine or thick needle in the occurrence of adhesion formation (52% with fine needle vs 88% with a thick needle, RR 0.59, 95% CI 0.39 to 0.91) in laparoscopic ovarian drilling in patients with PCOS.[405] [evidence level Ib]

A retrospective study showed that three punctures per ovary appeared to be the plateau dose for laparoscopic ovarian diathermy.[406] [evidence level III]

Laparoscopic ovarian diathermy can impose technical problems and anaesthesiological risks in obese women with PCOS.[407] There are no data on the long-term health consequences of ovarian drilling.

Recommendation:

Women with polycystic ovary syndrome who have not responded to clomifene citrate may be offered laparoscopic ovarian drilling because it is as effective as gonadotrophin treatment and is not associated with a risk of multiple pregnancy. [A]

Research recommendation:

Further research is needed to evaluate the effect of ovarian drilling on the formation of adhesions.

9.4 Gonadotrophin use in ovulation induction therapy for ovulatory disorders

For women with PCOS who do not respond to clomifene citrate or who have not become pregnant after 12 months of treatment with anti-oestrogens, gonadotrophins have been used as ovulation induction agents.{5587} Human menopausal gonadotrophin is a purified extract from human post-menopausal urine; it contains both FSH and LH. FSH alone is available in a variety of preparations, which are either derived from human menopausal urine or from cultured cells.

A systematic review of 14 RCTs found no significant differences between hMG (both FSH and LH) and urinary FSH in terms pregnancy rate per cycle (OR 0.89; 95% CI 0.53 to 1.49), multiple pregnancy rate (OR 0.62; 95% CI 0.11 to 3.58), miscarriage rate (OR 0.85; 95% CI 0.24 to 2.95), ovulation rate per cycle (OR 0.75; 95% CI 0.52 to 1.07),or overstimulation rate per cycle (OR 0.85; 95% CI 0.40 to 1.81).{5587} [evidence level Ia] No significant differences on the above outcomes were found between the use of subcutaneous pulsatile and intramuscular injection of gonadotrophins;{5587} daily and alternate day administration; or step-up' and standard regimens.{5587} [evidence level Ib]

A systematic review of four RCTs compared recombinant FSH (rFSH) and urinary FSH (uFSH) in PCOS patients who were resistant to clomifene citrate found no significant differences between pregnancy rate (OR 0.95; 95% CI 0.64 to 1.41), miscarriage rate (OR 1.26; 95% CI 0.59 to 2.70) multiple pregnancy rate (OR 0.44; 95% CI 0.16 to 1.21) or ovulation rate (OR 1.19; 95% CI 0.78 to 1.80).{4918} No significant differences were shown in these outcomes between administering rFSH as a chronic low dose or conventional regimen.{4918}

Recommendation:
Women with WHO group II ovulation disorders such as polycystic ovary syndrome who do not respond to treatment with anti-oestrogens or who have not become pregnant after 12 months of treatment with anti-oestrogens should 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 cost when prescribing. [A]

9.5 Gonadotrophin use during in vitro fertilisation treatment

Human menopausal gonadotrophin and urinary follicle-stimulating hormone

A 1995 meta-analysis of eight RCTs showed that the use of FSH is associated with a significantly higher clinical pregnancy rate per cycle (OR 1.71, 95% CI 1.12 to 2.62) when compared with hMG.[408] There were insufficient data to assess miscarriage, multiple pregnancy rates and OHSS incidence.

A more recent meta-analysis of 15 RCTs, which included seven new RCTs, reached similar conclusions.[409] [evidence level Ia]

Urinary-derived gonadotrophins vs recombinant follicle-stimulating hormone

Four meta-analyses involving a total of 30 RCTs were identified. There is some overlap between the trials included in the different meta-analyses with each meta-analysis using different inclusion and exclusion criteria for the intervention.[410-413]

Urinary follicle-stimulating hormone vs recombinant follicle-stimulating hormone

This systematic review of 18 RCTs included only trials comparing uFSH with rFSH. It found that rFSH significantly increased clinical pregnancy rate per cycle (OR 1.21, 95% CI 1.04 to 1.42), ongoing pregnancy rate per cycle (OR 1.29, 95% CI 1.08 to 1.54) when compared with uFSH.[411] [evidence level Ia] There were no significant differences between rFSH and uFSH in the rates of spontaneous abortion (OR 0.80, 95% CI 0.56 to 1.13), multiple pregnancy (OR 0.80, 95% CI 0.56 to 1.13) or OHSS (2% with rFSH vs 1.4% with uFSH; RR 1.50, 95% CI 0.88 to 2.58).[411] [evidence level Ia] It included 14 RCTs used by another recent meta-analysis, but also excluded 4 RCTs used by the latter.[414] [evidence level Ia]

Urinary-derived gonadotrophins vs recombinant follicle-stimulating hormone

This recent systematic review of 20 RCTs included trials comparing urinary gonadotrophins (including hMG, FSH-P and FSH-HP) versus rFSH. It showed no significant difference between rFSH and in clinical pregnancy rate (OR 1.07, 95% CI 0.94 to 1.22). Subgroup analyses found no significant difference in clinical pregnancy rate between rFSH and hMG (OR 0.81, 95% CI 0.63 to 1.05), between rFSH and FSH-P (OR 1.24, 95% CI 0.98 to 1.58), or between rFSH and FSH-HP (OR1.14, 95% CI 0.94 to 1.40).[414] [evidence level Ia] Sensitivity analysis showed stability of results, whether or not the trials were sponsored by drug companies. It included 14 RCTs used in the previous systematic review.[411]

One systematic narrative review of eight RCTs (included in the previous systematic review) was excluded due to limitation of the review methods used; there was no clear assessment of selection, quality and validity of included studies).[412] [evidence level Ib–IIa]

One RCT not included in any of the above reviews found a non-significant increase between rFSH and uFSH in pregnancy rate per woman (24% with rFSH vs 11.4% with uFSH; RR 2.10, 95% CI 0.77 to 5.75) and take-home baby rate (19% with rFSH vs 11.4% with uFSH; RR 1.81, 95%CI 0.55 to 6.01).[415] [evidence level Ib]

Human menopausal gonadotrophins vs rFSH

This systematic review of 8 RCTs included only trials comparing hMG vs rFSH. Four trials were included in the previous recent review.[413] It showed no significant differences between hMG and rFSH in ongoing/live birth rate (OR 1.27, 95% CI 0.98 to 1.64), miscarriage rate (OR 1.18, 95% CI 0.63 to 2.20), multiple pregnancy rate (OR 1.46, 95% CI 0.98 to 2.16), cycle cancellation rate (OR 0.93, 95% CI 0.52 to 1.68) or OHSS rate (OR 1.45, 95% CI 0.57 to 3.69) when used with a long GnRH agonist protocol. There was, however, a borderline significance in clinical pregnancy rate in favour of hMG (OR 1.28, 95% CI 1.00 to 1.64) using the long GnRH agonist protocol.[410] [evidence level Ia] No significant differences were shown in these outcomes comparing hMG and rFSH used in a short GnRH agonist protocol, or when no down-regulation was administered.[410] [evidence level Ia] Four of the RCTs were included in a previous review [413]

An additional RCT found no significant differences between hMG and rFSH in ongoing pregnancy rate (OR 1.14, 95% CI 0.78 to 1.66), miscarriage rate (OR 0.90, 95% CI 0.47 to 1.73), multiple gestation rate (OR 0.84, 95% CI 0.42 to 1.67) and moderate to severe OHSS rate (OR 1.67, 95% CI 0.44 to 6.85). Both hMG and rFSH were used following down-regulation with GnRH agonist.[409] [evidence level Ib]

Cost-effectiveness

We identified four cost-effectiveness studies relating to gonadotrophins.

Two studies reported cost per ongoing pregnancy. The first health economic evaluation used effectiveness data from a systematic review of 12 RCTs. This review was later updated to include 18 RCTs.[416;417] [evidence level Ia] The conclusions of the most recent

review were that the use of recombinant FSH compared to urinary FSH in IVF treatment increased the total number of ongoing pregnancies at 12 weeks' gestation (OR 1.20, 95% CI 1.02–1.42). The review concluded that the increased costs of rFSH were outweighed by its greater efficacy.

The third health economic evaluation used clinical effectiveness data largely based on one RCT, which compared rFSH and uFSH-HP/hMG. This RCT did not detect a difference between the different gonadotrophins (OR 1.19, 95% CI 0.90–1.58).[418] [evidence level Ib] However in their economics model in spite of the fact there is no difference detected between the groups they used these estimates to predict a cumulative pregnancy rate after 3 cycles of 57% for rFSH and 44% for both uFSH-HP and hMG. The authors concluded that rFSH was more cost effective. This trial is incorporated in a systematic review of 20 RCTs used in this guideline.[413] Overall the pregnancy rates with rFSH and uFSH-HP/hMG are not different (OR 1.07 95% CI 0.94–1.22). The use of a predictive model to suggest a difference in clinical effectiveness between treatments where no statistically significant difference was detected led to an inappropriate conclusion in the cost effectiveness analysis.

Taken overall, the systematic review undertaken for this guideline concluded that there is no difference in the clinical effectiveness of the different gonadotrophins. In this case consideration should be given to costs when prescribing.

A United Kingdom economic evaluation of urinary gonadotrophins (highly purified menotropin, or HP-hMG) compared with rFSH has undertaken recently.{Kennedy et al., in press} This study was based on an RCT that found no difference in pregnancy rate or on-going pregnancy at 10 weeks between uFSH and rFSH regimens. Since the RCT reported no statistical difference in effectiveness, the economic study was able to focus on the cost of the drugs. Both resource use and cost were reported in this study, and this added to the transparency of the study. It was concluded that HP-hMG was the least expensive option since it was offered at a lower price to the NHS. Sensitivity analysis was undertaken to explore whether discounted prices would change this result. However, the discounting rate

was applied equally to both forms of the drug. It was not made clear whether these prices might change rapidly over time or whether they would change differentially (that is, increasing or decreasing the relative difference in cost) between the drugs. Since the cost of these drugs was the driver of the relative difference in cost-effectiveness (and not other differences either in effectiveness or in use of other health care resources) this result could be highly time-sensitive to the prices of these drugs.

At the prices reported in the most recent paper described above, the cost of gonal- (rFHS) per 75 unit ampoules was £26.25 and HP-hMG around £14 for the same dose. Other uFSH drugs were advertised at around £13 in the British National Formulary{16122} and around £23 for rFSH preparations. Some older uFSH preparations are delivered intramuscularly and cannot be administered by patients alone. Therefore additional costs of GP/practice nurse time to administer these drugs could offset the lower drug cost. Where drug regimens are similar and they are of equal effectiveness, the decision to opt for the cheaper regimen could release considerable NHS resources to pay for additional IVF cycles or other services. With over 30,000 IVF cycles annually, uFSH could represent a potential cost saving (where other services remain the same) of £14 million to £15 million.

Recommendations:

Human menopausal gonadotrophin and recombinant follicle-stimulating hormone are both effective in improving pregnancy rates when used following down-regulation with gonadotrophin-releasing hormone agonist. [A]

For ovarian stimulation during in vitro fertilisation treatment urinary-derived gonadotrophins and recombinant follicle-stimulating hormone are equally effective when used with pituitary down-regulation. Consideration should be given to cost when prescribing. [A]

9.6 Gonadotrophin-releasing hormone analogues in ovulation induction therapy

Gonadotrophin-releasing hormone (GnRH) agonists can be used in conjunction with gonadotrophins to achieve pituitary down-regulation and facilitate cycle control in ovarian stimulation. However, they are not widely used in ovulation induction therapy for ovulatory disorders.

A systematic review of 3 RCTs comparing pre-treatment with gonadotrophin-releasing hormone analogue (GnRH-a) and gonadotrophin to gonadotrophin alone did not detect differences in pregnancy rate (OR 1.50; 95% CI 0.72 to 3.12) or OHSS rate (OR 1.40; 95% CI 0.50 to 3.92).{5313} [evidence level Ia] One further RCT with pre-treatment with GnRH-a and FSH compared with FSH alone did not improve the pregnancy rate (10% vs 0%) or the ovulation rate (20% vs 90% RR 0.22; 95% CI 0.06 to 0.78).[419] [evidence level Ib] When gonadotrophins were used concomitantly with GnRH-a, the risk of OHSS was significantly increased (OR 3.15; 95% CI 1.48 to 6.70), but no conclusions could be drawn about miscarriage and multiple pregnancy rates due to insufficient data.{5587}.[420] [evidence level Ia]

Recommendations:

Women with polycystic ovary syndrome who have not responded to clomifene treatment should not be offered treatment with gonadotrophin-releasing hormone agonist concomitantly with gonadotrophins because this does not improve pregnancy rates, but may be associated with an increased risk of ovarian hyperstimulation. [A]

9.7 Gonadotrophin-releasing hormone analogues during in vitro fertilisation treatment

GnRH agonists are widely used in conjunction with gonadotrophins to achieve pituitary down-regulation and facilitate cycle control in ovarian stimulation during IVF treatment. The different GnRH agonist and antagonist drugs, their routes of administration and protocols are discussed below.

Gonadotrophin-releasing hormone agonist protocol vs no gonadotrophin-releasing hormone agonist protocol

A meta-analysis of 17 RCTs showed significant improved clinical pregnancy rate per cycle after GnRH agonist use for IVF (pooled OR 1.80, 95% CI 1.33 to 2.44), for GIFT (pooled OR 2.37, 95% CI 1.24 to 4.51) when compared with no GnRH agonist use.[420] [evidence level Ia] There was a significant reduction of cycle cancellation with the use of GnRH agonist protocols (OR 0.33, 95% CI 0.25 to 0.44).[420] [evidence level Ia] There were no significant differences in multiple pregnancy rate after GnRH agonist use (pooled OR 2.56, 95% CI 0.95 to 6.91) or spontaneous abortion rate between GnRH agonist and standard protocols (pooled OR 0.84, 95% CI 0.41 to 1.73). Relevant data were not available to assess OHSS rates.[420] [evidence level Ia]

Gonadotrophin-releasing hormone agonist protocols: long vs short vs ultrashort

In long protocols, GnRH agonists are administered either in the midluteal phase or in the early follicular phase to achieve pituitary down-regulation in about 8 to 21 days before commencing gonadotrophins.

Both the short and ultrashort protocols are administered early in the follicular phase. They take advantage of the increased secretion of gonadotrophin resulting from the initial direct stimulation of the pituitary gland by GnRH agonist before desensitisation occurs. The duration of GnRH agonist administration is about 10-14 days in short protocols and about 3 days in ultrashort protocols.

Another systematic review of 26 RCTs found increased clinical pregnancy rate per cycle with long GnRH agonist protocol (pooled OR 1.32; 95% CI 1.10 to 1.57) when compared with short and ultra-short GnRH agonist protocols. The pooled OR for clinical pregnancy rate per cycle in long vs short GnRH agonist protocol was 1.27 (95% CI 1.04 to 1.56);and in long vs ultra-short GnRH agonist protocols was 1.47 (95% CI 1.02 to 2.12).[421] [evidence level Ia]

An earlier meta-analysis of 17 RCTs included quasi-randomised trials and is therefore excluded from this review.

Gonadotrophin-releasing hormone agonist protocols: depot vs daily dose

There are two types of GnRH agonist used in the long protocol: one consisting of daily GnRH agonist low doses (Buserelin, nafarelin nasal spray) and one with the administration of the agonists in higher long-acting doses (depot)(triptorelin, leuprorelin, goserelin). The main difference between the two approaches is in the GnRH agonist composition.

A systematic review of six RCTs found no significant differences between depot GnRH agonist and daily GnRH agonist in clinical pregnancy rate per woman (OR 0.94, 95% CI 0.65 to 1.37), ongoing/delivered pregnancy rate per cycle (OR 0.85, 95% CI 0.54 to 1.36), multiple pregnancy rate (OR 0.95, 95% CI 0.27 to 3.39), miscarriage rate (OR 1.17, 95% CI 0.43 to 3.15) and OHSS incidence (OR 0.72, 95% CI 0.14 to 3.74).[422] However, the use of depot GnRH agonist increased gonadotrophin requirements and duration of ovarian stimulation when compared with daily GnRH agonist.[422] [evidence level Ia]

A meta-analysis of nine RCTs found no significant differences between intranasal GnRH agonist vs other GnRH agonist protocols in clinical pregnancy rate per embryo transfer (32% with intranasal GnRH agonist vs 30% with other GnRH agonists; common OR 0.93, 95% CI 0.57 to 1.51) and in cycle cancellation rate (5% vs 6%; common OR 0.88, 95% CI 0.44 to 1.79).There were no data on pregnancy rate per cycle.[423] [evidence level Ia]

Gonadotrophin-releasing hormone antagonists vs gonadotrophin-releasing hormone agonists

Gonadotrophin-releasing hormone antagonists (such as cetrorelix and ganirelix) produce immediate and direct pituitary suppression. These allow treatment cycles to be shorter (within 1 month) and avoid oestrogen withdrawal effects associated with the use of GnRH agonists. They may also reduce the dose of gonadotrophins required. As a result, they may be preferred by patients.

A systematic review of five RCTs showed that the use of GnRH antagonist resulted in reduced clinical pregnancy rates per woman (OR 0.79, 95% CI 0.63 to 0.99) when compared with long protocol GnRH agonist.[424] [evidence level Ia] There were no significant differences between these two protocols in terms of multiple pregnancy rates (OR 0.74, 95% CI 0.48 to 1.16), incidence of severe OHSS (OR 0.47, 95% CI 0.18 to 1.25), miscarriage rates (OR 1.03, 95% CI 0.52 to 2.04) or cycle cancellation rates (OR 0.88, 95% CI 0.56 to 1.40).[424] [evidence level Ia] Patient satisfaction was not considered in this systematic review.

A second systematic review[425] included the five RCTs considered in the review discussed above, plus an additional RCT and a non-randomised study. The results of this review were similar to those of the above review.

Recommendations:

For pituitary down-regulation as part of in vitro fertilisation treatment, using gonadotrophin-releasing 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 agonist in long protocols during in vitro fertilisation is therefore recommended. [A]

The use of gonadotrophin-releasing hormone antagonists may allow for shorter treatment cycles and lower doses of gonadotrophin, but their use is associated with reduced pregnancy rates and is therefore not recommended as a first line of treatment. [A]

Research recommendation:

Further research is needed to compare the clinical effectiveness (incuding patient satisfaction) and the cost-effectiveness of the gonadotrophin-releasing hormone agonists and antagonists during in vitro fertilisation treatment.

9.8 Growth hormone as an adjunct to ovulation induction therapy

For women with clomifene citrate-resistant PCOS, co-treatment with recombinant human growth hormone plus GnRH-a, or growth hormone plus hMG has no significant effect on the amount and duration of hMG used, ovulation (93% vs 93%; 88% vs 100% respectively) and pregnancy rates (26% vs 20%; 25% vs 13%) when compared with GnRH-a and hMG alone.[426] [evidence level Ib] It has been suggested that co-treatment with growth hormone may improve ovarian responses to exogenous gonadotrophins, thus reducing the overall gonadotrophin requirement.[427]

Recommendations:

There is no role for the use of adjuvant growth hormone treatment with gonadotrophin-releasing hormone agonist/human menopausal gonadotrophin in ovulation induction in women with polycystic ovary syndrome who are resistant to clomifene citrate. [A]

9.9 Pulsatile gonadotrophin-releasing hormone

A systematic review of three RCTs, one non-RCT and 18 uncontrolled case-series studies found insufficient evidence for or against a beneficial effect of pulsatile GnRH in patients with clomifene citrate-resistant PCOS when compared with other ovulatory agents (hMG, FSH, with and without pre-treatment with GnRH-a).{4824} [evidence level Ia]

Recommendation:

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

9.10 Monitoring ovulation induction

Ovarian monitoring provides information on ovarian response to ovulation induction agents by ascertaining the number and size of the developing follicles.

Ultrasonography is regarded as a safe, accurate and efficient method of monitoring follicular development in response to ovulation induction,[428-430] in helping to reduce multiple pregnancy rates, especially in women with PCOS[349] when compared with oestrogen monitoring. [evidence level IIb] Oestrogen monitoring provides no additional information compared with ovarian ultrasound.[428] [evidence level IIb] Ultrasonography was found to have good predictive value in the occurrence of OHSS which was associated with larger number of immature follicles at time of hCG administration.[431] [evidence level III] An observational study reported that follicular sonography performed during ovarian stimulation predicted 88% of cycle decisions.[432] [evidence level III]

Ovarian hyperstimulation syndrome

Fertility drug therapy to stimulate ovulation carries a risk of OHSS. This can be a potentially fatal condition when many follicles are stimulated, leading to ascites, pleural and pericardial effusion, haemoconcentration and coagulopathy.[433]

The exact incidence of severe OHSS has not yet been determined. Available data suggest an incidence of 3% of cycles when hMG is used,[434] and in 0.2% to 1.0% of all assisted reproduction cycles.[435-437] Current incidence is unknown.

Clinics that provide ovarian stimulation should have protocols in place for the prevention, diagnosis and management of OHSS (see Section 15.8).

Multiple pregnancy

Prevention of iatragenic multifetal gestation involves judicious use of fertility drugs and rigorous monitoring of patients on ovulation induction therapy with ultrasound to chart follicular development and is best carried out in a specialist clinic.

There is a strong correlation between the initial number of fetuses, the final number and the risks of pregnancy loss and prematurity.[438;439] [evidence level III] Higher initial numbers fare worse. Multiple gestations are high risk pregnancies associated with higher obstetric complications, perinatal, neonatal and infant mortality[440] as well as significant financial[441;442] and psychological[443] consequences. [evidence level III] However, assisted reproduction multiple pregnancies do not appear to be at any more risk of poor obstetric and neonatal outcomes than those conceived spontaneously.[444;445] [evidence level III] However, recent surveys have suggested that multiple pregnancies may not be viewed as an adverse outcome by patients.[446-450] [evidence level III-IV]

Multiple pregnancy occurs in 2–13% of women with all causes of infertility taking clomifene,[451] compared with a spontaneous multiple pregnancy rate of about 1–2% of women in the North American and European populations,[452;453] and in 36% of women with clomifene citrate-resistant PCOS when conventional regimens of gonadotrophins are used to induce ovulation.[454] [evidence level III] In a one-year survey in the United Kingdom, triplet pregnancies accounted for 57% of all pregnancies and were attributable to clomifene.[455] [evidence level III] The increase in triplet deliveries following assisted reproduction has been linked to the increased sale and use of ovulation induction agents.[456] [evidence level III] A recent report by the French National In Vitro organisation (FIVNAT) showed that 7.3% of all IVF conceptions between 1986 and 1993 related to triplets or higher-order multiple gestation.[457] [evidence level III]

Multifetal pregnancy reduction refers to the termination of one or more normal fetuses in a multifetal pregnancy in order to improve the survival rates for the remaining fetuses and to decrease maternal morbidity.[438] [evidence level IV] For any initial number of embryos, reduction to twins has the highest survival rate.[439] [evidence level III] Reduction to singletons rather than twins is associated with a higher gestational age at delivery, but a lower survival rate.[438] [evidence level III]

Recommendations:

Couples who are offered ovulation induction 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 to reduce the risk of multiple pregnancy and ovarian hyperstimulation. [C]

9.11 Other risks and side effects associated with ovulation induction agents

Ovarian cancer

Ovarian cancer accounts for about 4% of all cancers in women and is the fourth most common cancer among women in England and Wales.[458] There has been increasing interest in recent years regarding a possible link between the drugs used for ovarian stimulation and the subsequent risk of cancers, particularly ovarian cancer.

A case-control study found that infertile women who had taken clomifene had a higher risk of developing an ovarian tumour than women who had not taken clomifene (RR 2.3, 95% CI 0.5 to 11.4).[401] [evidence level III] Prolonged use of clomifene for 12 or more cycles was associated with considerable increased risk of ovarian tumour (RR 11.1, 95% CI 1.5 to 82.3).[401] [evidence level III]

Case reports and epidemiological studies examining ovarian cancer risk in relation to the use of fertility drugs have shown conflicting results, mainly because of methodological problems such as low study power and misclassification bias. Reviews of these studies found insufficient evidence to support a direct causal relationship.[459-463] The association between fertility drug use and breast cancer, thyroid cancer, endometrial cancer, cervical cancer, colorectal cancer and melanoma has not been established.[463] Further studies are needed in this area.

The conflicting results may stem from the interaction between nulliparity, infertility and ovarian cancer. It is well established that there is an association between nulliparity and increased risk of ovarian cancer.[464-469] It is uncertain whether the increased risk of ovarian cancer amongst infertile women is caused by the relatively high proportion of nulliparous women in this population, or the use of infertility treatments per se. It is also uncertain which of these two factors carries the higher risk.

The first epidemiological report of cancer incidence following ovarian stimulation treatment in the United Kingdom found no evidence for a link between ovarian stimulation and increased cancer incidence, but this needs to be interpreted with caution because of methodological limitations.[470]

A survey of women attending an infertility clinic showed that 67% of women knew of a possible relationship between fertility drugs and ovarian cancer, while 21% would accept no risk, 6% would accept a maximum risk of more than 10%, and nearly all thought the benefits of infertility treatment outweighed the risks.[471] A recent survey of reproductive endocrinologists showed that 83% of those surveyed addressed this risk when obtaining consent from patients for infertility treatment,[472] and 40% of physicians routinely discussed the topic of ovarian cancer with their patients before prescribing fertility drugs.[471]

It has been suggested that informed consent for induction of ovulation should be obtained, that the number of treatment cycles be shortened, and that women who have received these drugs should be monitored rigorously.[473]

Prion disease

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.

It has been reported that abnormal prion protein has been identified in urine from patients with Creutzfedlt-Jacob disease.[474] Although it was noted that infectivity had not been demonstrated in animal experiments, the Committee on Safety of Medicines recommended that, as a precautionary measure, no human urine used in production of medicines should be sourced from a country with one or more indigenous cases of variant Creutzfedlt-Jacob disease. This reflects the position in the United Kingdom regarding the source of plasma used in the production of blood products.

One urinary product (Metrodin High Purity), which is manufactured using human urine sourced in Italy, was withdrawn by the Medicines Control Agency in February 2003 after a case of variant Creuzfeldt-Jacob disease was reported in Italy. Other urinary products available in the United Kingdom are not affected because the urine is sourced from countries with no reported cases of variant Creuzfeldt-Jacob disease. Recombinant gonadotrophins available in the United Kingdom comply with European safety requirements for transmissible spongiform encephalopies.

Recommendation:

Couples should be informed that the evidence for an association between ovarian cancer and ovulation induction therapy is unclear. [C]

Research recommendation:

Further research is needed to assess the long-term health effects of ovulation induction agents on women who have undergone ovulation induction therapy for their fertility problems.

Chapter 10 Tubal surgery

The potential advantage of tubal surgery if successful is that it may enable couples to conceive naturally without further intervention.[475]

Proximal tubal occlusion is a common cause of female tubal infertility. However, proximal tubal obstruction is probably over-diagnosed, as intra-uterine pregnancies occur spontaneously in women with proximal tubal blockage diagnosed by HSG and/or laparoscopy and dye.[476] [evidence level III]

10.1 Tubal microsurgery and laparoscopic tubal surgery

Microsurgical tubocornual anastomosis has been regarded as the standard treatment for proximal tubal blockage. However, we did not find any RCTs or controlled observational studies comparing microsurgery with no treatment or with IVF. A review of case series reported that women with proximal tubal blockage who had microsurgical tubocornual anastomosis achieved a term pregnancy rate of about 50%.[477;478] [evidence level III]

The success of tubal microsurgery assessed in case-series was reported to range from 5% term pregnancy rate at 36 months[102] to 25% cumulative pregnancy rates at 12 months, and 40% at 50 months.[479] [evidence level III] This included a heterogeneous group of women with proximal or distal tubal disease. Live birth rates of 20 to 30% have been reported in women with distal tubal occlusion following surgery.[479-481] [evidence level III] The severity of tubal damage was linked closely to outcome, with better results in those with filmy adhesions and limited damage, compared to those with more extensive pathology.

A non-randomised controlled trial[464] and several case series report pregnancy rates after tubal surgery that are comparable to those resulting from IVF in women with filmy adhesions, mild distal occlusion or proximal tubal blockage.[480;482-485] [evidence level IIa-III]

The appropriate therapeutic approach to tubal infertility will depend on careful patient selection according to the individual's clinical circumstances, and involving the couple in the decision-making process.[486-489]

Success rates with tubal surgery are thought to depend on the severity of the tubal damage as well as the age of the woman, duration of infertility, and other associated infertility factors.[479] [evidence level III]

A non-randomised controlled trial with a follow-up period of 3 years reported higher pregnancy rates in women who underwent tubal surgery compared to those who did not (29% with surgery vs 12% without surgery, $p < 0.05$).[464] [evidence level IIa] The effect was most marked in groups with milder pelvic disease (stage I, 67% with surgery vs 24% without surgery, $p < 0.05$; stage II, 41% with surgery vs 10% without surgery, $p < 0.05$; stage III, 12% with surgery vs 3% without surgery, not significant; and stage IV, 0% with surgery, pelvic disease so severe that surgery not offered).

Retrospective case series suggest that most pregnancies occur between 12 and 14 months after tubal surgery although conception may occur sooner in those with minimal disease.[480475;479;480;490-492] [evidence level III] It may be reasonable to discuss IVF with patients who have not conceived 18 months after tubal surgery.

A number of trials have evaluated different surgical techniques for tubal surgery. One systematic review of eight RCTs and 14 non-RCTs evaluating various surgical techniques for treating tubal infertility found no difference in pregnancy rates between the different techniques used such as CO_2 laser adhesiolysis vs diathermy adhesiolysis (53% with laser vs 52% with diathermy; OR 1.04; 95% CI 0.65 to 1.67), with laser salpingostomy vs diathermy salpingostomy (35% with laser vs 27% with diathermy; OR 1.30; 95% CI 0.77 to 2.19), or the use of an operating microscope versus magnifying lenses (loupes) (72% with microscope vs 78% with loupes; OR 0.75; 95% CI 0.26 to 2.15).{5942} [evidence level Ia] Women with proximal and distal tubal disease and reversal of sterilisation were included in

this review. [evidence level Ia] The review of the 14 non-RCTs did not detect a difference between laparoscopic adhesiolysis and microsurgical adhesiolysis in improving outcome. [evidence level IIb]

One systematic review of five RCTs (n=588) found no improvement in pregnancy rates with the use of post operative hydrotubation (OR 1.12; 95% CI 0.57 to 2.21), or hydrotubation with steroids (OR 1.10; 95% CI 0.74 to 1.64), or hydrotubation with antibiotics (OR 0.67; 95% CI 0.30 to 1.47), or second look laparoscopy with adhesiolysis (OR 0.96; 95% CI 0.44 to 2.07). The comparison groups received no treatment but the trials were small and of poor quality.{5363} [evidence level Ia]

It has also been suggested that specialised training, experience and availability of equipment have a major impact on the outcome of tubal surgery.[2] [evidence level IV]

Recommendation:
The effectiveness of tubal surgery is uncertain, but it may be effective for women who have mild tubal disease. [C]

Research recommendation:

Further evaluation of the effectiveness of tubal surgery for women compared with no treatment and other treatment options is needed.

10.2 Selective salpingography and catheterisation

Selective salpingography can provide valuable diagnostic information on the status of both the proximal and distal fallopian tubes. One RCT (n=273) reported that selective salpingography is a better diagnostic test for proximal tubal obstruction than laporoscopic dye studies.[493] [evidence level Ib] Selective salpingography combined with tubal

cannulation can be adopted as a 'see and treat' approach for proximal tubal obstruction in appropriately selected patients.

We found no RCTs that compared the effect of selective salpingography plus tubal catheterisation with no treatment on pregnancy rates in women with proximal tubal obstruction. A systematic review combined data from 10 cohort and other observational studies of selective salpingography and tubal catheterisation (n=482 women), and four observational studies of hysteroscopic cannulation for proximal tubal blockage (n=133 women). It found that hysteroscopy vs selective salpingography and tubal catheterisation was associated with a higher pregnancy rate (49% with hysteroscopy vs 21% with salpingography).{12618} [evidence level IIb–III] As no untreated group was included in any of the studies reviewed, the likelihood of spontaneous pregnancy without treatment cannot be determined. Intra-uterine pregnancy in patients with proximal tubal blockage diagnosed by both HSG and laparoscopy/dye does occur without surgical treatment.[476] [evidence level III]

Tubal perforation (a complication associated with tubal cannulation) has been reported to occur in 2% of women undergoing tubal cannulation,[494] but this does not seem to be clinically significant.[495] [evidence level III] Ectopic pregnancy occurred in 3–9% of patients undergoing selective salpingography plus tubal catheterisation.{12618} [evidence level IIb–III]

Recommendation:

Selective salpingography plus tubal catheterisation or hysteroscopic tubal cannulation may be considered for patients with proximal tubal obstruction to improve the chance of pregnancy. [B]

Chapter 11 Management of fertility problems associated with endometriosis

Management strategies for fertility problems associated with endometriosis can be particularly difficult and are described in overview in Section 8.3. Endometriosis of all severities may be managed using IVF treatment (see Chapter 14).

11.1 Medical management (ovarian suppression)

A systematic review of 13 RCTs found no evidence that treatment with ovulation suppression agents (medroxyprogesterone, gestrinone, combined oral contraceptives and GnRHa) was effective in improving clinical pregnancy rates in women with endometriosis-associated infertility (OR 0.83; 95% CI 0.5 to 1.39).{5310} [evidence level Ia] This review also showed no significant difference in pregnancy rates between Danazol and all other agents (OR 1.20; 95% CI 0.85 to 1.68).{5310} [evidence level Ia] This is supported by a subsequent RCT comparing medroxyprogesterone acetate and placebo.[496] [evidence level Ib] Two reviews in 1993 and 1994 which included RCTs and cohort studies also concluded that ovulation suppression is ineffective in the treatment of endometriosis-associated infertility.[497;498] [evidence level Ib-IIa]

Commonly used ovulation suppression agents have been known to cause significant side effects such as weight gain, hot flushes and bone loss.{5310}

Recommendation:
Medical treatment of minimal and mild endometriosis does not enhance fertility in subfertile women and should not be offered. [A]

11.2 Surgical ablation

Minimal and mild endometriosis

A systematic review of two RCTs (n=444) showed that laparoscopic ablation or resection of minimal and mild endometriosis increased pregnancy and live birth rates when compared with diagnostic laparoscopy in the treatment of endometriosis-associated infertility (OR 1.64; 95% CI 1.05 to 2.57).[499] [evidence level Ia] In women who had mild endometriosis as their only infertility factor, the pregnancy rate was higher after laser laparoscopy and laparotomy compared with medical treatment (81% with laser laparoscopy vs 84% with laparotomy vs 54% with medical treatment).[500] [evidence level IIb] The benefits of surgery should be balanced against the risks of general anaesthesia and surgical complications[501] such as post-operative adhesions.

Endometrioma/ovarian cysts

One RCT found that laparoscopic cystectomy increased cumulative pregnancy rates at 24 months when compared with drainage and coagulation in the treatment of large ovarian endometrioma (66.7% vs 23.5%; OR 2.83, 95% CI 1.01 to 7.50).[502] [evidence level Ib]

Recommendations:

Women with minimal and mild endometriosis who undergo laparoscopy should be offered surgical ablation or resection of endometriosis because this improves the chance of pregnancy. [A]

Women with ovarian endometrioma should be offered laparoscopic cystectomy because this improves the chance of pregnancy. [A]

Moderate and severe endometriosis

Cohort studes of patients with moderate and severe endometriosis operative treatment with laparoscopy or laparotomy suggest pregnancy rates may be the same or increased in those treated by laparoscopy. (54%-66%with operative laparoscopy vs 36%-45% with laparotomy).[503;504 505;506] [evidence level IIb]

Post-operative medical treatment

Two RCTs compared post-operative GnRH with expectant management and found no significant difference in pregnancy rates between the two regimens (11.6% with goserelin vs 18.4% with expectant management and 33% with leuprolide depot vs 40% with expectant management, respectively).[507;508] [evidence level Ib] Similar outcomes were shown between post-operative danazol (55% with danazol vs 50% with expectant management)[509] and between post-operative nafarelin and placebo (19% with nafarelin spray vs 18% with placebo),[510] in women with moderate to severe endometriosis. [evidence level Ib]

Recommendations:

Surgical treatment of moderate and severe endometriosis may improve fertility and should be offered. [B]

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

11.3 Intra-uterine insemination with ovarian stimulation

Since minimal-mild endometriosis may be managed as unexplained infertility, an appropriate treatment option is IUI. Evidence relating to the use of IUI in women with endometriosis, is discussed in Section 13.3.

11.4 In vitro fertilisation treatment for fertility problems associated with endometriosis

IVF treatment has become the final stage in the management of fertility problems associated with endometriosis. This is the case for all severities of endometriosis. Evidence relating to the use of IVF in women with endometriosis is discussed in Section 14.1.

Chapter 12 Management of male factor fertility problems

The management of male factor fertility problems is discussed in this chapter. However, IUI, IVF alone, and IVF with ICSI used to treat male factor fertility problems are discussed in Chapters 13, 14 and 15, respectively.

12.1 Hypogonadotrophic hypogonadism

Hypogonadotrophic hypogonadism accounts for less than 1% of male factor infertility.[342] It is caused by pituitary or hypothalamic dysfunction, resulting in a deficiency of LH and FSH, associated with failure of spermatogenesis and testosterone secretion. Treatments for hypogonadotrophic hypogonadism include exogenous gonadotrophin replacement or pulsatile GnRH to stimulate spermatogenesis.

We found no RCTs that evaluated treatment for this condition. Case series suggest that treatment with human chorionic gonadotrophin (hCG) increases sperm counts within the normal range in men with hypogonadotrophic hypogonadism of postpubertal onset. Treatment with hMG and hCG increases sperm count within normal range in men with hypogonadotrophic hypogonadism of prepubertal onset, except in men who also have cryptorchidism.[511] [evidence level III]

In a case series it was suggested that gonadotrophin (hCG and hMG) treatment may improve fertility (92%) in men with hypogonadotrophic hypogonadism.[512] [evidence level IIb] Self-administration of FSH and hCG was reported to be well-tolerated and effective in stimulating spermatogenesis in hypogonadotrophic hypogonadism men, with 80% achieving a positive sperm count.[513] [evidence level IIb]

Pulsatile GnRH may be as effective as hCG/hMG in enhancing sperm production in men with hypogonadotrophic hypogonadism.[514-516] [evidence level IIb]

Recommendation:
Use of gonadotrophin drugs can be effective in improving fertility in men with hypogonadotrophic hypogonadism. [B]

12.2 Primary testicular failure

Primary testicular failure is the most common cause of male infertility due to oligozoospermia and is the cause of non-obstructive azoospermia. Testicular failure may be due to cryptorchism, torsion, trauma, orchitis, chromosome disorders (Klinefelter's syndrome, Y-chromosome microdeletions), radiotherapy or chemotherapy, but in the majority of cases (66%) the cause is unknown. The diagnosis is based on reduction in testicular size and elevation of serum FSH levels. There is no effective treatment to restore fertility in primary testicular failure. Men undergoing treatments which cause infertility should be offered the opportunity to cryopreserve semen (see Section 19.1). Alternatively surgical sperm retrieval with assisted reproduction or donor sperm may be considered.[517]

Recommendation:
Men undergoing treatment such as chemotherapy or radiotherapy should be offered the opportunity to cryopreserve their semen. [D]

12.3 Obstructive azoospermia

Obstructive azoospermia is uncommon with a prevalence of less than 2%.[1] The diagnosis is based on normal testis size and normal serum FSH levels. This includes conditions such as congenital bilateral absence of vas deferens (CBAVD). CBAVD is commonly associated with cystic fibrosis mutations or renal tract abnormality (e.g. an absent kidney).

A case-series study of 370 men with obstructive azoospermia showed that epididymovasostomy with post-infective caudal block gave a patency rate of 52% and pregnancy rate of 38% respectively. Post-infective vasal blocks were better corrected by total anatomical reconstruction (patency of 73% and pregnancy rate of 27%) than by transvasovasostomy (patency 9% and no pregnancy).[518] [evidence level III] Another case series of 44 men found that 58% achieved patency and 23% of couples achieved a pregnancy following surgery for ejaculatory duct obstruction.[519] [evidence level IV] Another study showed that transurethral resection of ejaculatory ducts improved semen quality and gave an overall pregnancy rate of 20% in 46 couples where the male partner had ejaculatory obstruction.[520] [evidence level III] Recovery and cryopreservation of spermatozoa for use in assisted reproduction should be considered during surgical reconstruction to avoid a second surgical procedure at a later date (see Section 15.10). Alternatively men with CBAVD may be offered surgical retrieval of spermatozoa for use in assisted reproduction (see Section 16.3).

Recommendation:
For men with obstructive azoospermia, surgical correction of epididymal blockage may restore patency of the duct and improve fertility. Surgical correction may be considered as an alternative to surgical sperm recovery and in vitro fertilisation. [C]

12.4 Immunological factors

Immunological male infertility refers to the presence of antisperm antibodies in the seminal fluid or bound to spermatozoa. It accounts for about 3% of male factor infertility.[342]

Five RCTs compared corticosteroid treatment with placebo or no treatment in men with antisperm antibodies. No significant difference in pregnancy rates was found in three trials.[521-523] One RCT (n=60) showed a significant increase in pregnancy rate with prednisolone versus placebo (27% vs 7%).[524] Another RCT (n=77)showed a significant

increase in pregnancy rate with low dose prednisolone vs no treatment (18% vs 3%).{11981} All these trials have small sample sizes. Side effects (including dyspepsia, facial flushing, weight gain and rare complications such as aseptic necrosis of the hip) were reported.[521;525-527] [evidence level III]

Recommendation:
Couples should be informed that the significance of antisperm antibodies is unclear and the effectiveness of systemic corticosteroids is uncertain. [A]

12.5 Varicoceles

Varicocele is a collection of dilated veins in the spermatic cord and is a common physical anomaly. Varicoceles are found in 11.7% of men with normal semen and 25.4% of men with abnormal semen, respectively.[528] The mechanism by which varicocele might impair fertility and spermatogenesis is not clear. As well as impaired semen quality, varicocele may be associated with decreased ipsilateral testicular volume, elevated scrotal temperature and pain.[528-530] Occlusion of the spermatic vein by ligation or embolisation has been the treatment of choice.

A systematic review of five RCTs found insufficient evidence that treatment of varicocele (normal and abnormal semen analysis) in men from couples with otherwise unexplained infertility improves pregnancy rates (RR 1.06, 95% CI 0.57 to 1.94) when compared with no treatment.{5144} [evidence level Ia] Two additional RCTs were included in a more recent systematic review (total seven RCTs) which showed no significant difference in pregnancy rate between varicocele repair vs no repair (RR 1.01, 95% CI 0.73 to 1.40, using a fixed effects model; RR 1.04, 95% CI 0.62 to 1.75, using a random effects model).[531] [evidence level Ia] The trials reviewed were generally of poor methodological quality and there was clinical heterogeneity in the subjects selected. The possibility of benefit for men with varicocele and abnormal semen analysis needs further evaluation.

Recommendation:

Men should not be offered surgery for varicocele as a form of fertility treatment because it does not improve pregnancy rates. [A]

Research recommendation:

Randomised controlled trials to evaluate the benefit of treatment of varicocele in men with abnormal semen quality on improving fertility are needed.

12.6 Leukocytospermia

Leukocytospermia has been associated with adverse effects on semen parameters and functions.[532;533]

An RCT in men with leukocytospermia assigned patients to: antibiotic treatment; antibiotic with frequent ejaculation; frequent ejaculation at 1 month; or no treatment. The effect of these interventions on pregnancy rates is not clear, however treatment groups showed resolution of leukocytospermia (40% vs 68% vs 32% vs 4%).[534] The resolution was sustained at 2 and 3 months only in those who took antibiotics and frequently ejaculated.[534] [evidence level Ib]

Two other RCTs showed that treatment with antibiotics did not improve semen parameters in patients with leucocytospermia,[535] nor resolution of leucocytospermia.[536] [evidence level Ib] Pregnancy outcomes were not assessed in these trials.

In an RCT (n= 23) patients with male accessory gland infection (epididymo-prostao-vesiculitis), antibiotic treatment compared with placebo was shown to have no significant effect on pregnancy rates or sperm parameters (10% with antibiotics vs 8% with placebo).[537] Another RCT (n=122) showed significant improvement with antibiotics in

sperm parameters at 3 months and pregnancy rates (28.2% with antibiotics vs 5.4% with no treatment).[538] [evidence level Ib] Treatment with antibiotics did not affect pregnancy rates in couples with mycoplasma-related infertility.[539] [evidence level Ib]

One RCT (n=120) found that treatment with antibiotics and kallikrein improved sperm motility and pregnancy rates (32% with kallikrein plus antibiotics vs 17% with antibiotics alone; RR 1.84, 96% CI 0.95 to 3.56) in infertile men with genital tract infections.[540] [evidence level Ib]

Recommendation:
Men with white cells in semen should not be offered antibiotic treatment unless there is an identified infection because there is no evidence that this improves pregnancy rates. [A]

12.7 Treatment for idiopathic semen abnormalities

Idiopathic semen abnormalities occur in about 26% of infertile men[344] and various empirical non-specific treatments have been tried including hormonal and non-hormonal treatments.

Anti-oestrogens (clomifene and tamoxifen)

Two systematic reviews including 10 RCTs have examined the effect of anti-oestrogens in pregnancy rates.[541;542] [evidence level Ia] Neither review detected a beneficial effect of anti-oestrogens in pregnancy rates (OR 1.54, 95% CI 0.99 to 2.40) when compared with placebo or no treatment for men with oligo- and/or asthenozoospermia.

Androgens

A 1996 systematic review of nine RCTs showed no benefit of androgens in improving pregnancy rate (OR 1.10, 95% CI 0.75 to 1.61) when compared with placebo or no treatment.[543] [evidence level Ia]

Gonadotrophins

Two RCTs showed no significant difference in pregnancy rates between gonadotrophin treatment when compared with placebo (n= 65, 5.8% with rFSH vs 0% with placebo)[544] or no treatment (n=136, 44.8% with FSH vs 37.2% with no treatment) in couples with idiopathic male infertility.[545] [evidence level Ib]

Kinin-enhancing drugs

A systematic review of 12 RCTs did not provide conclusive evidence that kinin-enhancing drugs improve pregnancy rates (OR 1.65, 95% CI 0.98 to 2.77) when compared with placebo.{5923} Non-significant results were also reported in an additional RCT (9.6% vs 14%).[546] [evidence level Ia]

Bromocriptine

A 1996 systematic review of four RCTs found no benefit of bromocriptine on either sperm parameters or pregnancy rates (OR 0.70, 95% CI 0.15 to 3.24) when compared with placebo or no treatment in men with idiopathic semen abnormalities.[547] [evidence level Ia]

Anti-oxidants

Two placebo-controlled RCTs found that vitamin E has a beneficial effect on semen parameters in infertile men,[548;549] but improvement in pregnancy rates was only shown in one trial (n=87, 21% vs 0%).[549] Another RCT showed no significant improvement in semen parameters with vitamins C and E versus placebo and there was no pregnancy in either group.[550] [evidence level Ib] Selenium is also an antioxidant (see Section 5.1.12).

Glutathione was found to have a significant positive effect on sperm motility and morphology in one RCT, but pregnancy rate was not reported.[551] [evidence level Ib]

Alpha blockers

One RCT (n=31) showed that alpha blocker (bunazosin) significantly improved semen density and count, but not pregnancy rates, when compared with placebo (25% vs 6.7%).[552] [evidence level Ib]

Mast cell blockers

One RCT (n=46) found that treatment with mast cell blocker (tranilast) significantly improved semen parameters and pregnancy rate at 1 year (28.6% vs 0%) when compared with placebo in men with severe oligozoospermia.[553] [evidence level Ib]

Recommendation:
Couples should be informed that anti-oestrogens, gonadotrophins, androgens, bromocriptine and kinin-enhancing drugs have not been shown to be effective in the treatment of men with idiopathic semen abnormalities. [A]

Research recommendation:

Antioxidants, mast cell blockers and alpha blockers need further evaluation before they can be considered in the treatment of men with semen abnormalities.

12.8 Intra-uterine insemination

IUI is used in the management of male factor infertility where the semen is of higher quality than would be required for IVF or ICSI. The semen criteria for the use of IUI vary from clinic to clinic, and many clinics would specifiy that there should be in the range 2-5 million motile sperm available after sperm preparation. This is discussed in detail in Section 13.1.

12.9 In vitro fertilisation, gamete intrafallopian transfer, and intracytoplasmic sperm injection

Both IVF treatment and GIFT have been used in the management of male factor fertility problems since they are effective with relatively poor semen quality (see Chapter 14). Where the semen quality is not sufficient for IVF, micromanipulative fertilisation by means of ICSI has become the only valid form of management because very few sperm are needed (see Section 16). ICSI has also made it possible for azoospermic men to father children because small numbers of sperm may be obtained by invasive means from the epididymis or testis (see Section 15.10).

Chapter 13 Intra-uterine insemination

IUI has been used in the treatment of fertility problems associated with both unexplained infertility and male factor infertility. It may involve timed insemination in women in unstimulated cycles, or may involve insemination in women whose ovaries are stimulated using oral anti-oestrogens or gonadotrophins.

Clinical experience with IUI suggests that the cumulative pregnancy rate reaches a plateau after the three cycles. {?} [evidence level III]

13.1 Intra-uterine insemination for the management of male infertility

IUI is used to manage male factor infertility where semen is of higher quality than would be required for IVF or ICSI. The semen criteria for the use of IUI vary from clinic to clinic, and many clinics would specifiy that there should be in the range 2-5 million motile sperm available after sperm preparation.

We found two systematic reviews comparing IUI to timed intercourse in couples with male subfertility. The earlier review included 10 RCTs[554] both with timed intercourse or intra-cervical insemination. The later review includes 17 RCTs but excluded four of the RCTs which evaluated intra-cervical insemination. Comparing IUI vs timed intercourse, IUI was associated with increased pregnancy rate per cycle both in natural cycles (OR 2.4, 95% CI 1.6 to 3.9) and in ovarian stimulation cycles (OR 2.2, 95% CI 1.4 to 3.6).{5009} [evidence level Ia] This evidence suggests that for male infertility unstimulated and stimulated IUI are equally effective, however, it is recognised that stimulated IUI carries a risk of multiple pregnancy.

An RCT conducted in the Netherlands compared unstimulated and stimulated IUI in 51 couples (207 cycles) with male fertility problems.[555] [evidence level Ib] The study found that 37.5% of couples who received stimulated IUI achieved a live birth, compared with 64.7% of couples who received unstimulated IUI (RR 0.92, 95% CI 0.46 to 1.83). This study also reported the cost-effectiveness of IUI treatment at different female ages after a maximum of six treatment cycles for groups of 100 fictional couples (see Section 13.5).

One small crossover RCT found no significant difference in pregnancy rates between hCG/ultrasound timed IUI vs LH-timed IUI in patients with male factor (12.5% vs 0%), anovulation and unexplained infertility.[556] [evidence level Ib]

Recommendation:
Couples with male factor infertility where the man's semen is of appropriate quality should be offered three cycles of intra-uterine insemination because this increases the chance of pregnancy. [A]

Where intra-uterine insemination is used to manage male factor infertility, unstimulated and stimulated cycles are equally effective [A], but because stimulated cycles carry a risk of multiple pregnancy stimulated cycles are not recommended. [C]

Research recommendation:

Research is needed to define national semen quality criteria for intra-uterine insemination and intracytoplasmic sperm injection to be effective in the management of male infertility.

13.2 Intra-uterine insemination for the management of unexplained infertility

Evidence relating to whether ovarian stimulation should be used as part of IUI treatment for the management of unexplained fertility problems is discussed below. It is necessary to bear in mind the risk of multiple pregnancy that is associated with the use of drugs, especially where gonadotrophins are used.

We found three systematic reviews that compared gonadotrophin-stimulated IUI with gonadotrophins plus timed intercourse. The reviews included a total of 24 RCTs.[554;557;558] [evidence level Ia] The largest review included 22 RCTs (1117 couples and 5214 cycles); the other reviews included subsets of these studies plus one addional trial each, but all three reviews reached the same conclusions. The largest review was the best quality review and was used for this guideline.[558] [evidence level Ia] This review used an explicit and comprehensive search strategy, and explicit inclusion/exclusion criteria. In eight RCTs involving couples with unexplained fertility problems, the review found that gonadotrophin-stimulated IUI increased the chance of pregnancy compared with gonadotrophins plus timed intercourse (pooled OR 2.37, 95% CI 1.43 to 3.90).[558] [evidence level Ia]

One RCT conducted in the United States compared unstimulated with stimulated IUI in 465 couples (1335 cycles) with unexplained fertility problems. The study found that superovulation plus IUI significantly increased pregnancy rates compared to IUI alone (OR 1.7, 95% CI 1.2 to 2.6).[559] [evidence level Ib] However, ovarian stimulation increased multiple pregnancies: 17 twins, three triplets and two quadruplets occurred among the 77 pregnancies in the stimulated IUI group, whereas there were no multiple pregnancies among the 42 pregnancies in the unstimulated IUI group.[559]

It is possible that the drug doses in stimulated IUI in the United Kingdom are different to those in the United States. However, a multicentre observational study conducted in the United Kingdom reported the outcome of 1446 stimulated IUI cycles.{STIRMAS, 2000, BFS Edinburgh abstract} [evidence level III] Among the 126 pregnancies reported, there were 11 twins, two triplets, and one higher-order pregnancy.

An RCT conducted in the Netherlands compared unstimulated and stimulated IUI in 120 couples (486 cycles) with unexplained fertility problems.[555] [evidence level Ib] The study found that 36.1% of couples who received stimulated IUI achieved a live birth, compared with 23.7% of couples who received unstimulated IUI (RR 1.52, 95% CI 0.86 to 2.68). This study also reported the cost-effectiveness of IUI treatment at different female ages after a maximum of six treatment cycles for groups of 100 fictional couples (see Section 13.5).

A systematic review of five RCTs (n=231) compared oral (anti-oestrogen) and injectable (gonadotrophin) drugs for stimulated IUI in couples with unexplained fertility problems. In some of the RCTs, the oral anti-oestrogen treatment group received an hCG ovulation trigger. This review found no significant difference in live birth rates per couple (OR 0.40, 95% CI 0.15 to 1.08), miscarriage rates per couple (OR 0.61, 95% CI 0.09 to 4.01), or multiple birth rates per couple (OR 1.08, 96% CI 0.16 to 7.03).{13443} [evidence level Ia] However, the pregnancy rate per couple was significantly lower with oral anti-oestrogen-stimulated IUI than with gonadotrophin-stimulated IUI (OR 0.41, 95% CI 0.17 to 0.80).

An RCT (n=97) compared different gonadotrophin regimens. This RCT found no significant difference with conventional FSH plus IUI when compared with low dose and step-up FSH plus IUI in pregnancy rates (14.6% vs 14.3%; RR 1.02, 95% CI 0.39 to 2.69), miscarriage rates (14.3%vs 14.3%; RR 1.0, 95% CI 0.08 to 13.02)), or multiple pregnancy rates (28.6% vs 14.3%; RR 2.0, 95% CI 0.23 to 17.34). However, the incidence of OHSS was significantly higher in the conventional FSH plus IUI group (27.1% vs 8.3%; RR 3.32, 95% CI 1.16 to 9.46).[560] [evidence level Ib]

Another RCT evaluated three low-dose gonadotrophin protocols (4, 6 and 8 ampoules) before IUI in patients with unexplained fertility problems. This RCT showed no significant differences in ovulation rates (82% vs 81% vs 79%) or pregnancy rates (5.4% vs 0% vs 0%). There was no occurrence of cycle cancellation or OHSS.[561] [evidence level Ia]

A further RCT (n=91,131 cycles) compared two approaches to stimulated IUI (GnRHa plus gonadotrophins vs gonadotrophins) in couples with unexplained fertility problems. This RCT found no significant difference in pregnancy rates per cycle with GnRHa/gonadotrophin-stimulated IUI compared with gonadotrophin-stimulated IUI (13% vs 11.3%; RR 0.87, 95% CI 0.34 to 2.19).[562] [evidence level Ib]

A systematic review of five RCTS, of which two small RCTs compared IUI with IVF in couples with unexplained fertility problems, has been publlished.{10226} [evidence level Ia] This review found no significant difference in live birth rates between IVF and stimulated IUI (OR 1.2, 95% CI 0.55 to 2.4, n=118), or between IVF and unstimulated IUI (OR 1.96, 95% CI 0.88 to 4.4, n=113). There was no significant difference in multiple pregnancy rates between IVF and stimulated IUI (OR 0.63, 95% CI 0.27 to 1.5, n=118).{10226} However, the results of these RCTs should be interpreted with caution because of their limited sample sizes.

Recommendations:

Couples with unexplained fertility problems should be offered three cycles of intra-uterine insemination because it improves pregnancy rates. [A]

Where intra-uterine insemination is used to manage unexplained fertility problems, couples should be informed that stimulated intra-uterine insemination improves pregnancy rates, but is associated with an increased risk of multiple pregnancy compared to unstimulated intra-uterine insemination. [A]

Where gonadotrophin-stimulated intra-uterine insemination is used to manage unexplained fertility problems, a low dose follicle-stimulating hormone regimen may reduce the incidence of ovarian hyperstimulation syndrome. [A]

Research recommendations:

Research is needed to determine the relative effectiveness of oral (anti-oestrogen) and injectable (gonadotrophin) drugs in stimulated intra-uterine insemination in couples with unexplained fertility problems.

Research is needed to determine the relative effectiveness of intra-uterine insemination and in vitro fertilisation in couples with unexplained fertility problems.

13.3 Intra-uterine insemination for the management of endometriosis

Where IUI is used in the management of fertility problems associated with endometriosis the general approach is to consider that the endometriosis (generally minimal-mild) is of a degree equivalent to unexplained infertility. However, there some studies have reported on the use of IUI in this specific category. These studies are discussed below.

We found one systematic review of three RCTs comparing IUI with and without ovulation induction in women with minimal-mild endometriosis. These trials have reported inconsistent results. One RCT (n=104) found that IUI plus gonadotrophins significantly increased live birth rates when compared with no treatment (26% with IUI plus gonadotrophins vs 8% with no treatment; RR 3.3, 95% CI 1.2 to 9.4).[563] [evidence level Ib] The second RCT (n=49) showed no difference in birth rates between hMG plus IUI compared with expectant management (29% with hMG plus IUI vs 20% with expectant management; OR 1.46, 95% CI 0.5 to 4.0), but reported five cases of OHSS (20%).[564] [evidence level Ib] When combined, these two RCTs showed a RR of 2.3 (95% CI 1.1 to 4.6) in live birth rates with IUI plus gonadotrophins vs expectant management.

The third (cross-over) RCT (n=119, 57 of which had endometriosis) found that alternate cycles of gonadotrophins plus IUI increased pregnancy rates when compared with IUI alone (19% with gonadotrophins plus IUI vs 0% with IUI).[565] [evidence level Ib] Multiple pregnancy rates were reported to be between 18% and 33% in these three trials.

Recommendations:

Women with minimal and mild endometriosis should be offered three cycles of intra-uterine insemination with ovarian stimulation because this is more effective in increasing pregnancy rates than either no treatment or intra-uterine insemination alone in subfertile women. [A]

Couples should be informed of the risks of intra-uterine insemination (such as multiple pregnancy and ovarian hyperstimulation) and the response to treatment should be monitored with ultrasound scans. [GPP]

13.4 Single vs double intra-uterine insemination

A systematic review of three RCTs compared double vs single IUI. Two of the RCTs reported pregnancy rates per couple, and were based on couples with male factor and unexplained fertility problems. The review found no difference between double and single IUI in these RCTs (pooled OR 1.45, 95% CI 0.78 to 2.70).[566] [evidence level Ia]

Recommendation:

Where intra-uterine insemination is used to manage fertility problems, single rather than double insemination should be used. [A]

13.5 Cost-effectiveness of intra-uterine insemination

The cost-effectiveness of different drug regimens to stimulate ovarian induction alongside IUI has been addressed in some economic studies. However, there has been less focus on the economic consequences, such as multiple births, and their impact on the relative cost-effectiveness of stimulated vs unstimulated IUI. All the studies reported here present results for a single institution and costs are specific to the settings (public or independent sectors in different national contexts) in which these studies were undertaken.

Comparison of the cost-effectiveness of intra-uterine insemination drug regimens

An American retrospective cohort study considered the relative cost-effectiveness of various forms of treatment for sub-fertility: 54 couples underwent unstimulated IUI, 91 had clomifene citrate-stimulated IUI and 52 had hMG-stimulated IUI.[567] Tubal surgery was used as a comparator. Delivery rates were 5.8% for clomifene-stimulated IUI and 17.5% with hMG-stimulated IUI. Multiple birth rates were reported as 0% for unstimulated IUI, 6.3% for clomifene-stimulated IUI and 17.5% for hMG-stimulated IUI. The costs analysis included medical costs associated with the treatment, but not the longer term costs associated with multiple births. The cost per delivery was reported as $8674 for unstimulated IUI, $7808 for clomifene-stimulated IUI and $10282 for hMG-stimulated IUI.

A Dutch study considered the cost-effectiveness of three protocols for unexplained subfertility and male subfertility: unstimulated (spontaneous) IUI, stimulated IUI, and IVF.[568] One hunded and eighty-one couples were recruited to an RCT after stratifying for factors that might affect fertility (74 did not complete treatment). The delivery rate without treatment was 1.25% per month in the unexplained subfertility group, and 0.82% per month in the male factor subfertility group. Delivery rates were 31% for the couples who started unstimulated IUI, 37% for IUI with stimulation, and 38% with IVF. The multiple pregnancy rate was 29% of viable pregnancies with stimulated IUI, and 21% with IVF. In the unstimulated IUI group, there was one monozygotic twin pregnancy, but this pregnancy did not result in a live birth. The unit cost of an IVF cycle was reported to be 3.5 times higher than for stimulated cycles of IUI and five times higher than a spontaneous IUI cycle. The cost per pregnancy resulting in at least one live birth was Dfl. 8,423 for IUI alone ($4,035), Dfl. 10,661 ($5,107) for stimulated IUI, and Dfl. 27,409 ($13,131) for IVF (at 1995 prices).

Another American study addressed the efficacy and cost-effectiveness of treatments for unexplained fertility problems.[569] Unstimulated IUI was the baseline comparator. Clomifene-stimulated IUI and hMG-stimulated IUI were evaluated. The main effectiveness data were obtained from a systematic review (1985-1998) that included 45 published

studies. The measure of benefit in the economic analysis was pregnancy rate. The mean costs of clomifene- and hMG-stimulated IUI were $500 and $2,500, respectively. At a baseline pregnancy rate of 1.3% without treatment, the additional cost per additional pregnancy was reported to be $7,143 for clomifene citrate plus IUI and $15823 for hMG plus IUI. Raising the untreated pregnancy rate to 1.4%, the additional costs per pregnancy were $11,905 and $19,230 respectively.

The impact of multiple birth on the relative cost effectiveness of stimulated intra-uterine insemination

The key question that affects the overall cost of stimulated cycles of IUI is the rate of multiple births associated with drugs to promote ovarian stimulation compared with unstimulated cycles of IUI, since the cost of higher-order multiple births (more than twins) may offset the increase in efficacy (in terms of pregnancy or live birth rates) of stimulated cycles of IUI. This question has not been directly addressed in an economic evaluation since the cost (where this can be established) has included only those resources directly associated with birth and not the longer term consequences of multiple birth, such as the intensive care needs of low weight infants resulting from high-order multiple births. A recently published review has evaluated studies that reported the economic consequences of pre-term birth and low birth weight, both of which are associated with higher-order (more than twin) multiple births.[570] The evidence suggests that health service costs for infants born at less than 1000 g are more than four times higher on average than babies born at least 1500 g. This pattern was observed regardless of the quality of the economic studies. Furthermore, preterm and low birth weight babies were shown to be more likely to consume health and community care resources in the early years of infancy. Higher rates of survival of small babies (due to technological advances) have also increased the costs of care.

The relative cost-effectiveness of intra-uterine insemination and in vitro fertilisation

An American study compared a protocol with clomifene citrate and hMG plus IUI with a protocol of only hMG and IUI.[571] The study involved 99 subfertile couples undergoing a total of 225 cycles of IUI. The study design was a retrospective cohort and no explicit

control group was identified. It was reported that the clomifene/hMG/IUI protocol was around a third as expensive (around $660) as the hMG plus IUI protocol (around $1850). Cumulative pregnancy rates for clomifene/hMG plus IUI were similar to the more expensive regimen. The multiple pregnancy rate for clomifene/hMG plus IUI was reported to be 28% (all twin pregnancies).

A United Kingdom study has evaluated the efficacy and cost-effectiveness of stimulated IUI (clomifene citrate and FSH) vs stimulated IVF using the same drug regimen.[572] The study included 80 couples with unexplained fertility problems but with confirmed ovulation cycles who were randomised to a controlled trial (although this was compromised by treatment response and patient preference further on in the trial). There was no statistically significant difference in outcome per cycle completed (live birth rate) in a sample of 80 couples. The cost of treatment was £32280 in the stimulated IVF group, compared with £15384 in the stimulated IUI group. The cost of multiple birth was not included in the analysis. The authors calculated a cost per maternity of £4611 for IVF and £1923 for stimulated IUI. No statistical analysis or sensitivity analysis was performed to explore the robustness of these findings or the impact of small changes in outcome or in cost of treatment.

A retrospective cohort study undertaken in a Finnish fertility clinic considered the cost effectiveness of IUI with clomifene citrate/hMG/HCG stimulation protocol plus IUI using partners' sperm.[573] The IUI cost-effectiveness data were compared with IVF. No control group was explicitly identified. Data on 924 cycles of IUI were included in the analysis. A pregnancy rate of 12.7% per cycle was reported; 70.6% of the pregnancies were viable, 23.5% resulted in spontaneous abortion, and 5.9% resulted in ectopic pregnancy. A multiple pregnancy rate of 13.7% was reported. The cost per live birth was £1670 for clomifene/hMG/IUI, which was less than half the reported cost of IVF over the same period (£4,450). The longer term costs of multiple birth were not included in the analysis.

Another American study considered the cost-effectiveness of three different assisted reproduction protocols: ovarian stimulation only (with clomifene citrate); IUI with hMG; and

IVF.[574] The study was based on a non-systematic review of the literature and 'clinical experience'. This study was different from those discussed above because it considered protocols that used different combination of treatments, starting with the least expensive (clomifene citrate) and limiting the use of any type of treatment to three cycles. Using three cycles of clomifene citrate, plus three cycles of stimulated IUI and three cycles of IVF, the cost per delivery was $13,220 after the first cycle and $63,000 after completion of the whole protocol. When 50% of couples had conceived (between the sixth and seventh cycles of treatment in this case), the cost per couple was around $16,000. When clomifene citrate was dropped and only stimulated IUI and IVF were offered the cost per delivery was $22,380 after one cycle and $63,316 after the completed protocol. Around 50% of couples had conceived at a cost of $18,000 per couple. When IVF alone was used, the cost per delivery was $49,128 after one cycle and $71,825 after four cycles. It was estimated that 50% of couples would have had conceived after spending around $27,000. Thus the most cost-effective option turned out to be a protocol that began with the least expensive option.

Summary

Regimens with clomifene citrate are less expensive than hMG and this leads to lower costs per live birth. The consequences for the NHS of higher-order multiple births due directly to stimulated IUI are not well understood. A study addressing this issue directly would be highly informative since these economic consequences could have a significant impact on the relative cost-effectiveness of stimulated vs unstimulated IUI. IVF is a more expensive first line option for couples with unexplained fertility problems and continued ovulation.

Chapter 14 In vitro fertilisation

The main procedures involved in IVF treatment are:

- down-regulation — switching off the natural ovulatory cycle to facilitate controlled ovarian stimulation;
- ovarian stimulation — administration of gonadotrophins to encourage the development of several follicles followed by administration of hCG to mature eggs ready for collection;
- egg collection followed by semen production or sperm recovery
- IVF;
- transfer of resulting embryos to the uterus; and
- administration of hormones to aid implantation of the embryos (luteal support).

The HFEA considers that a fresh IVF treatment cycle starts when drugs are administered for ovarian stimulation or, if no drugs are used, when an attempt is made to collect eggs.[575] The HFEA also considers that a frozen IVF treatment cycle starts when a cryopreserved embryo is removed from storage in order to be thawed and then transferred.[575]

14.1 Effectiveness of in vitro fertilisation

Immediate vs delayed in vitro fertilisation

RCTs are not available for the assessment of the effectiveness of IVF in comparison with no treatment. One approach to evaluate the effectiveness of IVF has been studies comparing the effect of IVF carried out without delay with IVF where there is deliberate delay (immediate vs delayed IVF).

One RCT compared the effectiveness of immediate IVF with 6-month delayed IVF in couples with all causes of infertility. Patients in the treatment group received up to four cycles of IVF treatment. Patients in the control group were permitted to have any form of fertility treatment other than IVF. Intention to treat analysis for this study showed significant differences in pregnancy rates per couple (17% with immediate IVF vs 8% with delayed IVF; RR 2.43, 95% CI 1.18 to 5.07) and live birth rates per couple (12% with immediate IVF vs 5% with delayed IVF; RR 2.36, 95% CI 1.03 to 5.66). No details of the fertility treatment received by the control group were presented.[576] [evidence level Ib]

Another RCT compared early IVF with late IVF (after 6 months) in couples with all causes of infertility. Patients in the treatment group received one cycle of IVF treatment. The control group received other fertility treatments, such as IUI with superovulation, donor insemination and tubal surgery during the 6 month waiting period. Intention to treat analysis of all causes of infertility showed no significant differences in clinical pregnancy rates per couple (10% with immediate IVF vs 7% with delayed IVF; RR 1.51, 95% CI 0.65 to 3.51), nor in live birth rates per couple (9% with immediate IVF vs 5% with delayed IVF; RR 1.86, 95% CI 0.72 to 4.79).[577] [evidence level Ib]

The incidence of spontaneous pregnancy during IVF treatment has been examined in a retrospective study based on couples who had attempted one or more IVF procedures.[578] However, the study was based on 484 subfertile couples, having excluded 110 truly infertile couples. Spontaneous pregnancies occurred in 11.2% of couples. The only characteristic that differed between couples with spontaneous and IVF pregnancy was duration of infertility; shorter duration of infertility was associated with spontaneous pregnancy. [evidence level III]

The decision to recommend IVF treatment should take into consideration the likelihood of spontaneous pregnancy without treatment, in particular in cases where significant

spontaneous pregnancy rates may be expected, as in the case of mild endometriosis and unexplained infertility.[579] [evidence level III]

In vitro fertilisation for management of fertility problems associated with tubal disease

We found no RCTs comparing IVF vs no treatment specifically in the management of tubal infertility, although two RCTs compared immediate or delayed referral for IVF (see above). In one of the RCTs, a subgroup of patients with infertility due to tubal factors (n=45) reported a higher success rate with immediate IVF compared with delayed IVF; however caution is needed in interpreting this result as the subgroup analysis was not conducted on an intention to treat basis.[577]

Hydrosalpinx is dilation of the fallopian tube in the presence of distal tubal obstruction which may result from a number of causes.[580] In women undergoing IVF, the presence of hydrosalpinx is associated with early pregnancy loss and poor implantation and pregnancy rates,[580;581] probably due to alteration in endometrial receptivity.[582;583] [evidence level IIb]

A systematic review of three RCTs showed that tubal surgery such as laparoscopic salpingectomy significantly increased pregnancy rate (OR 1.75; 95% CI 1.07 to 2.86) and live birth rate (OR 2.13; 95% CI 1.24 to 3.65) in women with hydrosalpinges before IVF when compared with no treatment.{5364} [evidence level Ia] There were no significant differences in the odds of ectopic pregnancy (OR 0.42; 95% CI 0.08 to 2.14), miscarriage (OR 0.49; 95% CI 0.16 TO 1.52), treatment complication (OR 5.80; 95% CI 0.35 to 96.79) or implantation (OR 1.34; 95% CI 0.87 to 2.05).{5364}

In vitro fertilisation for management of fertility problems associated with endometriosis

One RCT (n= 245) compared immediate with delayed referral for IVF (see above). A subgroup analysis of 21 patients with endometriosis did not detect a significant difference in pregnancy rates between immediate and delayed IVF (33.3% immediate IVF vs 0% delayed IVF). However, this result should be interpreted with caution because it is a subgroup analysis based on a small sample.[577]

A systematic review of 22 observational studies of patients undergoing IVF treatment, suggested that those with endometriosis-associated infertility compared with couples with other causes of infertility, had a lower pregnancy rate (OR 0.63, 95% CI 0.51 to 0.77).[584] [evidence level IIb] The overall chance of achieving a pregnancy with IVF in these 22 studies was about 25%. [evidence level IIb] The effect of endometrioma on the outcome of IVF treatment is unclear.[585-588] [evidence level III]

Recommendation:
Women who have hydrosalpinges and who are having in vitro fertilisation should be offered laparoscopic salpingectomy because it improves the chance of a live birth. [A]

Research recommendations:

For women who have hydrosalpinges the effectiveness of draining of hydrosalpinges or performing salpingostomy on improving live birth rate during in vitro fertilisation needs further evaluation.

Further randomised controlled trials evaluating the effectiveness of in vitro fertilisation in comparison against no treatment are needed for different durations and causes of fertility problems.

14.2 Factors that affect the outcome of in vitro fertilisation treatment

14.2.1 Female age

Live birth rates

Analysis of HFEA data on all IVF cycles carried out in the United Kingdom between August 1991 and April 1994 showed that the overall live birth rate per cycle of treatment was 13.9%. The highest live birth rates were in the age group 25-30 years; younger women had lower rates and there was a decline in older women. At all ages over 30 years, use of donor eggs was associated with a significantly higher live birth rate than use of the woman's own eggs, but there was also a downward trend in success rate with the recipient's age.[589] [evidence level III]

More recent data from the HFEA database (covering the period 1995 to 1999) were analysed by single year of age for this guideline (see Tables 14.1, 14.2, 14.3, 14.4 and 14.5). The analyses were based on fresh and frozen IVF treatment cycles that were registered between January 1995 and March 1999 and involved use of the woman's own eggs. Data collected after March 1999 have not been used in this guideline because they have not been validated by the HFEA and are considered by the HFEA to be less reliable than data for the period January 1995 to March 1999.

Table 14.1 relates to live birth rates from fresh IVF cycles. This analysis was based on 110,538 IVF treatment cycles that were registered between January 1995 and March 1999 and involved use of the woman's own eggs and fresh embryo transfer. The overall live birth rate per fresh treatment cycle in the period January 1995 to March 1999 was 17.6%. Between the ages of 23 years and 33 years the live birth rate per treatment cycle exceeded 20%. The live birth rates for women aged 18 years to 22 years are shown in Table 14.1, but reliable conclusions cannot be drawn from the extremely small number of cases on which these rates are based (0.4% of all fresh IVF treatment cycles). Above the age of 33 years, live birth rates per treatment cycle declined, falling below 10% (i.e. less than half the rate in 23 to 33 year-olds) by the age of 40 years. Beyond the age of 40 years the live birth rate per treatment cycle was 6%. [evidence level III]

Since the effectiveness of IVF treatment for women aged less than 23 years is uncertain the use of IVF treatment can only be recommended where there is an absolute indication (for example, tubal blockage, very poor semen quality, or prior treatment for cancer).

Table 14.1 Comparison of live birth rates per cycle started by age of woman based on fresh (not frozen) embryo transfer and excluding donor eggs, 1995–1999 (Source: Human Fertilisation and Embryology Authority)

Age in years	Number of treatment cycles	Number of live births	Live birth rate per treatment cycle (%)
18	3	1	33.3
19	15	1	6.7
20	54	5	9.3
21	83	9	10.8
22	248	48	19.4
23	438	94	21.5
24	827	171	20.7
25	1365	291	21.3
26	2143	460	21.5
27	3324	696	20.9
28	4342	941	21.7
29	5656	1199	21.2
30	6991	1517	21.7
31	8266	1745	21.1
32	9061	1916	21.1
33	9435	1924	20.4
34	9850	1953	19.8
35	9301	1731	18.6
36	8337	1416	17.0
37	7623	1140	15.0
38	6597	870	13.2

39	5602	601	10.7
40	4021	371	9.2
41	2780	183	6.6
42	1818	72	4.0
43	1238	44	3.6
44	730	15	2.1
45	390	4	1.0

Table 14.2 relates to live birth rates from frozen IVF cycles. This analysis was based on 22,546 IVF treatment cycles that were registered between January 1995 and March 1999 and involved use of the woman's own eggs and frozen embryo transfer. The overall live birth rate per treatment cycle was 11.5%. Between the ages of 23 years and 38 years the live birth rate per treatment cycle varied between 10% and 16%. The live birth rates for women aged 18 years to 22 years are shown in Table 14.2, but reliable conclusions cannot be drawn from the extremely small number of cases on which these rates are based (0.3% of all frozen IVF treatment cycles). The live birth rate for women aged more than 38 years was less than 7%. [evidence level III]

Table 14.2 Comparison of live birth rates per cycle started by age of woman based on frozen embryo transfer and excluding donor eggs, 1995–1999 (Source: Human Fertilisation and Embryology Authority)

Age in years	Number of treatment cycles	Number of live births	Live birth rate per treatment cycle (%)
18	0	0	N/A
19	2	0	0.0
20	9	1	11.1
21	13	0	0.0
22	44	6	13.6

23	88	14	15.9
24	144	16	11.1
25	259	30	11.6
26	448	61	13.6
27	695	89	12.8
28	966	132	13.7
29	1212	180	14.9
30	1527	178	11.7
31	1883	246	13.1
32	1800	220	12.2
33	2020	257	12.7
34	2008	239	11.9
35	1909	209	10.9
36	1746	195	11.2
37	1486	177	11.9
38	1246	128	10.3
39	985	88	8.9
40	770	58	7.5
41	467	31	6.6
42	354	25	7.1
43	223	6	2.7
44	150	3	2.0
45	92	1	1.1

Four further studies have shown decreasing live birth rates with increasing female age using fresh embryo transfer.[590-593] [evidence level III] Two of these studies showed that live

birth rates were positively associated with donor insemination,[592] embryo quality,[592;593] number of embryos transferred,[593] and cause of infertility.[593]

Pregnancy rates

Table 14.3 relates to clinical pregnancy rates from IVF cycles. This analysis was based on 110,538 IVF treatment cycles that were registered by the HFEA between January 1995 and March 1999 and involved use of the woman's own eggs and fresh embryo transfer. The overall pregnancy rate per treatment cycle was 21.0%. Between the ages of 22 years and 36 years the pregnancy rate per treatment cycle exceeded 20%. The pregnancy rates for women aged 18 years to 22 years are shown in Table 14.3, but reliable conclusions cannot be drawn from the extremely small number of cases on which these rates are based (0.4% of all fresh IVF treatment cycles). The pregnancy rate for women aged more than 36 years was less than14%. [evidence level III]

Table 14.3 Comparison of clinical pregnancy rates per cycle started by age of woman based on fresh (not frozen) embryo transfer and excluding donor eggs, 1995–1999 (Source: Human Fertilisation and Embryology Authority)

Age in years	Number of treatment cycles	Number of clinical pregnancies	Clinical pregnancy rate per treatment cycle (%)
18	3	2	66.7
19	15	3	20.0
20	54	9	16.7
21	83	14	16.9
22	248	58	23.4
23	438	114	26.0
24	827	203	24.5
25	1365	333	24.4
26	2143	537	25.1

27	3324	812	24.4
28	4342	1100	25.3
29	5656	1413	25.0
30	6991	1769	25.3
31	8266	2016	24.4
32	9061	2201	24.3
33	9435	2257	23.9
34	9850	2307	23.4
35	9301	2053	22.1
36	8337	1709	20.5
37	7623	1403	18.4
38	6597	1114	16.9
39	5602	805	14.4
40	4021	520	12.9
41	2780	272	9.8
42	1818	126	6.9
43	1238	81	6.5
44	730	29	4.0
45	390	7	1.8

A cohort study has shown that pregnancy rates decline significantly after the age of 40 years, and again after the age of 42 years.[594] [evidence level IIb]

Several other studies have shown that pregnancy rates following IVF treatment decline after the age of 35 years,[595-598] 37 years{14045,14111} and 40 years.[262;599-606] [evidence level III]

The decline in pregnancy rates with age may be related to declining embryo quality.[592] Embryo quality is difficult to assess. For apparently equal embryo quality, maternal age does not significantly reduce pregnancy rates.[607] In women with good ovarian response to controlled ovarian hyperstimulation, there was no significant difference in pregnancy rates between women aged more than 40 years and those who were younger.[437] [evidence level III]

Ectopic pregnancy rates

Table 14.4 relates to ectopic pregnancy rates from IVF cycles. This analysis was based on 110,538 IVF treatment cycles that were registered by the HFEA between January 1995 and March 1999 and involved use of the woman's own eggs and fresh embryo transfer. The overall ectopic pregnancy rate per treatment cycle was 0.5%. The ectopic pregnancy rate in women aged 18 years to 25 years was 0.9%, and the rate in women aged more than 35 years was less than 0.3%. [evidence level III]

Table 14.4 Comparison of ectopic pregnancy rates per cycle started by age of woman based on fresh (not frozen) embryo transfer and excluding donor eggs, 1995–1999 (Source: Human Fertilisation and Embryology Authority)

Age in years	Number of treatment cycles	Number of ectopic pregnancies	Ectopic pregnancy rate per treatment cycle (%)
18	3	0	0.0
19	15	0	0.0
20	54	1	1.9
21	83	0	0.0
22	248	1	0.4
23	438	3	0.7
24	827	9	1.1
25	1365	14	1.0

26	2143	9	0.4
27	3324	16	0.5
28	4342	28	0.6
29	5656	33	0.6
30	6991	45	0.6
31	8266	43	0.5
32	9061	52	0.6
33	9435	75	0.8
34	9850	43	0.4
35	9301	41	0.4
36	8337	31	0.4
37	7623	20	0.3
38	6597	22	0.3
39	5602	19	0.3
40	4021	10	0.2
41	2780	5	0.2
42	1818	2	0.1
43	1238	1	0.1
44	730	2	0.3
45	390	0	0.0

Another study has shown that there is no significant difference in ectopic pregnancy rates following IVF in women over 35 years compared with younger women.[596] [evidence level III]

Miscarriage rates

Table 14.5 relates to miscarriage rates from IVF cycles. These rates are presented as per treatment cycle, and are therefore lower than if they were presented as per pregnancy. This analysis was based on 110,538 IVF treatment cycles that were registered by the HFEA between January 1995 and March 1999 and involved use of the woman's own eggs and fresh embryo transfer. The overall miscarriage rate per treatment cycle was 2.7%. The miscarriage rate in women aged more than 35 years was 2.4%. [evidence level III] These data were based on numbers of pregnancies shown in Table 14.3, and they give miscariage rates per pregnancy of 10.5% at 30 years, 13.1% at 35 years, 22.7% at 40 years, and 40.7% at 43 years.

Table 14.5 Comparison of miscarriage rates per cycle started by age of woman based on fresh (not frozen) embryo transfer and excluding donor eggs, 1995–1999 (Source: Human Fertilisation and Embryology Authority)

Age in years	Number of treatment cycles	Number of miscarriages	Miscarriage rate per treatment cycle (%)
18	3	1	33.3
19	15	1	6.7
20	54	1	1.9
21	83	3	3.6
22	248	7	2.8
23	438	11	2.5
24	827	16	1.9
25	1365	21	1.5
26	2143	49	2.3
27	3324	90	2.7
28	4342	124	2.9
29	5656	148	2.6
30	6991	186	2.7
31	8266	223	2.7

32	9061	218	2.4
33	9435	247	2.6
34	9850	296	3.0
35	9301	269	2.9
36	8337	240	2.9
37	7623	226	3.0
38	6597	203	3.1
39	5602	170	3.0
40	4021	118	2.9
41	2780	78	2.8
42	1818	41	2.3
43	1238	33	2.7
44	730	12	1.6
45	390	3	0.8

Several other studies have reported increased miscarriage rates following IVF in women aged more than 34 years[603], 35 years[596;598;608] and 40 years.[599;602;609;610] [evidence level III]

Fertilisation rates

Several studies have reported decreased fertilisation rates following IVF in women aged more than 35 years,[595] 37 years[611] and 40 years[610]. Two other studies found significantly lower fertilisation rates in older women[612;613] and after previous IVF failure.[613] However, no significant decline in fertilisation rates with age was found in a further study.[262] [evidence level III]

Implantation rates

Two studies have reported decreased implantation rates following IVF in women aged more than 35 years[596] and 37 years.[614] However a third study showed no significant difference in implantation rates between women aged over 35 years and younger women.[615] Although advancing maternal age predisposes to a reduced chance of success from IVF treatment, maternal age alone is not a useful predictor of embryo implantation or endometrial receptivity in completed IVF treatment cycles.[615] [evidence level III]

Oocyte number and quality

The decline in success rates with age following IVF may be due to reduced oocyte production. In one study, the number of retrieved oocytes decreased with increasing age, without alteration of the cleavage rate.[616] It has also been reported that the number of oocytes recovered and the number of embryos cleaved after two consecutive cycles of IVF treatment did not differ between women aged less than or over 35 years, although conception rates in older women were lower than the overall pregnancy rate in the IVF programme during the same time period.[597] [evidence level III]

Older women with good ovarian response, producing more than three embryos suitable for transfer, may have a pregnancy rate similar to younger patients. Cycles yielding less than three embryos have a poor prognosis.[617] [evidence level III]

Treatment discontinuation rates

A high percentage of women discontinue IVF treatment after unsuccessful cycles. An analysis of the FIVNAT database showed that 40-50% of women discontinued IVF treatment after unsuccessful treatment cycles.[618;619] [evidence level III] One study found that 17.7% of women aged less than 30 years and 50% of women aged 38-40 years discontinued IVF treatment after unsuccessful cycles.[620] [evidence level III] Another study found significant increases in discontinuation rates with age (38% for women aged 25-39 years, 50% for women aged 40-43 years, and 70% for women aged 44-45 years).[591] [evidence level III]

Although age alone may not be a deterrent to fertility treatment, older patients require thorough counselling regarding the decreased likelihood of success of IVF treatment as the woman's age increases.

4.2.2 Number of embryos to be transferred and multiple pregnancies

Multiple gestations are associated with more complications during pregnancy, increased perinatal, neonatal and infant morbidity and mortality[440] as well as significant financial[441;442] and psychological[443] consequences for the parents. Recent surveys have suggested that the prospect of multiple pregnancies may not be viewed as an adverse outcome by prospective patients.[446-450] [evidence level III]

Much of the increased risk for multiple births is due to the increased risk of pre-term birth. The care required for these infants also has resource implications for the health services. However, in assisted reproduction, multiple pregnancies do not appear to be at any more risk of poor obstetric and neonatal outcomes than those conceived spontaneously.[444;445] [evidence level III] The increase in incidence of multiple births in most countries is reported to be almost entirely the result of the use of gonadotrophins and other agents for ovulation induction or assisted reproduction.[621] [evidence level IIb]

In IVF the number of embryos transferred to the uterus is the main determinant of the maximum number of babies that might result. In the United Kingdom and before the regulation of IVF by the HFEA the maximum number of embryos transferred was four, with many clinics restricting the number to three. Under the regulation provided by the HFEA since 1991 the maximum number of embryos transferred has been three. In November 2001 the HFEA recommendation was that the number of embryos transferred should be limited to a maximum of two except in exceptional circumstances when three might be transferred.[622] In most United Kingdom IVF clinics this development has been

accompanied by a continuing downward trend in the proportion of treatment cycles which involve three embryo transfer.

An RCT (n=932) comparing superovulation vs no superovulation and intracervical insemination vs intra-uterine insemination found that 23.6% of superovulation live births were twins, 5.6% were triplets and 4.2% were quadruplets.[559] [evidence level Ib] There were no multiple pregnancies in the no superovulation group. In the United Kingdom, analysis of data from the HFEA (1991–1995) showed that among 29,262 transfers of three embryos, 1,755 of 6,091 deliveries (28.9%) were twins and 5.8% were triplets or more.[623] [evidence level III]

Analysis of data from 7,170 IVF and 530 ICSI cycles reaching fresh embryo transfer at one fertility centre in the United Kingdom between 1984 and 1997 showed that 1889 cycles (25%) resulted in pregnancy. A total of 1,256 of these pregnancies continued to delivery (16% per transfer), and 355 (28%) of the resulting births were multiple: 292 (23%) twins, 58 (5%) triplets and 5 (0.4%) quadruplets. The probability of birth has increased but the probability of multiple birth has remained unchanged, despite HFEA legislation limiting the number of embryos transferred to three in 1991.[624] [evidence level III]

Provisional data from the HFEA showed birth rates for twins and triplets per started cycle of IVF (using fresh and frozen embryos) to be 6.2% and 0.52% in 1999–2000, as compared with 6.2% and 0.43% in 2000–2001, respectively.[625] [evidence level III] The corresponding birth rates for twins and triplets per live birth were 30% and 2.5% in 1999-2000, and 28.6% and 1.9%, in 2000-20001 respectively.[625] [evidence level III]

The most recent validated data from the HFEA database (covering the period 1995 to 1999) were analysed for this guideline. This analysis was based on 110,538 IVF treatment cycles that were registered by the HFEA between January 1995 and March 1999 and involved use of the woman's own eggs and fresh embryo transfer. The overall multiple live birth rate per treatment cycle was 5%.

A systematic review of the literature reported results from two completed and one ongoing RCTs which compared transfers of one vs two embryos.[626-628] [evidence level Ib] All three RCTs had excluded women who had a poor prognosis (i.e. increased age, history of failed treatment and poor embryo numbers or quality). Sample sizes were small in all three RCTs. A meta-analysis of results from the first (fresh) treatment cycle in each of the RCTs showed that the combined odds ratio for pregnancy rate per cycle in favour of single embryo transfer was 0.54 (95% CI 0.32 to 0.91). The combined OR for live birth was 0.48 (95% CI 0.27 to 0.86). These results indicate that pregnancy rate per cycle is significantly lower following single embryo transfer. The multiple pregnancy rate associated with single embryo transfer was significantly lower (combined OR 0.17, 95% CI 0.07 to 0.40).

Cumulative pregnancy rates were reported in two of the RCTs.[627;628] [evidence level Ib] In the first RCT, 47.3% of women who received a single embryo transfer achieved a clinical pregnancy, whereas 58.6% of women who received a double embryo transfer achieved a clinical pregnancy.[628] In the second RCT, 36.4% of women who received two single embryo transfers (in separate treatment cycles) achieved a clinical pregnancy, whereas 28.6% of women who received a double embryo transfer (in a single treatment cycle) achieved a clinical pregnancy.[627]

These data suggest that in selected groups of women, while single embryo transfer significantly reduces the risk of multiple pregnancy, it is associated with lower pregnancy and live birth rates per cycle of treatment. Cryopreservation of surplus embryos and replacement in subsequent cycles may be associated with higher cumulative pregnancy rates. Larger, definitive RCTs are required with cumulative live birth as the end point.

No randomised trials which compared transfers of two vs three embryos could be identified. A single controlled observational study[629] compared two embryo transfers (n=80) in ‘good prognosis’ women with three embryo transfers (n=130) in a similar non-randomised group. The clinical pregnancy rates were similar (OR 1.26, 95% CI 0.70 to

2.26). Multiple pregnancy rates were higher in the three embryo transfer group but the difference did not reach statistical significance (OR 2.17. 95% CI 0.98 to 4.82). [evidence level IIb]

A single randomised trial which compared transfers of two vs four embryos was identified.[630] The results fail to show a difference in either clinical pregnancy rates (OR 1.34 95% CI 0.46 –3.87), live birth rates (OR 2.88, 95% CI 0.95 – 8.72) or multiple pregnancy rates per cycle (OR 2.27, 95% CI 0.51 – 10.18). The wide confidence levels reflect the imprecision of the results due to the small sample size.

It has been demonstrated that an increase in the number of embryos transferred invariably results in higher likelihood of multiple birth but without necessarily improving the overall success rate of IVF.[623] [evidence level III] This observational study suggests that when more than four eggs are fertilised and available for transfer, the woman's chance of a birth is not diminished by transferring only two embryos.[623] [evidence level III]

Economic consequences

An American study based on a single retrospective cohort study in a single IVF centre followed 413 treatment cycles.[631] This study reported cost differences of about US$39,000 for single and twin pregnancies, and US$342,788 for triplet and quadruplet pregnancies.

A Scottish study examined the costs associated with IVF before and after the introduction of a policy to restrict the number of embryos transferred. There were 92 women in the 'before' group (historical cohort), and 93 women in the 'after' group (later cohort).[632] There was no significant difference in clinical pregnancy rates between the two groups. A higher rate of multiple births in the historical cohort was associated with higher rates of preterm birth and low birth weight. The cost analysis included cost of intensive care, midwifery, drugs and equipment. In the historical cohort, 50 intensive care days and 115 special care

cost days were recorded at a cost of over £500,000. In the later cohort, the costs of these additional services associated with multiple births were £56,000.

A Swedish study examined the transfer of one embryo compared with two in a single institution setting.[633] A decision tree was used to model 1488 transferred embryos. The final outcomes were based on case series and opinion and not on robust research evidence. The model assumed that for IVF with one embryo transfer the chance of having a child was 21% and the chance of a twin pregnancy was 0.0021%. The transfer of two embryos was associated with a 24.8% chance of a singleton child and a 7.8% chance of twin children, with a 64% chance of no baby. The total costs of IVF with one embryo were reported to be about SEK11,000 (£822) and SEK43,286 (£3,320) for two embryos. These costs included sick leave, hospital care during pregnancy, cost of delivery, neonatal care and disability care.

These studies suggest that there may be significant resource savings from adopting a policy of limiting embryo transfer after IVF.

Research recommendation:

Further research is needed to evaluate the clinical effectiveness of single embryo transfers.

14.2.3 Number of previous treatment cycles

The largest study to address the success of IVF treatment according to the number of previous unsuccessful cycles used the HFEA database of all IVF cycles carried out in the United Kingdom between 1991 and 1994 (n= 33,701 cycles).[589] [evidence level III] This study reported that the probability of success decreased with each IVF treatment cycle from 14.0% (95% CI 13.5-14.5) at the first attempt, to 13.0% (95% CI 12.2-13.7) at the second attempt, 11.4% (95% CI 10.4-12.5) at the third attempt, 11.5% (95% CI 10.1-13.2)

at the fourth attempt, 8.9% (95% CI 7.2-11.2) at the fifth attempt, 9.3% (95% CI 6.7-12.9) at the fifth attempt, and 10.2% (95% CI 7.7-13.7) at the sixth to ninth attempts.

In addressing the effectiveness of IVF treatment in the context of the number of previous unsuccessful cycles, the HFEA was unable to provide these data for all 110,538 fresh IVF cycles registered in the period January 1995 to March 1999 that involved use of the woman's own eggs. However, the HFEA was able to provide these data for a subset of 2,247 of these cycles (see Table 14.6). The data show that the live birth rate per treatment cycle is largely unchanged over the first four attempts, but the sample sizes for the fifth, sixth and seventh attempts are too small to make valid conclusions. [evidence level III]

Table 14.6 Comparison of live birth rates per cycle started by number of previous unsuccessful treatment cycles based on fresh (not frozen) embryo transfer and excluding donor eggs, subset of 1995–1999 data (Source: Human Fertilisation and Embryology Authority)

Number of previous treatment cycles	Number of treatment cycles	Number of livebirths	Live birth rate per treatment cycle (%)
0	2247	408	18.2
1	688	118	17.2
2	213	40	18.8
3	62	12	19.4
4	13	4	30.8
5	5	1	20.0
6	2	0	0.0
7	1	0	0.0

Further data relating to the success of IVF treatment according to the number of previous unsuccessful cycles were provided by the Oxford Fertility Unit for this guideline (see Table 14.7). This analysis was based on 5,028 IVF treatment cycles started between January

1995 and December 2001 and involved use of the woman's own eggs and fresh embryo transfer. These data show that for women aged less than 39 years, and those aged 39 years and over, the live birth rate per treatment cycle is largely unchanged over the first three attempts (the live birth rate for women aged 39 years and over with two previous unsuccessful cycles is less reliable than the other rates because it is based on fewer cycles). [evidence level III]

Table 14.7 Comparison of live birth rates per cycle started by age and number of previous unsuccessful treatment cycles based on fresh (not frozen) embryo transfer and excluding donor eggs, 1995–2001 (Source: Oxford Fertility Unit)

a) Women aged less than 39 years

Number of previous treatment cycles	Number of treatment cycles	Number of livebirths	Live birth rate per treatment cycle (%)
0	2396	575	24.0
1	1280	310	24.2
2	631	138	21.9

b) Women aged 39 years and over

Number of previous treatment cycles	Number of treatment cycles	Number of livebirths	Live birth rate per treatment cycle (%)
0	334	34	10.2
1	228	22	9.7
2	159	26	16.4*

* The live birth rate for women aged 39 years and over with two previous unsuccessful cycles is less reliable than the other rates because it is based on fewer cycles.

Data from 8,362 patients who underwent a first cycle of IVF treatment between 1988 and 1989 have been analysed using the FIVNAT database.[618] This study found a decline in pregnancy rate with rank of attempt, although the transfer rate and the number of transferred embryos increased with successive attempts. A more recent analysis of the FIVNAT database using data on 35,714 couples who underwent IVF treatment between 1990 and 1996 showed that the clinical pregnancy rate per oocyte recovery decreased from 20.2% on the first attempt to 17.4% on the second attempt, 16.0% on the third attempt, 13.3% on the fourth attempt, 13.4% on the fifth attempt, 12.7% on the sixth attempt, 7.3% on the seventh attempt, and 11.9% on the eighth attempt.[619] This relationship was independent of the woman's age and the cause of infertility. However, the woman's age remained the most important factor: the cumulative pregnancy rate decreased from 60% for women aged less than 35 years to 17% for those aged more than 41 years.[619] [evidence level III]

Another study reported data from 4,225 patients (8,207 IVF cycles) who underwent IVF treatment in Australia between 1993 and 1997.[634] [evidence level III] This study showed that clinical pregnancy rate per oocyte recovery using fresh or frozen embryo transfer decreased from 20.7% on the first attempt to 20.1% on the second attempt, 17.5% on the third attempt, 6.2% on the fourth attempt, 15.0% on the fifth attempt, 14.8% on the sixth attempt, and 11.7% on the seventh to tenth attempts.[634] [evidence level III]

A multicentre retrospective study conducted in the United States reported pregnancy rates per cycle for cycles 1, 2, 3, 4 and > 4 to be 33.7%, 33.9%, 28.9%, 25.9% and 21.0%, respectively; the corresponding delivery rates were 27.0%, 27.4%, 23.4%, 16.1% and 15.4%, respectively.[635] [evidence level III] The pregnancy and delivery rates decreased significantly after the fourth cycle and third cycles, respectively. A smaller study found that pregnancy and live birth rates declined with successive treatment cycles.[603] [evidence level III] Another small study found that implantation rate was significantly associated with

rank of attempt.[614] [evidence level III] Another study reported similar clinical pregnancy rates for up to seven treatment cycles (25%, 29%, 28%,33%, 35%, 30%, and 40%, respectively).[609] [evidence level III]

14.2.4 Pregnancy history

Analysis of the HFEA database showed that previous pregnancy and live birth were associated with increased treatment success.[589] Rates of secondary infertility are higher in the general population than in clinic referrals.[636] IVF for secondary infertility generally has better results than for primary infertility. Another study showed that women with primary infertility were significantly younger than women with secondary infertility; they also had significantly more oocytes and fewer embryos, and significantly decreased fertilisation and pregnancy rates.[637] A further study examined the relationship between the first cycle of IVF and subsequent cycles.[605] This study found that a previous pregnancy significantly improved a couple's probability of conception in a later IVF cycle. [evidence level III]

14.2.5 Duration and cause of infertility

Duration of infertility has been shown to be an important factor in determining the chance of pregnancy, with or without treatment.[638] Of those couples who have not conceived within one year 50% will do so spontaneously in the subsequent year. Couples who have not conceived after three years have only a 12% chance of conceiving in the following year. [evidence level III]

Analysis of the HFEA database showed a significant decrease in the IVF live birth rate with increasing duration of infertility from 1 to 12 years, which persisted after adjusting for the woman's age.[589] The cause of infertility did not have a significant effect on outcome, but previous pregnancy and live birth increased the chance of treatment success. Another study found no significant differences in cumulative pregnancy rates between causes of infertility in women undergoing IVF treatment.[604] [evidence level III]

Cumulative conception and live birth rates among women undergoing IVF treatment were reported to be lowest in patients with male infertility or multiple infertility factors. Cumulative pregnancy rates were significantly higher in couples with secondary infertility, when compared with couples with primary infertility. In cases of tubal, endocrinological and unexplained infertility the success rate of IVF was comparable with the probability of natural conception of young and fertile couples.[603;606] [evidence level III]

14.2.6 Cost-effectiveness of in vitro fertilisation treatment

The cost-effectiveness models for IVF treatment are described in detail in Appendix A. These show cost-effectiveness by age and by the number of treatment cycles.

Age-specific model

Age-specific costs per live birth using three cost estimates (baseline, lower and upper) for IVF treatment and an OHSS incidence rate of 0.2% were calculated. The costs per live birth were very similar for ages 24 years to 33 years, after which they rose steeply with increasing age. For example, using the baseline cost of IVF treatment (£2,771), the costs per live birth were £11,917 at 24 years, £12,931 at 35 years, and £20,056 at 39 years. Sensitivity analyses using lower and higher costs for IVF treatment (£1,771 and £3,500, respectively) resulted in costs per live birth of £8,103 and £14,697 at 24 years, £8,800 and £15,943 at 35 years, and £13,723 and £24,673 at 39 years.

Cycle-specific models

Cycle-specific costs where the live birth rate varied by cycle were also calculated using the baseline cost estimate for IVF treatment and the HFEA live birth rates by number of previous unsuccessful IVF cycles shown in Table 14.6. The cost per live birth in the first cycle of IVF treatment was £15,281. The corresponding costs for the second, third and fourth cycles of IVF treatment were £16,169, £14,793, and £14,336. These costs reflect the varying live birth rates by number of previous unsuccessful IVF cycles. Sensitivity analyses using the lower and higher costs for IVF treatment are presented in Appendix A.

Cycle-specific costs were also calculated using the baseline cost estimate for IVF treatment and the Oxford Fertility Unit live birth rates by number of previous unsuccessful IVF cycles shown in Table 14.7. For women aged less than 39 years, the cost per live birth in the first cycle of IVF treatment was £11,694. The corresponding costs for the second and third cycles of IVF treatment were £11,548 and £12,758. For women aged 39 years and over, the costs per live birth were £27,611 for the first cycle of treatment, £28,938 for the second cycle of treatment, and £12,835 for the third cycle of IVF treatment. These costs reflect the varying live birth rates by number of previous unsuccessful IVF cycles (see Table 14.7), and the cost per live birth for the third cycle of treatment is not very reliable because of the small number of cycles on which the live birth rate was based.

International comparison

The cost-effectiveness ratios (cost per live birth) presented here can be compared with cost-effectiveness ratios reported for other countries using RCT clinical effectiveness evidence. A recent review of this evidence shows far higher cost-effectiveness ratios (cost of IVF per delivery) in the United States (as might be expected), but similar results in Scandinavian countries.{12361} The data reported below are for the year 1994.

Sweden	£10,295
Denmark	£11,858
Norway	£13,413
Finland	£11,211
Iceland	£7,400

Recommendations:

Couples should be informed that the chance of a live birth following in vitro fertilisation treatment decreases with the woman's age. Women aged 23–35 years have more than a 20% chance of a live birth per treatment cycle. However, those aged 36–38 years have a 15% chance, those aged 39 years have a 10% chance, and

those aged 40 years and older have a 6% chance. The effectiveness of in vitro fertilisation treatment where the woman is younger than 23 years of age is uncertain because very few women have in vitro fertilisation treatment in this age range. [C]

Couples should be informed that the optimal woman's age range for in vitro fertilisation treatment is 23–39 years, inclusive. [GPP]

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. Balancing the chance of 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. [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. [C]

In vitro fertilisation treatment should consist of a maximum of three complete 'fresh' treatment cycles (that is, ovarian stimulation and an attempt at egg collection) to achieve a live birth. Embryos not transferred in a fresh treatment cycle may be suitable for freezing. If two or more embryos are suitable for freezing then they should be transferred before the next fresh treatment cycle because this will minimise ovarian stimulation and egg collection, both of which carry risks for the woman and use more resources. [GPP]

Couples who meet the following criteria should be offered in vitro fertilisation treatment: [GPP]

- **either**
  - **the woman is within the optimal age range for in vitro fertilisation (that is, the woman is aged 23–39 years) and**
  - **there is an appropriately diagnosed cause of infertility of any duration, or unexplained infertility of at least 3 years' duration (including mild endometriosis and mild semen abnormality);**
- **or**
  - **the woman is younger than 23 years of age and**
  - **there is an absolute indication for in vitro fertilisation treatment (for example, tubal blockage, very poor semen quality, or prior treatment for cancer).**

14.3 Gamete intrafallopian transfer and zygote intrafallopian transfer

Gamete intrafallopian transfer

GIFT is a technique which has been developed alongside IVF using much of the same technology, but where eggs, once collected, are transferred laparoscopically to the fallopian tube with prepared motile sperm to allow fertilisation to occur in vivo. GIFT is not widely used. It has been most commonly used in the management of unexplained fertility problems, but has also been used in the management of male factor fertility problems.

We did not find any RCTs that compared GIFT with no treatment in couples with unexplained infertility.

One RCT compared GIFT with stimulated and unstimulated IUI in woman with unexplained infertility. It found higher pregnancy rates with GIFT (0.12, 95% CI 0.02 to 0.20 with GIFT vs 0.018, 95% CI 0 to 0.05 with IUI plus OS; vs 0.018, 95% CI 0 to 0.05 with IUI in spontaneous cycle).[639] [evidence level Ib]

Another RCT compared GIFT and conventional infertility treatments in couples with female infertility excluding tubal factors. Overall, it showed higher pregnancy rates in the group receiving GIFT, but in the subgroup of woman with unexplained infertility (number of women not specified) there was no significant difference in pregnancy rates per cycle (23.6% with GIFT vs 36.8% with conventional treatments).[640] [evidence level Ib]

The third RCT (n=39) compared GIFT with ovarian stimulation in couples with unexplained infertility or failure of donor insemination. It found no significant difference in pregnancy rates between the two interventions in those women with unexplained infertility (8% with GIFT vs 13% with ovarian stimulation; RR 0.63, 95% CI 0.10 to 3.98).[641] [evidence level Ib]

A small RCT (n= 13) found no significant difference between GIFT and IVF in terms of pregnancy rates (33% with GIFT vs 28.5% with IVF) in couples with male factor fertility problems.[642] [evidence level Ib]

A systematic review of five RCTs based on couples with unexplained infertility found no significant difference in live birth rates per couple between IVF and IUI with ovarian stimulation (OR 1.15, 95%CI 0.55 to 2.42) or between IVF and IUI without ovarian stimulation (OR 1.96, 95% CI 0.88 to 4.36).{10226} [evidence level Ia] However, these results were based on a single RCT that did not specifiy the age range of the women involved in the study.

Zygote intrafallopian transfer

ZIFT is a technique which is not widely practised; it has been developed alongside IVF using much of the same technology, but where embryos are transferred laparoscopically to the fallopian tube after fertilisation in vitro.

One cross-over RCT compared ZIFT and IVF in couples with unexplained infertility and found no significant differences between the two interventions in ongoing pregnancy per embryo transfer (25% with ZIFT vs 31% with IVF; RR 0.74, 95% CI 0.40 to 1.39), miscarriage and multiple pregnancy rates.[643] [evidence level Ib] The maximum number of embryos transferred in this study was three.

The dominant adverse effect of female age on the success of IVF, GIFT and ZIFT has been highlighted in two cross-sectional studies, with a higher cycle cancellation rate and pregnancy loss rate associated with older women with unexplained infertility undergoing assisted reproduction.[644;645] [evidence level III]

Recommendation:

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

Chapter 15 Conduct of in vitro fertilisation

Welfare of the child

The Human Fertilisation and Embryology Act 1990 (HFE Act) requires that any fertility clinic in the United Kingdom offering licensed treatment services, such as IVF or use of donated gametes, must take account before treatment of the welfare of the child (including the need of that child for a father) and of any other existing child who may be affected by the birth. Details on the issues of assessment of people seeking treatment, confidentiality, information, consent and counselling are referred to the HFEA Code of Practice.{7807} (The 6th edition – to be published 2003.)

15.1 Medical assessment and screening

In addition to a detailed clinical assessment involving history taking and physical examination, careful screening before assisted reproduction aims to protect recipients and offspring from transmission of infections (including Chlamydia; see Section 5.3.6) and genetic diseases. It should be noted that there is a risk of viruses surviving cryopreservation, and that welfare of the children resulting from assisted reproduction should be considered in relation to screening.

A case-series study showed that among patients seeking infertility treatment at an IVF clinic, 0.06% were seropositive for HIV, 0.5% were seropostive for the hepatitis B virus, and 0.54% were seropositive for the hepatitis C virus.[646] [evidence level III]

Recommendation:

To prevent transmission between patients and their gametes patients undergoing in vitro fertilisation treatment should be offered screening for HIV, hepatitis B virus and hepatitis C virus, and those found to be positive should be treated appropriately. [B]

15.2 Ovulation induction

IVF ovulation induction techniques are based on the use of the same drugs which are used in ovulation induction for ovulatory disorders. However, there are specific aspects of the use of these drugs which will be different in the IVF context. The more generic aspects of drug use (and their risks), especially in relation to gonadotrophins and GnRH analogues, are discussed in Chapter 9, whereas those drug techniques that are more specific to IVF are discussed below.

Natural cycle in vitro fertilisation

A literature review of studies involving 1800 cycles, 819 embryo transfers and 129 ongoing pregnancies reported an embryo transfer rate of 45.5% per cycle, an ongoing pregnancy rate of 7.2% per cycle and a cycle cancellation rate of 29% in natural cycle IVF.[647] [evidence level IIb–III] Natural cycle IVF was associated with no risk of OHSS or multiple pregnancy rate when a single embryo was transferred.[647] [evidence level IIb – III]

Natural cycle vs clomifene-stimulated cycle

An RCT showed no significant difference in clinical pregnancy rate between clomifene citrate cycle and natural cycle IVF (18% with clomifene citrate cycle vs 0% in natural cycle), but cycle cancellation rate was significantly higher in natural cycle IVF (10 cycles vs none).[648] [evidence level Ib]

Another RCT found a significantly higher pregnancy rate per cycle in patients undergoing clomifene citrate cycle IVF compared with natural cycle IVF (18% with clomifene citrate

cycle vs 4% with natural cycle; RR 5.14, 95% CI 1.81 to 14.55).[649] [evidence level Ib] Modest side effects were reported following clomifene.

Natural cycle vs gonadotrophins

A cross-over RCT found a significant improved clinical pregnancy rate per cycle with hMG cycle IVF vs natural cycle IVF (23% with hMG cycle vs 0% with natural cycle). There were no data on side effects or multiple pregnancy rate.[650]

Drugs for cycle control

In assisted reproduction, ovarian stimulation protocols enable the production and collection of multiple oocytes, which are fertilised in vitro and the resulting embryos then transferred into the uterus. IVF treatment is based predominantly on superovulation induced using gonadotrophins (such as hMG, uFSH and rFSH) in order that multiple follicles develop. In IVF treatment, gonadotrophins are most commonly used alongside gonadotrophin-releasing hormone (GnRH) agonists (such as goserelin, nafarelin and luprolide) and sometime antagonists (cetrorelix and ganirelix). Since many aspects of gonadotrophin and GnRHa use overlap with their uses in ovulation induction for ovulatory disorders, the evidence relating to these agents in IVF treatment is discussed in Chapter 9.

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

Management of women with a poor ovarian response

The lack of a consistent definition of poor ovarian response makes it difficult to develop or assess any protocol to improve the outcome. Women with poor ovarian response have lower pregnancy rates characterised by fewer follicles and no.of oocytes retrieved, likely to be associated with diminished ovarian reserve.[651;652] [evidence level IIII]

A narrative systematic review of available studies including RCTs found limited data which assessed the effectiveness of different management strategies in women with poor ovarian response.[652] There is minimal or no benefit with the use of increased dose of gonadotrophins. There is insufficient evidence that the use of rFSH improved pregnancy rates when compared with uFSH in poor responders. Flare-up GnRH agonist protocols were reported to produce better results than standard long luteal protocols. Luteal initiation of FSH has not been shown to improve pregnancy outcome. The use of GnRH antagonists did not show any benefits. There were no studies reporting the use of corticosteroids involving poor responders. Data were limited on the use of nitrous oxide donors such as L-arginine in improving pregnancy rate in poor responders. Pre-treatment with combined oral contraceptives before ovarian stimulation may be beneficial. No benefit was shown with standard use of ICSI or assisted hatching of zona pellucida. Comparable pregnancy rates were reported between natural and stimulated cycles in poor responders. Further evaluation with large-scale and well-designed RCTs is needed to verify the role of these different approaches.[652] [evidence level IIb]

Adjuvant growth hormone therapy

A systematic review of six RCTs found no significant difference between growth hormone augmented ovulation induction vs non growth hormone augmented ovulation induction in pregnancy rate per cycle in women with no previous poor response (OR 0.97, 95% CI 0.34 to 2.76) or in poor IVF responders (OR 2.55, 9%% CI 0.64 to 10.12).[653] [evidence level Ia]

Three additional RCTs were found. One small RCT showed no significant difference between adjuvant growth hormone GH 4 IU vs growth hormone GH 12 IU vs no growth hormone in down-regulated ovulation induction in pregnancy rate per embryo transfer (0% vs 29% vs 0%).[654] [evidence level Ib] Another RCT showed no significant difference between growth hormone-releasing factor vs placebo in clinical pregnancy rate (8.3% vs 8%) and live birth rate (5.2% vs 4%) in poor responders.[655] [evidence level Ib] One quasi-randomised trial showed no significant difference between growth hormone vs no growth hormone in down-regulated ovulation induction in pregnancy rate (0% vs 7.7%) in poor responders.[656] [evidence level IIa]

Recommendation:
The use of adjuvant growth hormone with gonadotrophin during in vitro fertilisation cycles does not improve pregnancy rates and is therefore not recommended. [A]

15.4 Oocyte maturation — human chorionic gonadotrophin

Human chorionic gonadotrophin (hCG) has been used as a surrogate LH surge to induce final oocyte maturation before oocyte retrieval in assisted reproduction.

An RCT found no significant differences between rhCG and uhCG in clinical pregnancy rate (33% with rhCG vs 24.7% with uhCG), and live birth rate (27% with rhCG vs 23% with uhCG) and OHSS incidence (7.2% with rhCG vs 6.4% with uhCG).[657] [evidence level Ib]

Another RCT showed no significant differences between 250 µg and 500 µg of rhCG and uhCG in clinical pregnancy rate (35.1% vs 36% vs 35.9%), live births (87.9% vs 84.4% vs 84.8%) or OHSS incidence (3.25% vs 9% vs 3.1%).[658] [evidence level Ib]

Recommendations:
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. [A]

Recombinant human chorionic gonadotrophin is as effective as urinary human chorionic gonadotrophin for oocyte maturation. [A]

15.5 Monitoring of stimulated cycles

In assisted reproduction, the purpose of monitoring ovarian response is to ensure safe practice in reducing the incidence and severity of OHSS, and to optimise the timing of luteinisation before oocyte retrieval.

An average number of three ultrasound scan monitoring is commonly practiced: at the start of ovarian stimulation in GnRH agonist-controlled cycle, to assess at day 7-9 and to determine timing of hCG administration at days 11-14. The extent of monitoring is reduced in GnRH antagonist controlled cycles.[659] [evidence level III]

One RCT (n=114) found no significant differences between ultrasonic ovulation control with hormone determination vs ultrasound alone in pregnancy rate per embryo transfer (27.2% vs 29.5%) and OHSS rate (5.3% vs 7%) in women undergoing GnRHa-hMG during IVF-embryo-transfer for the first time.[660] [evidence level Ib]

One RCT (n=279) found no significant differences between cycle monitoring using both serum E2 and ultrasound vs ultrasound alone in clinical pregnancy rate (34.3% vs 31.4%) and OHSS rates (4.9% vs 4.1%) in normal responders undergoing GnRHa-rFSH during IVF-embryo-transfer.[661] [evidence level Ib]

A non-RCT (n=206) found no significant differences between ultrasound with hormonal determination vs ultrasound alone in clinical pregnancy rate (22.9% vs 23.4%), take home baby rate (14.3% vs 14.8%) and OHSS rate (1.04% vs 0.9%) in women undergoing GnRHa-hMG/hCG during IVF-embryo-transfer.[662] [evidence level IIa]

Recommendations:

Ultrasound monitoring of ovarian response should form an integral part of the in vitro treatment cycle. [C]

Monitoring oestrogen levels during ovulation induction is not recommended because it does not give additional information compared to ultrasound monitoring. [A]

15.6 Ovarian hyperstimulation syndrome

OHSS is an iatrogenic and potentially life-threatening complication of superovulation. The incidence of OHSS varies between 0.6% - 10% in vitro fertilisation (IVF) cycles. The severe form of the condition occurs in 0.5-2% of IVF cycles.[663]

Several risk factors have been associated with the development of OHSS (see Table 15.1).[576;664]

Table 15.1: Risk factors for OHSS

Young age (less than 30 years)
Lean physique
Polycystic ovary syndrome patients
High serum estradiol (greater than 2500 pg/ml or 9000pmol/l)
Rapidly increasing estradiol levels (greater than 75% from previous day)
Size and number of follicles and ultrasonographic ovarian 'necklace sign' of multiple small follicles
Human chorionic gonadotrophin administration
Number of oocytes retrieved (greater than or equal to 20)
Multiple pregnancy

Criteria for classifying the severity of OHSS are shown in Table 15.2.[665]

Table 15.2: Classification of severity of OHSS

Mild

Abdominal bloating, mild pain

Ovarian size usually less than 8cm*

Moderate

Increased abdominal discomfort accompanied by nausea, vomiting and/or diarrhoea

Ultrasound evidence of ascites

Ovarian size usually 8-12 cm*

Severe

Clinical ascites, sometimes Hydrothorax

Haemoconcentration (Haematocrit greater than 45%, white blood cell count greater than 15000/ml)

Oliguria with normal serum creatinine

Liver dysfunction

Anasarca

Ovarian size usually greater than 12 cm*

Critical

Tense ascites
Haematocrit greater than 55%, white blood cell count greater than 25000/ml
Oliguria with elevated serum creatinine
Renal failure
Thromboembolic phenomenon
Ovarian size usually greater than 12 cm*

*Ovarian size may not correlate with severity of OHSS in cases of assisted reproduction because of the effect of follicular aspiration. Nevertheless, recording ovarian measurements of ovarian size is not currently considered useful as a prognostic indicator nor as an indicator of the stage of the disease.[664]

Prevention of ovarian hyperstimulation syndrome

There is no evidence to support the superiority of either hMG or rFSH[410] (OR 1.60, 95% CI 0.60-4.3) or urinary preparations[411] (OR 1.36, 95% CI 0.79-2.33) in preventing OHSS.

Cycle cancellation

Cancellation of a treatment cycle is a strategy that has been considered if serum estradiol levels are excessively high and/or ovarian ultrasound reveals a large number of developing follicles. The principle behind this decision is to withhold the ovulatory trigger (hCG). In cycles where gonadotrophin-releasing hormone (GnRH) agonists have not been used this may not completely prevent early-onset OHSS as a natural LH surge may still occur.[665]

Coasting

Coasting involves discontinuation of gonadotrophins in cycles with an excessive response and delaying hCG administration, whilst continuing GnRH agonist administration in the

presence of ultrasound and endocrine monitoring.[666] It is an alternative to cycle cancellation in situations where there is a substantial risk of OHSS associated with high serum estradiol levels above 2500pg/ml (9000 pmol/l). The aim is to allow follicle-stimulating hormone (FSH) levels to drop thus inhibiting granulosa cell proliferation and subsequent availability for luteinisation. The patient is monitored until the estradiol level falls below a safe limit (<2500pg/ml or 9000 pmol/L). Although shown to be effective in observational studies, there is insufficient evidence to advocate the use of coasting in routine practice. It can potentially reduce the number of oocytes recovered, and may even compromise pregnancy rates. A Cochrane review on the role of coasting for the prevention of OHSS identified only one RCT. Compared with elective unilateral follicular aspiration, there was no convincing benefit associated with the use of coasting (OR 0.76, 95% CI 0.18-3.24).[667]

Elective cryopreservation of all embryos

Following oocyte recovery in assisted reproductive treatments, fresh embryo transfer may be deferred if there are excessive numbers of follicles and oocytes recovered (>20). All embryos are cryopreserved and electively replaced at a later date. The idea is to prevent a conception cycle and hence late-onset OHSS. A recent Cochrane review has concluded that there is insufficient evidence to support routine cryopreservation in cases with a high risk of OHSS (OR 5.33, 95% CI 0.51-56.24 for elective cryopreservation vs intravenous albumin; OR 0.12, 95% CI 0.01- 2.29 for elective cryopreservation vs fresh embryo transfer).[667]

Luteal phase support

A systematic review[668] has confirmed the effectiveness of routine luteal phase support after embryo transfer in IVF cycles involving the use of gonadotrophin-releasing hormone agonists. The use of hCG in this situation can aggravate OHSS and progesterone should be the preparation of choice in high-risk women.[669]

Prophylactic albumin administration

It has been suggested that administration of intravenous albumin around the time of oocyte recovery could be used as a preventative measure in the high risk patient. The

exact mode of action of albumin is unknown, but it is thought to bind to vasoactive substances involved in the pathogenesis of OHSS. It also increases the intravascular oncotic pressure, thereby preventing loss of water from the intravascular compartment.[664] The results of a recently updated systematic review{4828} indicate that the use of intravenous albumin at the time of oocyte retrieval significantly reduces the incidence of severe OHSS in high-risk women undergoing IVF (OR 0.28, 95% CI 0.11-0.73). However the optimal timing and dose of albumin are unclear, as is its effect on implantation. There are also growing concerns about the possibility of febrile reactions, anaphylactic shock and the potential risk of virus and prion transmission.[670] In one study{4828} 18 women at risk needed to be treated with albumin infusion in order to prevent a single case of severe OHSS. This needs to be taken into account in the context of clinical decision making.

The alternative to albumin is infusion of hydroxyethyl starch solution, which is a plasma colloidal substitute. It may be a safer, cheaper and effective method that needs evaluation in an RCT, and there are concerns about its interaction with the blood-coagulation system.[671]

Role of follicular aspiration

Recovery of immature oocytes (which can then be cultured in vitro and subsequently used for IVF) has been suggested as a means of preventing OHSS when hCG is withheld.[672]

Follicular aspiration alone cannot be relied on to avert the development of OHSS or to arrest clinical deterioration in a pre-existing case. Despite this, practitioners are known to attempt meticulous puncture and aspiration of all stimulated follicles at time of oocyte recovery in the belief that this interferes with the mechanisms leading to production of the ovarian mediators of OHSS.[664]

Other methods of prevention

A number of other methods of preventing OHSS have been advocated. These include the use of recombinant LH[673] and GnRH antagonists like ganirelix or cetrorelix.[674;675] A meta-

analysis of five RCTs[424] suggested that treatment with GnRH antagonists does not significantly reduce the incidence of severe OHSS in comparison with those treated with agonists (OR 0.51, 95% CI 0.22-1.18).

In a prospective randomised trial,[676] ovarian electro diathermy in women with polycystic ovaries before IVF was compared with IVF alone. There was no significant difference in the incidence of OHSS in women treated by ovarian diathermy or not.

Treatment of ovarian hyperstimulation syndrome

Treatment of OHSS is mainly supportive.[665] Multidisciplinary local protocols involving gynaecologists, anaesthetists and haematologists should be generated and strictly followed. The condition is self-limiting and resolution parallels the decline in serum hCG levels (about 7 days in non-pregnant women and 10-20 days in pregnant women). Mild OHSS is usually benign and resolves with the onset of the first period. Moderate to severe cases need hospital admission and monitoring. The principles of care include appropriate specialist involvement, circulatory support using intravenous fluids, maintenance of renal function, thromboprophylaxis and drainage of third space accumulation.

Recommendations:

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

Prophylactic albumin treatment may be of benefit but more research on timing and dose is required. [B]

Women who have a significant risk of developing ovarian hyperstimulation syndrome should not be offered human chorionic gonadotrophin. [A]

15.7 Oocyte retrieval

Conscious sedation and anaesthesia/analgesia

Guidance on the safe use of sedative drugs for patients undergoing healthcare procedures has been published by the Academy of Medical Royal Colleges[677] and must be followed.

It is well accepted that transvaginal oocyte retrieval is unpleasant and painful. It is therefore important to provide effective anaesthesia/analgesia to minimise side effects experienced by patients and to minimise toxic effects on embryo cleavage rates and pregnancy rates.

A narrative review of anaesthesia methods used for transvaginal retrieval of oocytes found that general anaesthetics can traverse into the follicular fluid and may be detrimental to cleavage rates of embryo and pregnancy rate. Epidural anaesthesia avoids many of the side effects of general anaesthetics and it may shorten recovery time. However, it requires the expertise of an anaesthetist. Local anaesthesia (paracervical block) or no anaesthesia can cause unnecessary discomfort. Conscious sedation requires less-specialised equipment, causes relatively few complications and is well-tolerated by patients, though there is a theoretical risk of agents contaminating the follicular fluid.[678] [evidence level IIb–III]

One RCT showed significantly higher median vaginal pain and abdominal pain levels in patients given paracervical block with placebo when compared with paracervical block with conscious sedation. There was no significant difference in pregnancy rate per cycle.[679] [evidence level Ib]

Another RCT found significantly higher anxiety levels, vaginal and abdominal pain levels in patients given placebo when compared with patients given premedication with anxiolytic during oocyte retrieval.[680] [evidence level Ib]

An RCT showed no significant difference in mean pain score and patient satisfaction rate between fentanyl administration via a patient-controlled analgesia delivery system vs administration by a physician. Significantly more fentanyl was used in the patient-controlled analgesia group.[681] [evidence level Ib]

Another RCT found significantly higher mean pain score with sedation (midazolam and ketamine) when compared with general anaesthesia (with fentanyl and propofol), though the higher pain score with sedation was not sufficiently high to render it unacceptable. There was no significant difference between the two groups in pregnancy rate per embryo transfer (22.7% with sedation vs 23.8% with general anaesthesia). The mean number of embryos transferred was significantly higher in the sedation group (2.8 vs 1.9). Patient satisfaction did not differ between the two groups.[682] [evidence level Ib]

A cohort study (n=202) compared the effects of general anaesthesia vs sedation on oocyte retrieval and IVF outcome. This study found that significantly more oocytes were collected in the general anaesthesia group compared with the sedation group, but there were no differences in cleavage and pregnancy rates between the two groups (23.6% with general anaesthesia vs 31.3% with sedation).[683] [evidence level IIb] Another cohort study found no differences in fertilisation rates and cleavage characteristics between women receiving general anaesthesia and those receiving a paracervical local anaesthetic block during oocyte retrieval.[684] [evidence level IIb]

Follicle flushing

Follicle flushing is traditionally employed during transvaginal ultrasound directed oocyte recovery for IVF in the belief that flushing allows a larger number of oocytes to be collected which would otherwise be missed if aspiration alone were used.

An RCT showed no significant differences between follicular aspiration with flushing and follicular aspiration only in mean number of oocytes retrieved (7.0 vs 8.5), fertilisation rate (64% vs 60%) and ongoing pregnancy rate (17% vs 19%). Significantly longer time was required for the procedure of flushing.[685] [evidence level Ib]

Another RCT found no significant differences between follicular aspiration with flushing and follicular aspiration only in mean number of oocytes retrieved (9 vs 11), fertilisation rate (60% vs 55.6%) and clinical pregnancy rate per woman (26% vs 24%; RR 0.92, 95% CI 0.47 to 1.82). Significantly longer time and higher doses of pethidine were required for the procedure of flushing.[686] [evidence level Ib]

Recommendations:

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

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

Follicle flushing is not associated with improvements in pregnancy rates or numbers of oocytes retrieved, and it increases the duration of the procedure and associated pain. It is therefore not recommended. [A]

Research recommendation:

Further research is needed to evaluate the effect of general anaesthesia on oocyte retrieval and outcome of IVF treatment.

15.8 Sperm recovery

Spermatozoa can be retrieved from both the epididymis and the testis using a variety of techniques with the intention of achieving pregnancies for couples where the male partner has obstructive and non-obstructive azoospermia. Sperm recovery is also utilised in ejaculatory failure and where only non-motile spermatozoa are present in the ejaculate. Surgically collected sperm in azoospermia are immature (because they have not traversed the epididymus) and have low fertilising ability with standard IVF. It is therefore necessary to use ICSI.

The surgical techniques available for sperm retrieval from the epididymis or the testis include :

- percutaneous epididymal sperm aspiration (PESA);
- testicular sperm aspiration (TESA), which is also described as testicular fine needle aspiration (TEFNA);
- testicular sperm extraction (TESE) from a testicular biopsy; and
- microsurgical epididymal sperm aspiration (MESA).

In obstructive azoospermia sperm can usually be obtained from the epididymis (PESA or MESA) and from the testis (TESA or TESE). In some patients sperm can be recovered from naturally occurring spermatoceles by percutaneous puncture.

In non-obstructive azoospermia sperm needs to be obtained directly from the testis by aspiration (TESA) or biopsy (TESE). The chance of finding sperm is reduced. PESA and TESA can be performed under local anaesthesia in an outpatient clinic.[687;688] PESA does not jeopardise future epididymal sperm retrieval.[689]

A systematic review that includes one RCT (n=59) compared MESA to epididymal micropuncture with perivascular nerve stimulation techniques and aspiration in men with

obstructive azoopsermia such as CBAVD. MESA achieved lower pregnancy (OR 0.19, 95% CI 0.04 to 0.83) and fertilisation rates (OR 0.16, 95% CI 0.05 to 0.48). Caution is required in the interpretation of this trial as the method of randomisation used was not reported clearly, nor was there any drop out or loss to follow up reported.[690] [evidence level Ia]

PESA and TESA are two alternatives to MESA. MESA is more invasive, costly, and technically more difficult but may be performed at the same time as correction of epididymal obstruction. In order to avoid subsequent scrotal surgery, cryopreservation of supernumerary spermatozoa during MESA should be undertaken.[691] Facilities for genetic screening with a view to referral to preimplantation genetic diagnosis should be available in any sperm retrieval programme.[692]

The best method of extracting spermatozoa from the testicular tissue in non-obstructive azoospermia is uncertain. The relative merits of TESA and TESE using small (5mm), multiple or large (10-15mm) segments is unknown.[693-697] Compared with TESE, TESA has a reduced rate of sperm recovery but is less invasive.[698-701]

The likelihood of successful sperm recovery (failure rates of retrieval)

Reported failure rates of sperm retrieval vary with study and with technique (see Table 15.3). A further complication is added by the inconsistent method of reporting (for example, per attempt, per patient, or per couple).

In non-obstructive azoospermia, testicular size, plasma FSH levels and testicular histology are related to spermatogenesis, but they cannot be relied upon to exclude the presence of any spermatozoa within the testis.[692;694;702-710] The quality of the sperm retrieved vary widely among aetiological groups, but are of no value in predicting fertilisation or pregnancy rates, or the embryo cleavage rate following PESA/ICSI cycles.[711]

Table 15.3 Failure rates of sperm retrieval

	Procedure	Quoted failure rate
Obstructive azoospermia	MESA	1.7% of patients (1/59)[712] 22% of patients (2/9)[713]
	PESA*	17% of initiated cycles (30/181)[689] 15.8% of initiated cycles (43/234)[687] 11% in patients with CBAVD (7/62) and 5% in men with failed reversed vasectomy (3/60)[714]
	TESA	0% of patients (1/197)[715]
Non-obstructive azoospermia	TESE	13% of patients (2/15)[716] 19.7% of patients (39/159)[712] 38% of patients (6/16)[702] 8% of patients (10/124)[717] 57% of patients (21/37)[694]
	TESA	66% of patients (34/51)[715]

* These studies may include some of the same patients.

The clinical outcomes of using surgically recovered sperm (success rates of epididymal, testicular, or ejaculate spermatozoa)

Epididymal and testicular spermatozoa yield similar fertilisation, cleavage and ongoing pregnancy rates using ICSI[718;719] and are both successful for establishing pregnancies.[706;713] Some authors report these success rates as being lower than those achieved by spermatozoa from the ejaculate. One study[720] found that the normal fertilisation rate was significantly higher with ejaculated spermatozoa than with epididymal or testicular spermatozoa, but no differences were observed with regard to embryo quality, the percentages of transfer after ICSI and the clinical pregnancy rates in the three groups of patients. However, another study[689] showed that the outcome of PESA-ICSI treatment compares favourably with that of ICSI using ejaculated spermatozoa. One study[687] also found that the results of PESA/TESA were similar to ejaculate sperm.

Another study[721] found that the normal fertilisation rates with testicular and MESA spermatozoa did not differ significantly from each other, but with testicular spermatozoa the rate was significantly lower than that obtained with ejaculated spermatozoa and ICSI in matched couples. Spermatozoa can be retrieved from the testis in couples in whom epididymal aspiration failed.[692;719;722] When spermatozoa cannot be recovered by one technique another one can be employed, for example, TESE after MESA.[713] Testicular spermatozoa can be successful in achieving fertilisations and pregnancies for couples in whom epididymal aspiration failed.[692;707] However, some studies report fertilisation or

pregnancy rates lower than those achieved with epididymal spermatozoa. For example, one study.[692] found a transfer rate lower with TESE than with epididymal spermatozoa, but there was little difference in pregnancy rate using epididymal or testicular spermatozoa. Also, the spermatozoa could not be frozen and saved for use in future cycles. PESA, MESA or TESE and ICSI are effective in patients with CBAVD and in those with failed reversal of vasectomy.[714;719;723]

Variation in outcome using testicular sperm in non-obstructive azoospermia compared with obstructive azoospermia has been demonstrated by various studies.[724-726] Results in non-obstructive azoospermia are generally inferior.

Testicular sperm cryostorage (fresh vs thawed sperm)

Cryopreservation of spermatozoa does not negatively influence the outcome. Various studies have shown that the fecundity rate, clinical pregnancy rate, overall rate of clinical pregnancy rate per embryo transfer, or clinical abortions after ICSI using cryopreserved or fresh surgically retrieved spermatozoa are not significantly different.[692;718;727] In one study[692] the only significant factor appeared to be the age of the female. Using cryopreserved testicular sperm (cryo-TESE) for ICSI is an effective and successful approach for the treatment of severe testicular insufficiency.[712] Because cryopreservation of spermatozoa has many additional advantages (for example, in comparison to the use of native testicular sperm with the necessity of repetitive testicular biopsies), it is routine in the performance of MESA/ICSI and TESE/ICSI.[712;718] Testicular tissue which is intentionally obtained well before any planned ICSI cycle and cryopreserved could then serve as an efficacious sperm source in a subsequent ICSI cycle. This approach should be an alternative to repeated testicular tissue sampling, and the availability of spermatozoa is assured before the initiation of ovulation induction. This tissue can be harvested at the same time as diagnostic biopsy, thereby minimising the number of surgical procedures.[728]

A retrospective consecutive case series[729] compared the results of ICSI with fresh and with frozen-thawed epididymal spermatozoa obtained after MESA in 162 couples suffering from infertility because of CBAVD, failed microsurgical reversal for vasectomy or

postinfectious epididymal obstruction, irreparable epididymal obstruction, ejaculatory duct obstruction or anejaculation. Overall, 176 MESA procedures were performed in the male partners, followed by 275 ICSI procedures with either fresh (n=157) or frozen-thawed (n=118) epididymal spermatozoa. The overall pregnancy rate (as indicated by raised hCG levels) per ICSI cycle was significantly lower when frozen-thawed epididymal spermatozoa were used (26.3% vs 39.5%). However, no significant differences were found either in clinical or ongoing pregnancy rates, or in implantation rates, and there were no differences in pregnancy outcome. In patients suspected of having obstructive azoospermia with no work-up or an incomplete one, the authors prefer MESA as a method for sperm recovery because a full scrotal exploration can be performed and, whenever indicated, a vasoepididymostomy may be performed concomitantly. Recovery of epididymal spermatozoa for cryopreservation during a diagnostic procedure is a valid option in these patients since ICSI may be performed later or even in another centre using the frozen-thawed epididymal spermatozoa without jeopardising the ICSI success rate. In a retrospective study[730] the authors aimed to determine whether fertilisation and implantation rates after ICSI with fresh or frozen-thawed testicular spermatozoa were comparable. They found that the fertilisation rate after ICSI with frozen-thawed testicular spermatozoa was significantly lower than with fresh testicular spermatozoa (71% vs 79%), the pregnancy rate was similar for both groups (38% and 27%), the implantation rate per transferred embryo was significantly lower in the frozen-thawed rather than in the fresh testicular sperm group (9% vs 25%), and the live birth rate per transferred embryo was higher in the group in which fresh testicular spermatozoa were used (19% vs 8%).

A retrospective analysis of consecutive ICSI cycles[731] compared the outcome of ICSI with fresh and frozen-thawed testicular spermatozoa in patients with nonobstructive azoospermia. No statistically significant differences were noted in any parameters examined between ICSI cycles with fresh or cryopreserved testicular spermatozoa from the same nine patients and comparing all ICSI cycles performed (two-pronuclear fertilisation, embryo cleavage rates, implantation rates, and clinical pregnancy rate). The delivery or ongoing pregnancy rate using fresh sperm was better, but the difference was not statistically significant. Cumulative clinical pregnancy rates and ongoing pregnancy rates per testicular sperm extraction procedure were 36% and 24%, respectively.

Recommendation:
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 made available. [C]

15.9 Assisted hatching

This section will require further revision following publication of a systematic review by Edi-Osagie et al. in Human Reproduction (expected August 2003).

Assisted hatching has been proposed as a method to disrupt the zona pellucida which may facilitate and enhance implantation and pregnancy rates.

A narrative review of 10 RCTs found considerable heterogeneity in study methodology, populations selected, indications and techniques of assisted hatching. It reported that assisted hatching might be suggested for women aged over 38 years, those with elevated day-3 serum FSH and repeated IVF failures. Data from this review did not support generalised assisted hatching for all patients.[732] [evidence level Ib]

We identified several RCTs that were published since the above review. These RCTs are summarised below.

Women with good prognosis

One RCT (n=20) found no significant difference between assisted hatching vs no assisted hatching in clinical pregnancy rates (23% vs 42%) and delivery rates (15% vs 42%) in

women with good prognosis (under age 30 years and with basal FSH less than 10 mIU/ml).[733] [evidence level Ib]

Repeated failure of in vitro fertilisation

One RCT showed significant differences between women who had both ultraviolet laser treated embryos (n=216) and untreated embryos (n=223) vs women with only ultraviolet laser treated embryos (n=218) in clinical pregnancy rates (36.4% vs 44.4%). These women had repeated IVF failure. Significant differences were also found in clinical pregnancy rate when compared with a control group (n=407 embryos) (36.4% vs 44.4% vs 19.3%). There were no significant differences in the outcome of ongoing pregnancies across the three groups.[734] [evidence level Ib]

One RCT (n=100) showed no significant differences between assisted hatching vs no assisted hatching in implantation rates (9.7% vs 5.6%) or in pregnancy rates (36.7% vs 19.6%) in women with repeated IVF failure who received standard IVF vs IVF with tubal embryo transfer. However, when only patients receiving standard IVF were considered, assisted hatching significantly improved implantation rates (11% vs 3.7%) and pregnancy rates (42.4% vs 16.1%).[735] [evidence level Ib]

One RCT (n=248 cycles) found significant differences between assisted zona hatching vs no assisted hatching in clinical pregnancy rates per cycle (31% vs 10%) in women over age 38 years. The clinical pregnancy rates were 36% vs 17% respectively in women with more than three IVF failures. There was no significant difference in miscarriage rates between the intervention and control groups (22% vs 21%). No significant differences were found in women who were both aged 38 years and had more than three IVF failures.[736] [evidence level Ib]

One RCT (n=173, 248 cycles) found significant differences between assisted hatching vs no assisted hatching in clinical and ongoing pregnancy rates with good quality embryos

(22.4% vs 3.4 % with low quality embryos; 7.4% in control group with good quality embryos, 3.7% with low quality embryos) in women with over two IVF failures.[737] [evidence level Ib]

Maternal age

An RCT (n=89) showed no significant differences between assisted hatching vs no assisted hatching in clinical and ongoing pregnancy rates (39% vs 41% and 29.3% vs 35.4% respectively) in women aged 36 years or over.[738] [evidence level Ib]

Another RCT (n=103) found no significant differences between assisted hatching vs no assisted hatching in clinical pregnancy rates per embryo transfer (33.3% vs 40.38%) in women below the age of 37 years undergoing ICSI due to male factor infertility.[739] [evidence level Ib]

A further RCT (n=100) found no significant differences between zona thinning vs no zona thinning in clinical pregnancy rates (16% vs 22%) in women over the age of 38 years who were undergoing ICSI due to male factor infertility.[740] [evidence level Ib]

High follicle-stimulating hormone levels

Preliminary results from an RCT (n=79) showed significantly higher clinical pregnancy rates in assisted hatching vs no assisted hatching (27% vs 7.1%) in women with high day-3 FSH. However, miscarriage rate was high in the assisted hatching group (40%).[741] [evidence level Ib]

Embryo quality

One RCT (n=240) found significant differences between zona-free vs zona-intact blastocyst transfer in implantation rates (25.4% vs 18.9%) in women undergoing ICSI for

male factor infertility. There were no significant differences between the two groups in clinical pregnancy rates per embryo transfer (53.7% vs 43.75) or in miscarriage rates (9.2% vs 11.5%). Subgroup analysis showed a significant increase in implantation rates (18.5% vs 6.4%) in women with poor quality blastocyst transfer.{Urman 2002} [evidence level Ib]

Difficult oolemma penetration

An RCT (n=77) found significant differences between laser-assisted hatching and no hatching in clinical pregnancy rates (36.6% vs 13.6%) in women whose oocytes were difficult to penetrate during ICSI.[742] [evidence level Ib]

Multiple gestations

Monoamniotic multiple gestations may be increased in zona-manipulated cycles. The potential obstetric risks and complications of zona manipulation should be discussed with patients. In an anonymous survey of 42 IVF centres in the United States,[743] 143 pregnancies were ascertained from zona-manipulated cycles (ICSI, subzonal sperm injection, zona drilling, and mechanical assisted hatching). A multiple gestation frequency of 16.1% was reported. There were five monoamniotic twin gestations (all of which resulted in live births), four being from manipulated cycles and one being from a non-manipulated cycle. There has also been one case report of conjoined twins in a triplet pregnancy after IVF and assisted hatching.[744] [evidence level III]

Recommendation:
Assisted hatching should not be offered because it has not been shown to be effective in increasing pregnancy rates. [A]

Research recommendation:

Randomised controlled trials are needed to evaluate the possible benefits of assisted hatching in certain subgroups, such as women aged older than 38 years.

15.10 Embryo transfer techniques

Use of ultrasound

Four RCTs, one quasi-RCT and one non-randomised controlled trial comparing ultrasound guided vs clinical touch embryo transfer were identified.[745-750]

A meta-analysis was performed including data from all six trials.[745-750] The combined OR in favour of routine use of ultrasound was 1.45 (95% CI 1.20 – 1.76), suggesting that routine ultrasound use at embryo transfer improved pregnancy rates. Results of a second meta-analysis (after exclusion of a quasi-randomised trial,[748] which looked specifically at measuring the uterocervical angle before transfer) still supported the use of ultrasound (combined OR = 1.41, 95% CI 1.13 to 1.76). There was clinical heterogeneity among different groups of women and in the specific role of ultrasound in each trial. However the results suggested that use of ultrasound is beneficial at the time of embryo transfer.

Recommendation:
The use of ultrasound during embryo transfer appears to increase pregnancy rates and is therefore recommended. [A]

Day 2/3 versus day 5/6 transfers

This has been the subject of a Cochrane systematic review.[751] A single quasi randomised trial showed no difference in live birth rates between day 2/3 transfer and blastocyst transfer on days 5/6 (OR 1.59, 95% CI 0.80, 3.15). A meta-analysis of the results of four trials also failed to show any advantage associated with day 5/6 transfers (combined OR 0.86, 95% CI 0.57, 1.29). It is not possible to do an intention to treat analysis for blastocyst transfer and so the results of these studies may be biased.

A review of the literature was undertaken for this guideline in order to identify trials published since the last update of the Cochrane review. Four new trials were identified.[752-755] Results from these trials were combined with those from the earlier studies. A new meta-analysis shows the following results.

Pregnancy and live birth rates per ovum pick up (that is, intention to treat analysis) OR 1.08 (95% CI 0.94, 1.25) and embryo transfer OR 0.92 (95% CI 0.64, 1.32) are similar in the two groups, suggesting no difference between the groups.

Pregnancy rate per embryo transfer (14 RCTs, combined OR 1.20 (95% CI 1.04, 1.38) and live birth rate per embryo transfer (five RCTs, combined OR 1.41, 95% CI 1.0, 1.98) are higher in the day 5/6 transfer group.

Some caution should be exercised in interpreting the results of these meta-analyses as combining cycles as opposed to patients can affect the precision of the results and widen the confidence intervals.

Day 5/6 transfers appears to offer no advantage over day 2/3 transfers in terms of increased pregnancy and live birth rates per cycle started. The apparent advantage in terms of pregnancy/live birth rate per embryo transfer at 5/6 days may be achieved at the cost of a number of women who do not proceed to embryo transfer.

Recommendation:

Day 2/3 transfers and day 5/6 transfers appear to be equally effective in terms of increased pregnancy and live birth rates per cycle started. [B]

Research recommendation:

Further research into the effect of cleavage (day 2/3) and blastocyst (day 5/6) stage methods of embryo transfer on live birth rates is needed.

Type of catheter

There have been a number of trials comparing different types of embryo transfer catheters. Seven of them, comparing a number of different catheters have been identified in the course of this review.[756-759]{?,?,?} The results of these trials suggest that choice of embryo transfer catheter can affect pregnancy rates. In particular, data from large recently published trials suggest that certain types of soft catheter are more effective that other types of catheter. Data from the various studies could not be aggregated due to significant clinical heterogeneity and differences between individual catheters.

Research recommendation:

Type of catheter may affect pregnancy rates but further research is needed.

Endometrial thickness

The role of endometrial thickness as a single factor in predicting pregnancy following IVF is controversial. Most studies agree that it has a poor predictive value for pregnancy. Its main use is as a negative predictor of pregnancy when a minimum endometrial thickness is not reached. The additional ultrasound parameter that is often used together with endometrial thickness is the structure of the endometrium and specifically its 'multi-layered' or 'triple-echo' appearance.[760] In their review of a large number of retrospective series, there was no case in which the endometrium was less than 5 mm which resulted in pregnancy. In such circumstances the IVF cycle should be abandoned and consideration given to preparing the endometrium with exogenous hormones before a frozen embryo replacement cycle.

Recommendation:

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. [B]

Bed rest vs no bed rest

One RCT (n= 182) found no significant difference in pregnancy rate per embryo transfer between 20 minutes' bed rest vs 24-hours' bed rest following embryo transfer (24% vs 23.6%), spontaneous miscarriage rate (19% vs 18%) and multiple pregnancy rate (14% vs 13.6%).[761] [evidence level Ib] Another RCT (n= 211) assessed the role of fibrin sealant for embryo transfer and found no significant difference in implantation and pregnancy rates when both study and control groups were instructed to routine activities without any bed rest after embryo transfer. There was no group which was assigned to bed rest.[762] [evidence level III]

Recommendation:
Couples 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. [A]

15.11 Luteal support

Progesterone vs no support in non-down-regulated cycles

A 1988 meta-analysis of five RCTs found no significant difference between luteal phase progesterone support in non-down-regulated IVF cycles and no such support in pregnancy rate (OR 1.25, 95% CI 0.93 to 1.66) in patients undergoing IVF or GIFT after ovarian stimulation with clomifene and hMG.[763] [evidence level Ia]

Human chorionic gonadotrophin vs no treatment/ human chorionic gonadotrophin vs progesterone in down-regulated cycles

A meta-analysis of 18 RCTs showed significantly higher pregnancy rate per cycle in patients treated with hCG compared with no treatment (OR 1.9, 95% CI 1.3 to 3.1, based

on five RCTs) when used with GnRH agonist.[668] [evidence level Ia] A significantly higher pregnancy rate per cycle was also found in groups treated with intramuscular or oral progesterone (progestagen) compared with no treatment (OR 1.2, 95% CI 1.0 to 1.7, based on eight RCTs). In three RCTs that compared hCG luteal support with intramuscular or oral progesterone, pregnancy rate per cycle was significantly higher in patients treated with hCG compared with progesterone (OR 2.0, 95% CI 1.1 to 3.9). However, this effect was to due a difference in the effectiveness of hCG and oral (rather than intramuscular) progesterone. There was no significant difference in spontaneous abortion rate between patients given luteal support or no support (OR 0.8, 95% CI 0.4 to 1.7, based on seven RCTs). The overall incidence of OHSS with hCG was 5% (n=220) vs 0% (n=193) with progesterone or no treatment.[668] [evidence level Ia]

Another meta-analysis of 30 RCTs showed that intramuscular hCG significantly improved clinical pregnancy rate when compared with no treatment (RR 2.72, 95% CI 1.56 to 4.90, based on four RCTs). Intramuscular progesterone significantly improved clinical pregnancy rate (RR 2.38, 95% CI 1.36 to 4.27, based on three RCTs), ongoing pregnancy rate (RR 3.8, 95% CI 1.42 to 11.38, based on three RCTs) and delivery rate (RR 5.50, 95% CI 1.25 to 35.53, based on one RCT) when used with long GnRH agonist protocol. Intramuscular hCG significantly improved clinical pregnancy rate (RR 8.36, 95% CI 1.44 to 173.74, based on four RCTs) and ongoing pregnancy rate (RR 7.43, 95% CI 1.22 to 156.64, based on four RCTs) when compared with oral progesterone used in a short GnRH agonist protocol.[764] [evidence level Ia]

The same meta-analysis reported that intramuscular progesterone significantly improved clinical pregnancy rate (RR 1.33, 95% CI 1.02 to 1.75, based on five RCTs) and delivery rate (RR 2.06, 95% CI 1.48 to 2.88, based on two RCTs) when compared with vaginal progesterone. There were no significant differences in fertility outcomes when comparing: vaginal progesterone with no treatment; different doses of progesterone; intramuscular progesterone with oral progesterone; intramuscular hCG with oral progesterone in both long and short GnRH agonist protocols; intramuscular hCG with intramuscular progesterone; oestrogen plus progesterone with progesterone only in long GnRH agonist protocols; hCG plus progesterone with vaginal progesterone in long and short GnRH

agonist protocols; intramuscular progesterone plus oestrogen with hCG.[764] [evidence level Ia] The review did not consider patient satisfaction. However in one of the RCTs, 4/30 women discontinued treatment because of their inability to administer intramuscular progesterone.

The two meta-analyses show inconsistency in the relative effectiveness of the different drugs and routes of administration for luteal support. Although the meta-analyses involved a total of 18 and 30 RCTs, respectively, most of the detailed comparisons were based on meta-analyses of very few RCTs.

Patient satisfaction was assessed as part of a non-randomised multicentre study conducted in the United States.[765] [evidence level III] Women were asked to report their preferences between vaginal progesterone and intramuscular progesterone; 94% of the women found vaginal progesterone easier to use, and 84% preferred vaginal progesterone to intramuscular progesterone.

Recommendation:
Couples who are undergoing in vitro fertilisation treatment using gonadotrophin-releasing hormone agonists for pituitary down-regulation should be offered luteal support using human chorionic gonadotrophin or progesterone because they improve pregnancy rates. [A]

Research recommendation:

Further research is needed to compare the effectiveness (incuding patient satisfaction) of different drugs and routes of administration for luteal support during in vitro fertilisation using agonist cycles.

Chapter 16 Intracytoplasmic sperm injection

ICSI is a technique used within the IVF treatment process where it is necessary to use micromanipulation to achieve the fertilisation. ICSI is usually required when the number of sperm is too low for fertilisation to occur through the incubation of motile sperm with an egg, which is the standard approach in IVF. As a result, ICSI makes possible fertilisation of an egg with a single spermatozoon, and therefore it has become the standard approach to treatment where there is very spoor semen quality, or where spermatozoa have to be retrieved surgically because the man has azoospermia (see Section 15.10).

16.1 Indications for intracytoplasmic sperm injection

A review of the activities of European centres performing ICSI between 1993 to 1994 showed that the fertilisation rates achieved with ejaculated, epididymal and testicular spermatozoa were 64%, 62.5% and 52% respectively.[766] Approximately 90% of couples had an embryo transfer and 19-22% of them achieved a viable pregnancy, irrespective of the origin of the spermatozoon.

The use of intracytoplasmic sperm injection in oligozoospermia and other causes of poor semen quality

A systematic review[767] of 10 RCTs compared ICSI with other types of IVF technique (eight compared ICSI with conventional IVF, one compared ICSI with subzonal sperm injection, and one compared ICSI with additional IVF). The review showed that for couples with normal semen there is no evidence of a difference in fertilisation rates per retrieved oocyte or pregnancy rates between IVF and ICSI. However, there was a slight benefit of ICSI over IVF when fertilisation rate per inseminated oocyte was considered (combined OR 1.42 95%CI 1.17-1.72). For couples with borderline semen (concentration 10-20 million/ml, motility 30-50%, morphology 4-14% normal forms) ICSI results in higher fertilisation rates, whatever the denominator, compared with conventional IVF (combined OR 3.79, 95%CI 2.97-4.85 per oocyte retrieved, combined OR 3.90, 95%CI 2.96-5.15 per oocyte inseminated). Couples with very poor semen (concentration <10million/ml, motility <30%,

morphology <4% normal forms) will have better fertilisation outcomes with ICSI than with subzonal sperm injection or additional IVF, but there were only two RCTs that considered couples with very poor semen quality. [evidence level Ia]

One RCT (n=73) compared ICSI with IVF using a standard insemination gradient and IVF with a high insemination gradient in couples with male infertility defined by abnormal semen. The unit of randomisation was sibling oocytes. There was significant difference between standard IVF and ICSI in overall fertilisation rate per oocytes injected (37.4% with IVF vs 64.3% with ICSI; RR 1.7, 95% CI 1.4 to 2.1) but no significant difference between IVF with high insemination gradient and ICSI (59.6% with high insemination gradient/IVF vs 67.6% with ICSI; RR 1.13, 95% CI 0.99 to 1.29). Pregnancy outcomes were not measured.[768] [evidence Ib] A meta-analysis of this trial and eight other RCTs, including three RCTs from the previous systematic review,[767] showed that ICSI significantly improved the probability of fertilisation in couples with male subfertility (RR 1.9; 95% CI 1.4 to 2.5) when compared with IVF, but 3.1 ICSI cycles may be needed to avoid one complete fertilisation failure after conventional IVF (95% CI 1.7 to 12.4).[768] [evidence Ia]

One RCT found significant differences between ICSI and conventional IVF in ongoing pregnancy rate (10.8% with ICSI vs 25.7% with IVF) in cases of moderate teratozoospermia (as defined by a minimum concentration of 5 million/ml and morphology of 4-20%). The mean number of embryos per transfer was 2.2.[769] [evidence level Ib]

It has been reported in case-series studies that despite severe semen impairment such as crypto-zoospermia, total astheno- or teratozoospermia, fertilisation failure after ICSI was mainly caused by immotile sperm,[770] poor sperm morphology,[771] and poor quality oocytes.[772]

The use of intracytosplasmic sperm injection in azoospermia

Obstructive azoospermia: A case-series study reported that aspiration of sperm by MESA, TESA and TESE was 100% successful in men with obstructive azoospermia before ICSI

with a pregnancy rate of 41%.[773] [evidence level III] Another case-series study reported an ongoing pregnancy rate of 42% per couple and 26% per treatment cycle after 39 ICSI procedures in 24 couples with obstructive azoospermia using similar sperm retrieval techniques.[722] [evidence level III]

Non-obstructive azoospermia: A case-series study (n=15) reported a two-pronuclear fertilisation rate of 48% and an ongoing pregnancy rate of 25% (3 out of 12 embryo replacements) in men with azoospermia due to testicular failure.[716] [evidence level III]

Inferior outcome in non-obstructive azoospermia relative to obstructive azoospermia has been demonstrated in three case-series studies.[706;724;726] [evidence level III]

ICSI outcomes of fertilisation rates with epididymal spermatozoa in obstructive azoospermia were reported to be significantly higher than those achieved using testicular spermatozoa in men with non-obstructive azoospermia (57% vs 81%), clinical pregnancy rate was not significantly higher.{16046] [evidence level III] Two case-series study reported significantly higher fertilisation rate after ICSI with testicular spermatozoa in obstructive azooospermia than those with non-obstructive azoospermia,{14073}{Vernaeve 2003} with similar pregnancy and implantation rates between the two groups,[730] but lower rates in the group with obstructive azoospermia.[774] [evidence level III]

The use of intracytoplasmic sperm injection in couples with failed fertilisation

ICSI is offered to couples with previously failed fertilisation in IVF cycles, with good results.[775] However, the outcome of ICSI may depend on its indications. Case-series studies have found that ICSI is better for treating severe male factor infertility than for treating previously failed fertilisation in an IVF cycle when the male has otherwise normal sperm parameters.[776-779] [evidence level III] Others found that none of the sperm parameters of the original semen analysis were associated with the outcome of ICSI cycles[780] and that fertilisation and pregnancy rates did not differ between patients who had previously failed fertilisation in conventional IVF, patients with moderately poor semen

quality, patients with semen parameters of 1-10 million/ml, and patients with less than 1 million/ml.[771] Another case-series study[781] showed that clinical pregnancy and delivery rates did not differ between groups with prior failed fertilisation, prior poor fertilisation, or sperm parameters unsuitable for IVF and no difference was found in three basic sperm parameters between those patients who produced a pregnancy and those who did not, although the fertilisation rate was higher in patients with more adequate sperm parameters. [evidence level III]

Poor ICSI results may be due to the co-existence of oocyte defects not bypassed by ICSI.[776;779] A number of studies have found a significant negative correlation between female age and pregnancy results,[613;780;781] especially after the age of 35 years.[782] This may be because of low oocyte yield or poor oocyte quality associated with increased female age and shows that ICSI does not always overcome female factors. A comparative study on factors influencing ICSI outcomes reported a significant correlation between the occurrence of pregnancy with female age (90th quantile: 38 years), number of oocytes retrieved (10th quantile: five oocytes) and number of oocytes injected (10th quantile: four oocytes). Sperm origin (epididymal or testicular), status (freshed or thawed), male partner's age and serum FSH had no significant effect on implantation, pregnancy per embryo transfer or spontaneous miscarriage rates.[783] [evidence level III]

One study[784] examined how fertilisation failure after ICSI might impact upon ICSI treatments. This study suggested that fertilisation failure in one ICSI cycle does not preclude successful fertilisation and delivery in a later ICSI treatment cycle.

Recommendation:

The recognised indications for treatment by intracytoplasmic sperm injection include:

- **severe deficits in semen quality in the male partner**
- **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. [B]

16.2 Information for couples

The likelihood of genetic abnormalities (such as chromosomal abnormalities) is greater in men with non-obstructive azoospermia than in men with obstructive azoospermia. The clinical features of obstructive and non-obstructive azoospermia and CBAVD are important to elicit. For example, in non-obstructive azoospermia testis volumes are lower and a diagnosis of CBAVD can only be made on clinical examination. Therefore, couples should undergo appropriate clinical examination and laboratory investigations.

The need for proper clinical assessment is further supported by the increased risk of testicular cancer in infertile men. A case control study[785] evaluated the association between subfertility in men and the subsequent risk of testicular cancer and found a reduced risk of testicular cancer associated with paternity (RR 0.63, 95% CI 0.47-0.85), although a higher number of children than expected was not associated with a corresponding protective effect. These associations were similar for seminoma and non-seminoma and were not influenced by adjustment for potential confounding factors. Although the general cure rate in patients with testicular cancer is high, not only is spermatogenesis already so severely impaired before treatment that fertility is lower than in healthy men, but radiotherapy and chemotherapy both induce dose-dependent impairment of spermatogenesis. Recovery of spermatogenesis after treatment may take longer than 5e years in some patients.[786] These men, therefore, need counselling about their reproductive function with respect to semen cryopreservation, chance of recovery of spermatogenesis, fertility, and the possible need for androgen replacement.[786] Effective

counselling depends on understanding the illness itself, on the context of patients' lives, the assault on the sense of self, the impact on intimate relationships, and treatment options and psychosexual effects.[787] Infertility after testicular cancer can be treated effectively with IVF or ICSI.[788] For example, one study[789] obtained an ongoing pregnancy rate of 57% per cycle.

Recommendations:

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. [C]

Independent counselling should be offered to couples considering intracytoplasmic sperm injection. [GPP]

16.3 Genetic issues and counselling

Male infertility due to severe oligozoospermia and azoospermia has been associated with a number of genetic factors, including numerical and structural chromosomal abnormalities, [790] microdeletions of the Y chromosomes,[791;792] and mutations in the cystic fibrosis transmembrane conductance regulator gene, commonly associated with congenital vas deferens abnormalities.[793;794]

Chromosomal abnormalities have been detected in 2.1-8.9% of men attending infertility clinics,[795] compared with 1% of the general male population.[796] In couples undergoing ICSI, chromosomal abnormalities have been reported in 2.0-3.3% of male partners and 3.3-5.4% of female partners.[797;798] [evidence level III] Higher prevalences of chromosomal abnormalities in the male rather than the female partner of couples referred for ICSI has also been reported.{14174, 14178, 14175 [evidence level III] Genetic abnormality was identified in 24% of men with extreme oligozoospermia and azoospermia in couples requesting ICSI.{15531} [evidence level III] Sperm of non-obstructive azoospermic men

has been reported to have a higher incidence of chromosomal abnormalities, of which sex chromosome aneuploidy was the most prominent.[799] [evidence level III] Application of ICSI in these couples can result in offspring with an enhanced risk of genetic abnormalities and possibly decreased fertility. Genetic testing and counselling is indicated for these couples before ICSI is considered. However, chromosome studies should be undertaken in both members of the couple before ICSI.

A number of clinical syndromes which present with normal virilisation have also been shown to have a genetic origin. These include cystic fibrosis and CBAVD. Cystic fibrosis is the most common autosomal recessive condition in northern Europeans and more than 95% of males with cystic fibrosis are infertile. CBAVD leads to obstructive azoospermia in otherwise normal men and is responsible for approximately 2% of male infertility.[800]

When these conditions are known or suspected, or in Kartagener syndrome or primary ciliary dyskinesia, appropriate genetic counselling and testing should be offered.

A review[801] found that 13.7% of men with azoospermia and 4.6% of men with oligozoospermia had an abnormal karyotype. In men with azoospermia, sex chromosome abnormalities (for example, 47XXY, mosaics of 46XY/47XXX) were present in 1.9 to 22.1%, while autosomal abnormalities were found in only 0.6 to 3.7% of such men.[800] Amongst oligozoospermic men sex and autosomal abnormalities are found in 0.9 to 3.6% and 0.9 to 4.9%, respectively. Robertsonian and reciprocal translocations occur most frequently, but their roles in the aetiology of oligozoospermia are not clear, since the spermatogenic defect in these men can vary from severe impairment to almost normal spermatogenesis. Where the indication for ICSI is a severe deficit of sperm quality or non-obstructive azoospermia, the male partner's karyotype should be established.

The Y chromosome is an important carrier of genetic information for the control of spermatogenesis. Microdeletion of the azoospermic factor region of the Y chromosome occur in 1-29% of oilgozoospermic and azoospermic men.[802] The prevalence is higher in

azoospermic than oligospermic men.[803] [evidence level III] One comparative study found a significantly lower fertilisation rate in Y-deleted men when compared with a control group without this genetic disorder who underwent ICSI (55%, 95% CI 41 to 69% vs 71%, 95% CI 67 to 74%; $p < 0.01$), but no significant differences in pregnancy, implantation or take-home baby rates were found.[802] [evidence level III] The presence of Y deletions was reported to have no impact on fertilisation and pregnancy rates in one case-series study.[804] [evidence level III]

Several screening programmes have confirmed the common occurrence of microdeletions in the Yq part of the chromosome amongst patients with otherwise unexplained oligo- or azoospermia.[805;806] De-novo microdeletions in Yq that are not present in fathers' or brothers' chromosomes have been reported with a prevalence of between 3% and 18% of men studied.[800] They cause the azoospermic or oligozoospermic phenotype and are likely to be passed on to the sons of these infertile men if ICSI is carried out.[807;808]

Testing for Y chromosome microdeletions should not be regarded as a routine investigation before ICSI. A recent survey among staff working in United Kingdom infertility clinics found that despite some benefits, screening for sperm aneuploidy is not a common practice. The benefits are that screening would enable couples to make informed decisions about the genetic repercussions of ICSI before treatment, and screening would also facilitate a larger research study to assess the safety of ICSI. However, there are counter-arguments that most couples would have ICSI regardless of results and that sex chromosome abnormalities are clinically not severe enough to worry about in this context.[809] [evidence level III]

Recommendations:

Before treatment by intracytoplasmic sperm injection consideration should be given to relevant genetic issues. [B]

Where a specific gene 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. [B]

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. [C]

16.4 Ejaculatory failure before intracytoplasmic sperm injection

We found no RCTs that investigated ejaculatory failure before ICSI, and much of the available evidence is based upon small case series and individual case reports.

Anejaculation is a relatively uncommon occurrence in the general population.[810] It may result from spinal cord injury, retroperitoneal lymph node dissection, diabetes mellitus, transverse myelitis, multiple sclerosis, or psychogenic disorders.

Anejaculation is not uncommon on the day of egg collection and is usually caused by anxiety. Anxiolytic drugs and/or sildenafil may be helpful, as may alpha 2 adrenoreceptor blocking agents (such as yohimbine or idazoxan) or dopamine receptor stimulants (bromocriptine or apomorphine).[811] One study[812] presented a successful outcome of an IVF cycle complicated by failure to produce a sperm sample on the morning of oocyte retrieval, by the use of testicular aspiration of sperm for ICSI.

Failure of the normal ejaculatory mechanism may occur in retrograde ejaculation. This is an uncommon cause of male infertility and can be congenital, acquired (for example, in the case of transurethral prostatectomy, retroperitoneal lymphadenectomy, or diabetic neuropathy), or idiopathic in origin. One study[813] evaluated the clinical incidence of sexual dysfunction after transurethral resection of the prostate in 253 patients and found that only 7% of patients retained ejaculation after the operation. The incidence of ejaculatory dysfunction following retroperitoneal lymphadenectomy is determined by the size and position of residual lymph node masses after chemotherapy and can be kept to a minimum by a careful nerve sparing operative technique.[814] Autonomic neuropathy is almost certainly the cause of the ejaculatory failure that may be present in up to 40% of men with diabetes.[815]

One study[816] reported on 25 patients with retrograde ejaculation/loss of emission who were treated with ephedrine sulphate or imipramine hydrochloride. Seventeen of them suffering from both diabetes and retrograde ejaculation were treated with ephedrine or, in cases where ephedrine failed to convert retrograde ejaculation into anterograde ejaculation, with imipramine. Positive results were obtained in 29.3% patients (17.6% and 11.7% patients on ephedrine and imipramine, respectively). The daily dose of ephedrine was 50 mg and that of imipramine 75 mg, during a four-week period. In the group with retroperitoneal lymphadenectomy, after treatment with ephedrine, only one (12.5%) had retrograde ejaculation while the remaining patients (n = 7) continued to lack semen emission. These seven patients were treated with imipramine, and three of them (42.8%) achieved anterograde ejaculation. In this study in one third of patients with retroperitoneal lymphadenectomy and diabetes, with retrograde ejaculation or loss of semen emission, conservative treatment offered improvement or conversion to anterograde ejaculation.

If pharmacologic attempts to restore antegrade ejaculation fail, sperm recovery from the urine and IUI are usually indicated.[817;818] Urine is deleterious to sperm motility and early resuspension of spermatozoa may be necessary in addition to ovulation induction, IVF and ICSI if there is poor sperm motility.[819-822] Careful handling of the retrieved spermatozoa enables isolation of sperm cells with good quality for insemination of ovulated oocytes (in vivo) or retrieved oocytes (in vitro).[823]

In men with primary or secondary anorgasmia it may be possible to induce ejaculation by vibration or by electroejaculation.[824-827] Vibroejaculation is to be preferred as semen is of better quality[828;829] and has a higher patient preference.[828] One study[826] obtained a pregnancy rate of 21% per cycle and a live birth rate of 16.5% per cycle. The quality of the semen is often poor and for this reason ICSI is sometimes necessary. Another study[830] obtained a clinical pregnancy rate of 61% in 18 cycles with a live birth rate of 50%. Another study[831] presented the case of a tetraplegic man who fathered a child with the aid of electroejaculation with ICSI.

One study[832] combined electroejaculation with IUI in 18 cycles (10 couples). Four couples went on to receive therapy by electroejaculation plus IVF, along with six other couples (15 cycles total) with semen too poor for IUI. One term pregnancy arose in the electroejaculation-IUI group, and one term pregnancy plus one continuing pregnancy arose from two couples (three cycles) who underwent IVF with conventional insemination after electroejaculation. Six couples (nine cycles) had embryos arising only from gamete micromanipulation transferred, and this yielded two term pregnancies, one spontaneous abortion, and a biochemical pregnancy. Two couples (three cycles) failed to achieve fertilisation even with micromanipulation; however, donor-inseminated eggs gave rise to two term pregnancies and one continuing pregnancy in these patients. This study confirmed the feasibility of IVF in conjunction with electroejaculation and extends the therapy to incorporate gamete micromanipulation.

A retrospective clinical study[833] evaluated sperm characteristics and fertility potential in ejaculates obtained after electroejaculation in 29 men with psychogenic anejaculation who underwent 55 sessions of electroejaculation. In all patients, sperm density and motility rates were unsatisfactory. IUI performed in eight couples did not result in a pregnancy. Four couples underwent IVF treatment. Two pregnancies were achieved with overall success rates of 22% per cycle. Five couples were treated using ICSI. Although good quality embryos were transferred, none of the treatments resulted in a pregnancy. Psychogenic failure to ejaculate may be treated by electroejaculation. However, the

average motility of the sperm obtained is diminished. The combination of electroejaculation with IVF, including the ICSI procedure, should improve chances of fertilisation and pregnancy in these cases.

One case report[834] described the possibility of achieving a pregnancy in the partner of a patient suffering from idiopathic anejaculation who failed to respond to therapeutic modalities such as psychotherapy, sex therapy, and vibrostimulation. ICSI in combination with electroejaculation was performed. Two IVF procedures were performed of which the second resulted in an ongoing pregnancy and the delivery of a healthy child. Electroejaculation may offer fertility chances in a patient suffering from idiopathic anejaculation resistant to conventional treatment modalities. When sperm quality shows very low motility, ICSI should be offered to improve pregnancy chances.

One study[835] reported on 26 men (aged 24-48 years) who underwent a total of 84 electroejaculations. Causes of anejaculation included spinal cord injury (n=23) and retroperitoneal lymph node dissection (n = 3). Super-ovulation was carried out in female partners to improve the pregnancy rate. Ten couples attempted conception. Fifty cycles of IUI were performed, resulting in four normal term infants and one spontaneous abortion (pregnancy rate 10% per IUI). One patient failed to conceive with eight cycles of IUI, but became pregnant with IVF with micromanipulation using electroejaculates. Two couples elected to have donor sperm insemination after failing to conceive by IUI with electroejaculates and both became pregnant.

An alternative approach is to collect spermatozoa by microsurgical vasostomy as such spermatozoa usually have good motility and a pregnancy rate of 37.5% was obtained with standard IVF.[836] One study[837] described the achievement of a pregnancy after IUI with sperm obtained from microsurgical aspiration of the vas deferens in a patient with neurologic ejaculatory dysfunction. The intra-uterine insemination of electroejaculated sperm had failed to achieve a pregnancy on three previous occasions. One case report[838] described a couple who achieved pregnancy when ICSI was carried out with frozen-

thawed spermatozoa aspirated from the vas deferens of a man whose anejaculation was associated with diabetes mellitus.

The relative merits of electroejaculation and surgical sperm retrieval remain uncertain.

Recommendations:

The cause of ejaculatory failure should be diagnosed, and a range of treatment options should be offered, bearing in mind that it may be possible to restore fertility without the need for invasive methods of sperm retrieval or the use of assisted reproduction. [C]

Treatment options for ejaculatory failure should include drug therapy and surgical recovery of sperm from the vas deferens. [B]

16.5 Intracytoplasmic sperm injection vs in vitro fertilisation

There are no RCTs comparing ICSI with IVF or other interventions where semen quality is so poor that IVF would not achieve fertilisation. It is accepted that ICSI is the only treatment option in those circumstances. The role of ICSI where IVF can be expected to give a reasonable fertilisation rate has been investigated using RCTs.

A systematic review of 10 RCTs based on couples with mild-moderate male factor infertility, unexplained infertility or tubal subfertility showed no significant difference between ICSI and conventional IVF in terms of pregnancy rates per couple or per embryo transfer in couples with normal semen. However, the fertilisation rate per oocyte inseminated was significantly higher with ICSI for couples with normal semen (OR 1.42, 95% CI 1.17 to 1.72) and for couples with borderline semen (OR 3.90, 95% CI 2.96 to 5.15).[767] [evidence level Ia]

A systematic review of 10 RCTs compared ICSI vs IVF, ICSI vs additional IVF and ICSI vs subzonal sperm injection. In couples with normal semen (three RCTs), there was no significant difference in fertilisation per oocyte retrieved or in pregnancy rate between ICSI and IVF. One RCT examined pregnancy rates per embryo transfer in couples with borderline semen[839] and found no significant difference in pregnancy rates between ICSI and IVF. ICSI was associated with an increased fertilisation rate per oocyte retrieved (OR 3.79, 95% CI 2.97 to 4.85) and per oocyte injected (OR 3.90, 95% CI 2.96 to 5.15) for borderline semen (three RCTs). For couples with very poor semen (two RCTs), ICSI vs subzonal sperm injection significantly increased fertilisation rate per oocyte injected (33% with ICSI vs 16% with subzonal sperm injection, OR 2.59, 95% CI 1.11 to 6.04), and ICSI vs additional IVF significantly increased fertilisation rate per oocyte injected (63% with ICSI vs 0% with additional IVF, OR 13.77, 95% CI 7.96 to 23.82). No trials compared pregnancy rates between ICSI and IVF for couples with poor semen.{5907} [evidence level Ia]

Recommendation:
Couples with 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. [A]

16.6 Cost-effectiveness of intracytoplasmic sperm injection

The cost-effectiveness models for ICSI treatment are described in detail in Appendix A. We found no live birth rates for ICSI, and so the cost-effectiveness models were based on the same clinical effectiveness rates as IVF, but with additional costs. The cost per live birth for couples undergoing ICSI using the baseline cost of ICSI treatment (£2,936, which includes drugs) and an OHSS incidence rate of 0.2% was £14,029. At a lower cost per ICSI treatment (£1,936, which excludes drugs) the cost per live birth was £9,056.

Chapter 17 Donor insemination

17.1 Indications for donor insemination

Male infertility affects about 25% of all infertile couples.[1] Until ICSI became available the main technique for treating male factor infertility where azoospermia or severe abnormalities of semen quality were present was insemination with donated sperm. The need to prevent transmission of sexually transmitted diseases (including HIV) [840] by donor insemination has led to the mandatory quarantine of donor sperm for 6 months by cryopreservation prior to its use in the United Kingdom,[841] [evidence level III-IV] despite the fact that pregnancy rates are significantly higher when fresh sperm is used compared with cryopreserved sperm.[842] [evidence level Ib] Donor insemination is also indicated where the male partner is likely to pass on an inheritable genetic condition, an infection such as HIV or if severe rhesus incompatibility has been a problem because of the male partner's homozygous status.

Recommendation:
Recognised indications for donor insemination include:

- **severe deficits in semen quality in the male partner**
- **obstructive azoospermia**
- **non-obstructive azoospermia**
- **genetic or infectious disease in the male partner**
- **severe rhesus isoimmunisation. [B]**

17.2 Information and counselling

ICSI is often preferred to donor insemination in severe male factor infertility because the resulting child is genetically related to both parents when treatment is successful.[843] [evidence level III] The views of the couple in question should help decide what treatment is suitable for them and additional counselling may be required in order to help then

answer this question. Some couples choose donor insemination primarily because they object to the invasive nature of assisted reproduction techniques or through fear of potential genetic risks with ICSI. Conversely, when a couple has not achieved a successful pregnancy with ICSI, they may want to proceed to donor insemination as an alternative treatment. However, the most common motivation for choosing donor insemination was that IVF-ICSI was not financially affordable, therefore a balanced view of treatment options can only really be given when both ICSI and donor insemination are easily available to the couple.[843] [evidence level III]

Counselling is particularly important when donor gametes are considered, both for the donor and the recipient couple.

Recommendation:
It is important that any discussion with a couple about the relative merits of intracytoplasmic sperm injection and donor insemination takes place in a context that allows equal access to both treatment options, and that the couple has the opportunity for independent counselling regarding all the physical and psychological implications of treatment for themselves and the potential child. [C]

17.3 Screening of sperm donors

The British Andrology Society has published consensus guidelines on the selection and screening of semen donors specifically for the protection of the offspring of donor insemination treatment from heritable genetic disorders and of the offspring and recipient women from infection. The British Andrology Society recommends that sperm donors are screened for karyotyping of chromosomal abnormalities; autosomal recessive conditions such as cystic fibrosis, B-thalassaemia, sickle-cell disease and Tay-Sachs disease; and rhesus antigens.[841] [evidence level III–IV] The British Andrology Society also recommends the exclusion of sperm donors who are seropositive for HIV, hepatitis B virus, hepatitis C virus, syphilis, Chlamydia trachomatis and cytomegalovirus. There is an upper age limit of 40 years for sperm donors.[841] [evidence level III–IV]

The HFEA Code of Practice requires clinics to take all reasonable steps to avoid transmission of serious genetic disorders stating an upper age limit of 45 years for sperm donors. It is mandatory that pre- and post-test information and counselling are provided and appropriate advice and support given to donors by an appropriately trained person or a genetic counsellor.{7807} [evidence level IV]

The prevalence of sexually transmitted diseases in potential semen donors in an urban area of Canada was found to be 34.5% (n=29).[844] [evidence level III] A follow-up infection rate of 22.2% was found in this study. These results suggest that a high prevalence of sexually transmissible infections is present in potential semen donors, and that new infections are common during the follow-up period. Six confirmed cases and two possible cases of donor insemination-associated AIDS were reported in an American surveillance study which also identified self-insemination with unscreened sperm as the most likely source of risk of new infections associated with donor insemination.[845] [evidence level III]

Recommendations:

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. [C]

All potential semen donors should be offered independent counselling regarding the implications for themselves and any potential children resulting from donated or undonated semen. [GPP]

17.4 Assessment of the female partner

In order for donor insemination to be effective the female partner must be ovulating and have at least one patent tube. Treatment-independent pregnancy rates of 3.2% over 24

months have been reported (0% in the azoospermic group and 7.6% in the non-azoospermia cases) in a group of infertile couples requiring donor insemination.[846] [evidence level III] Before the use of frozen-thawed semen, donor insemination with fresh semen resulted in cycle fecundity rates that approached natural conception.[847-849] [evidence level III]

An observational study (n=305 couples, 1131 cycles) found that in couples using IUI with donor semen, there was a significant correlation between successful outcomes and the first treatment cycle, number of mature follicles, time of insemination, insemination after ovulation had occurred, and female age under 30 years.[850] [evidence level III]

Other factors that affect donor insemination success rates are female age and previous success with donor insemination. Female fecundity declines after the age of 30 years or 35 years, depending on the population studied, and more cycles are needed to achieve conception.[851-856] [evidence IIb-III] Previous success with donor insemination is associated with quicker conception with subsequent donor insemination attempts.[847;853] [evidence level III]

Before treatment with donor insemination begins the female partner is likely to have had a history taken confirming regular menstrual cycles and a mid-luteal phase progesterone assessment in order to confirm ovulation. If the female partner is oligo- or anovulatory, this can be corrected with an appropriate treatment which initially is likely to be an anti-oestrogen such as clomifene.[857] Recognition of such a problem requiring treatment is important as pregnancy rates in women with treated ovulatory dysfunction approach those with no other infertility factors, although conception may take more cycles.[848;858;859] [evidence level III]

Tubal assessment using HSG or laparoscopy should be performed before treatment in women with a history that is suggestive of tubal damage. Tubal disease will reduce the likelihood of success and cycle fecundability with donor insemination.[848;859] However, a low

incidence of abnormal HSG findings (2.8%) has been reported[840] in asymptomatic ovulatory women with no history of pelvic disease.[860] This significantly decreased fecundity in the first six cycles of treatment. No corresponding study using laparoscopy has been reported. [evidence level III]

Recommendation:

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. [C]

Women with no risk history should be offered tubal assessment within the first six cycles of unsuccessful treatment. [GPP]

17.5 Intra-uterine insemination vs intra-cervical insemination

A systematic review of 12 RCTs compared IUI with intra-cervical insemination using fresh and frozen donor sperm. The overall pregnancy rate per cycle was 18% in the IUI group vs 5% in the intra-cervical insemination group. When frozen semen was used, IUI significantly increased pregnancy rate per cycle (OR 2.63, 95% CI 1.85 to 3.73) and per patient (OR 3.86, 95% CI 1.81 to 8.25) in clomifene citrate cycles and in gonadotrophin cycles (OR 2.17, 95% CI 1.35 to 3.49 and OR 2.72, 95% CI 1.37 to 5.40, respectively). However, no significant difference was found in IUI or intra-cervical insemination when fresh semen was used (OR 0.90, 95CI 0.36 to 2.24).{5591} [evidence level Ia] The cost of using IUI has been estimated to be 1.5-2.0 times greater than intra-cervical insemination,[861] mostly because of the additional sperm preparation required.

A meta-analysis of seven RCTs (included in the previous systematic review{5591}) found significant higher fecundability rate with IUI compared with intra-cervical insemination using frozen sperm (OR 2.4; 95% CI 1.5 to 3.8).[862] [evidence level Ia]

Recommendation:

Couples should be offered intra-uterine insemination in preference to intra-cervical insemination because it improves pregnancy rates. [C]

17.6 Unstimulated vs stimulated donor insemination

Ovarian stimulation leads to an increased number of multiple pregnancies which should be avoided wherever possible. HFEA data showed a multiple birth rate of 1.9% per treatment cycle (67/3354) in 2000 and 1.8% per treatment cycle (54/3024) in 2001 in couples receiving donor insemination using stimulated treatment cycles.[625] [evidence level III]

Some female partners in couples where donor insemination is indicated may have additional infertility factors. Female partners of azoospermic men seem to conceive more quickly with donor insemination than female partners of men with abnormal semen quality,[854;858;859;863;864] [evidence level III] suggesting that in the latter case unexplained female factors are contributing to the couple's subfertility. Therefore, there will be cases where unstimulated donor insemination is initially unsuccessful. To reduce multiple pregnancies and their attendant risks, it would be reasonable to try six cycles of unstimulated donor insemination initially in regularly ovulating women. There is no evidence from RCTs to support this recommendation.

Recommendation:

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. [GPP]

17.7 Timing of donor insemination

Traditional methods for timing insemination have utilised basal body temperature charts or cervical mucus assessment. Newer methods involve kits to detect LH in urine. There are four RCTs that compare these two methods of timing insemination.[865-868] Two of these

trials used intra-cervical insemination whilst the other two were presumed to use insemination but did not clearly say so. Meta-analysis of these trials [869] showed no benefit of using the LH kits in terms of pregnancy rates per cycle (OR 0.98 95%CI 0.64-1.48) although one study[868] found a significant reduction in number of patient visits per insemination cycle and another[866] found it advantageous with regard to cost and time expenditure to use a urinary LH kit and one insemination as opposed to non-LH methods and two inseminations. [evidence level Ib] These findings could represent cost and organisational benefits from using LH detection in some circumstances. For stimulated IUI, insemination between cycle day 13 and 16 was shown to be significantly associated with a higher clinical pregnancy rate when compared with insemination after cycle day 13 (27.3% vs 14.5%).[850] [evidence level III]

Recommendations:

Couples should be informed that insemination may be timed using either measurement of urinary luteinising hormone or basal body temperature changes because there is no difference in the effectiveness of these methods. [A]

However, luteinising hormone surge detection may be beneficial in terms of clinic organisation and costs. [C]

17.8 Maximum number of cycles

The French national donor insemination programme reported a pregnancy rate per unstimulated cycle of 10.3% in up to six cycles in a four-year period.[870] Data from Sheffield[871] covering 980 treatment cycles over 4 years from 1992-1996 gave a live birth rate per cycle of 11.6% for the 768 unstimulated cycles. An observational study found that the pregnancy rate was highest in the first treatment cycle and the cumulative conception rate rose only slightly after the sixth IUI stimulated treatment cycle (26.5% at first cycle to 61% at the sixth cycle) although the monthly fecundability decreased with increasing number of cycles.[850] [evidence level III]

The decision about when to stop donor insemination and move on to another treatment such as ICSI or IVF or to accept their infertility is an arbitrary one that should be made in conjunction with the couple. There is already a shortage of donated sperm from some ethnic groups. In addition the possible introduction of prospective identification of sperm donors may further impact on the availability of sperm for donor insemination.

Recommendation:

Couples should be offered other treatment options after six to nine unsuccessful cycles of donor insemination. [GPP]

Chapter 18 Oocyte donation

18.1 Indications for oocyte donation and counselling

Premature ovarian failure

The major indication for use of donor oocytes is premature ovarian failure, either primary or secondary. Causes of premature ovarian failure which are potentially amenable to oocyte donation include surgical oophorectomy, irreversible gonadal damage after certain regimens of chemotherapy or radiotherapy, Turner syndrome and other chromosomal disorders causing gonadal dysgenesis. In addition, oocyte donation might be employed to avoid the risk of transmission of a genetic disorder in cases in which the carrier status of both partners is known.

One study[872] compared the effectiveness of donor oocytes in IVF in patients with premature ovarian failure vs those with other indications for donor oocyte IVF (non-premature ovarian failure) in a retrospective comparative clinical study. There were 86 donor oocyte IVF cycles from 32 premature ovarian failure patients (39 cycles) and 38 non-premature ovarian failure patients (47 cycles). Given limitations of sample size, there were no detectable differences in clinical pregnancy rate per cycle or per transfer, fertilisation rate, and implantation rate between premature ovarian failure and non-premature ovarian failure groups despite recognisable differences in recipient age and degree of male factor infertility. Donor oocyte IVF success rates were not different in patients with and without premature ovarian failure.

One study[873] suggests that women with markedly diminished ovarian reserve should be counselled on their low chances of conception using their own gametes, even with assisted reproduction, and should be offered the options of donor oocytes or adoption. Egg donation is the most successful technique for producing pregnancy in perimenopausal women.[874] Early menopause due to the exhaustion of the ovarian follicles occurs in approximately 1% of women before the age of 40, and when there is little remaining follicular capacity, ovum donation may represent the best chance of a successful

pregnancy.[875] Whilst oocyte donation for women with premature menopause has become widely accepted within the United Kingdom, the use of oocyte donation to achieve pregnancy after the start of natural menopause (typically between the ages of 45 years and 55 years) remains controversial.

Turner syndrome

Oocyte donation offers women with ovarian failure due to Turner syndrome the chance of pregnancy and live birth. Pre-treatment screening is essential to exclude phenotypic manifestations of the syndrome that might jeopardise successful pregnancy, including aortic dilation and cardiac lesions.[876] One study[877] presented the results of oocyte donation in Turner syndrome in a total of 29 women who had 68 cycles of oocyte donation using oral oestradiol valerate for endometrial preparation. The embryos/zygotes were transferred either fresh (50 cycles) or after cryopreservation (18 cycles) into the Fallopian tube (41 cycles) or uterine cavity (27 cycles). The pregnancy rate achieved was of 41.2% per treatment cycle and the implantation rate of 17.1% per embryo transferred. The recipient's age, chromosomal constitution and associated uterine or tubal anomaly had no influence on the treatment outcome. The implantation and pregnancy rates were significantly higher in subsequent than initial cycles (22.6% vs 9.99%; 51.3% vs 27.6%). An endometrial thickness of ≥ 6.5 mm was an important predictor of pregnancy but the endometrial echo pattern failed to predict the outcome. The number of oocytes fertilised affected the pregnancy rate irrespective of the number of embryos transferred. The implantation and pregnancy rates were significantly higher when fresh rather than frozen-thawed embryos were transferred (20.3% vs 8.2%; 48% vs 22.2%) but the route of transfer was of no statistical importance.

A retrospective study[878] evaluated whether endometrial receptivity is compromised in patients with premature ovarian failure due to Turner syndrome who undergo oocyte donation. The study included 53 patients with premature ovarian failure who underwent oocyte donation. These included seven patients with Turner syndrome (45,X) who underwent 22 embryo transfer cycles, 15 women with Turner variants (mosaics, deletions, or isochromosomes) who underwent 36 embryo transfer cycles, and 31 other patients with premature ovarian failure and a normal karyotype who underwent 69 oocyte donation

cycles. Oocyte donors were healthy women <34 years who underwent IVF themselves. Turner syndrome patients had a significantly higher rate of biochemical pregnancies (22.7% vs 4.3%), a lower clinical pregnancy rate (22.7% vs 33.3%), a significantly higher rate of early abortions (60% vs 8.7%), and a significantly lower rate of deliveries per pregnancy (20.0% vs 73.1%) compared with non-Turner patients. Patients with a complete or partial deficiency of an X chromosome had reduced pregnancy rates and an increase in early implantation failure after oocyte donation, which may indicate an inherent endometrial abnormality, possibly associated with a deficiency of X-linked genes regulating endometrial receptivity.

Ovarian failure following chemotherapy or radiotherapy

Anticancer treatment can cause ovarian failure and women face limited options for fertility preservation. Cryopreservation of oocytes has had very limited success; currently its use before chemotherapy is not a feasible option. However, cryopreservation of embryos is possible and another solution is oocyte donation followed by IVF.[879] Success following oocyte donation has been reported in women who had previously received chemotherapy or radiotherapy. One study[880] reported the first case of a full-term pregnancy with embryos from donated oocytes in a 36-year-old woman allografted for chronic myeloid leukaemia, six years after allogeneic bone marrow transplantation following total body irradiation and cyclophosphamide. The first attempt at implantation with her own cryopreserved oocytes had been unsuccessful. Following oocyte donation, one study[881] achieved a successful pregnancy in a patient with an early ovarian cancer associated with infertility (after radical surgery with uterine conservation and chemotherapy). However, after chemotherapy and particularly radiotherapy to the pelvis, the endometrial response to hormone replacement therapy may be impaired or fail altogether which will result in lower rates of implantation.[882]

In vitro fertilisation failure

Oocyte donation has also been advocated in certain cases of repeated failure of IVF, particularly those in which oocyte quality is compromised, although unexplained failure of fertilisation has also been treated using this method.

In a larger study involving a group of women who failed to conceive with conventional IVF[883] and were then treated with oocyte donation, a 24.5% pregnancy rate per cycle was achieved. To ascertain which women may be helped by oocyte donation, IVF data were analysed according to oocyte donation outcome. Variables found to have an effect on oocyte donation outcome included the number of previous natural conceptions and live births, and the IVF fertilisation rate. However, increasing female age did not affect outcome. The authors suggested new criteria for recommending oocyte donation to women who have previously failed to become pregnant with IVF treatment. Another study[884] obtained similar results using ICSI in 15 oocyte donation cycles in 15 infertile couples where oocytes had failed to fertilise after IVF, where the male partner had severe male factor infertility. The pregnancy rate obtained was 33.3% per started cycle and 38.4% per embryo transfer.

Genetic disorders

Heritable genetic diseases can be avoided with the use of donor oocytes. Another study[885] used donor oocytes from anonymous, matched, fertile donors in four women with heritable genetic disorders and found that use of donor oocytes was a practical, successful, and currently available technique for the prevention of genetic disorders.

Recommendation:

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. [C]

18.2 Screening of oocyte donors

A cross-sectional study (n=73) found that 11% of volunteer oocyte donors were inappropriate for donation because of their genetic history or genetic testing results. Cystic fibrosis mutations were identified in 7%, abnormal karyotype in 3.5% and autosomal dominant skeletal dysplasia in 1.4%.[886] [evidence level III]

Limiting oocyte donors to women of < 35 years old to decrease the risk of aneuploid offspring has also been suggested.[887] [evidence level III–IV]

The French national federation of centres for the study and preservation of human eggs and sperm analyses the genetic control of oocyte donors and sperm donors. One study[888] reported an analysis of 98 female donors and 1609 male donors. In all, 2% of women donors were excluded after genetic screening discussion and 2% were excluded following karyotype. Results for male donors were similar: 3.2% were excluded for genetic reasons (2.6% after genetic screening discussion and 0.6% following karyotype). The risk factor presence level was 27.8% on average, but varied considerably from one centre to another. Diseases most commonly encountered were: allergies, cardiovascular disorders and ophthalmological disorders.

One prospective study of 73 oocyte donor volunteers,[886] carried out genetic screening by pedigree analysis and laboratory studies (for cystic fibrosis carrier status, cytogenetic analysis for karyotype, enzymatic assay for Tay-Sachs disease carrier status, and complete blood count and haemoglobin electrophoresis). A significant proportion of women (8/73) who presented as candidates for oocyte donation were found to be inappropriate for donation because of their genetic history or genetic testing results: cystic fibrosis mutations were identified in 5%, abnormal karyotypes in 2%, and an autosomal dominant skeletal dysplasia was present in one woman.

Given the high prevalence of cystic fibrosis, which is the most common autosomal recessive disorder in northern Europeans, the HFEA[889] recommends screening both egg and sperm donors for carrier status. All licensed clinics are now required to inform patients whether or not a donor has been tested for cystic fibrosis, and of the risks for any child who may be born from fertility treatment. The HFEA encourages clinics to offer testing to couples. If donors agree to be tested for cystic fibrosis, they should be offered genetic counselling and be provided with information about the implications for themselves and their family if they were found to be carriers. The HFEA also considered the wider implications of genetic testing and decided that testing for other disorders was appropriate if there was an accurate test available and would help to prevent the transmission of a serious condition.

Regarding screening for infectious diseases, the HFEA does not recommend this in particular, but states that clinics should consider the welfare of any potential child and take into account the health of the couple requiring treatment.

Recommendation:
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. [D]

18.3 Oocyte donation and egg sharing

Oocyte donation

The number of treatment cycles undertaken in the United Kingdom using donated oocytes remains small, due to the practical difficulty of recruiting volunteer donors willing to undergo the time consuming and painful processes of pituitary down regulation, superovulation and transvaginal oocyte collection. Volunteers must undergo adequate counselling concerning the possible risks of the procedures, including the surgical risk of oocyte retrieval and the putative link between superovulation with gonadotrophins and the risk of ovarian cancer in later life.

The professional counselling of prospective donors with respect to the results of tests and the implications of test results with respect to their future medical and reproductive health are important parts of providing good care. In one study[890] only 50% of women wishing to participate in oocyte donation were considered suitable candidates; half of these women were scheduled an entry interview on completion of the formal medical, genetic and psychological screening process, and 18% of those actually interviewed were denied entry.

For many volunteer donors, guaranteeing anonymous oocyte donation plays a crucial role in their decision to donate.[891] In the United Kingdom, non-identifying information on the donor is recorded by statute in assisted reproduction with gamete donation. This may be made available eventually to the resulting children. One study[892] analysed forms from the HFEA completed by all donors at one IVF unit and found that 94% of oocyte donors did not respond to the question asking for a brief description of themselves, leaving only profession and interests as information to be given to the child in the future. There was a significant difference between the known and anonymous responders.

A survey of a sample of couples undergoing oocyte donation with known donors found that anonymity was a primary concern for recipients and donors: 80% of the sample had not confided in anyone at the time of the study and 70% did not intend to disclose any information at any time; 80% did not plan to inform the child.[893]

In a survey of women enquiring about anonymous oocyte donation, one study[894] found that concerns about complications and logistic factors such as travel and time commitment involved were major reasons for non-donation.

In a follow-up study[895] of the first 30 Finnish volunteer oocyte donors, most donors were very satisfied with the experience at 12-18 months after donation. The side effects of the

treatment had been slight and tolerable. A majority of the respondents reported that they had thought about the possibility of a child from their donation (89%) and would have liked to have known if pregnancy had been achieved in the recipient (67%). A majority thought the offspring should be told about its origin (59%). However, some 42% of the respondents preferred to receive no information concerning either the child or the recipient couple and 33% thought the child should be given identifying information about the donor. About half of the others would agree to the release of non-identifying information. All donations had been carried out anonymously and without payment and no one regretted their donation.

In a study in Iceland[896] of the attitudes of anonymous couples undergoing IVF toward sperm and oocyte donation, a high proportion of couples found the use of donor sperm acceptable for therapeutic, diagnostic and treatment purposes and 72%, 84% and 90% respectively were willing to donate oocytes for these purposes. Of potential oocyte donors 41% would agree to non-anonymous donation, 12% would wish to meet the recipient couple and although only 4% wanted to choose the recipient, a quarter of the couples would prefer a relative or friend as the recipient. Provision of non-identifying information about the donor to the recipient couple was acceptable to almost 70%, whereas 40% found giving the same information to the child acceptable.

One study[897] in the United States of 25 consecutive anonymous oocyte donors assessed their psychologic characteristics and postdonation satisfaction. Following oocyte donation, 80% of women stated that they would be willing to donate again. Postdonation satisfaction was high. Although monetary compensation for donation was provided, altruism was reported as the most salient motivating factor and a significant negative correlation was found between predonation financial motivation and postdonation satisfaction and between predonation ambivalence and postdonation satisfaction. The authors advised that donors with high levels of predonation financial motivation or ambivalence should be carefully screened and counselled before oocyte donation to ensure satisfactory psychological outcome.

In a study in the United States[898] 45 women were evaluated as candidates to donate oocytes to an infertile couple, 24 completed a cycle as oocyte donors, and follow-up data on donor satisfaction were obtained for 23. Ninety-one per cent were moderately or extremely satisfied with the experience and 74% would donate for another cycle given the chance. The transient adverse psychological symptoms reported by two donors were resolved with medical or psychological treatment.

In a United Kingdom study[899] attitudes towards egg and sperm donation were compared in four groups of subjects: patients receiving egg donation, patients receiving sperm donation, potential egg donors and a general population control group. Egg donation appeared to be as acceptable as sperm donation, but subjects overall were more in favour of donor anonymity for sperm donation than for egg donation, and the sperm recipients were more in favour of donor anonymity than egg recipients. Subjects demonstrated uncertainty on the issue of giving information to children conceived by gamete donation, but held positive attitudes towards the counselling of both donors and recipients.

A review of the methodological adequacy of the psychosocial literature on information access when donated gametes and embryos are used[900] identified 10 major flaws. The authors argued that these flaws prohibit any firm conclusions to be drawn either way about whether donors and/or recipients should disclose information, whether they should have access to information, or even whether donors and recipients want to have access to information about each other or to have information about themselves disclosed to the other party.

Generally, oocyte donation is acceptable with oocyte donors having a high satisfaction rate. Independent counselling could contribute to this, as well as to the understanding of the potential risks and complications associated with this process.

Egg sharing

One possible solution to the imbalance between the large number of potential recipients and the currently small number of donors is the practice of egg sharing. Egg sharing enables two or more infertile couples to benefit from a single IVF cycle.

A pilot study[901] to establish the place of egg sharing in an assisted reproduction programme was undertaken. This study followed HFEA guidelines on medical screening of patients, counselling, age and rigid anonymity between the donor and recipient. The study involved 55 women (25 donors and 30 recipients) in 73 treatment cycles involving fresh and frozen-thawed embryos. Donors were IVF patients, mostly with tubal infertility, who shared their eggs equally with matched anonymous recipients, who were either menopausal, perimenopausal or who had had previous poor response to ovulation induction with previous IVF attempts. The recipients were older than the donors (41.4 ± 0.9 yearsvs 31.6 ± 0.5 years). The results showed no differences in the number of eggs allocated, fertilisation rates or the mean number of embryos transferred.

When all the births from the transfer of fresh and frozen-thawed embryos were considered, the birth rate in recipients was higher than in donors (30% vs 20%), although the groups were too small to determine if this was statistically significant or not. The nine births in the recipient group were achieved from a total of 12 pregnancies, whereas the five births in the donor group were achieved from five pregnancies (birth rates per pregnancy, 75% vs 100%). The study demonstrated that the birth rate in recipients did not suffer because the eggs were provided by infertile women as the success rates appeared similar to the results obtained with other forms of egg donation. Similarly, the fresh treatment of the donors was not disadvantaged by them having only half the number of eggs for their own use because the success rates were similar to the rates achieved in the same programme for IVF without egg sharing. In another (prospective) study, a direct comparison of the use of fresh embryos in donor cycles (n=135) and standard IVF cycles (n=474) confirmed similar pregnancy rates (17.5% and 18.7%) and implantation rates (7.5% and 7.2%) in the two groups.[902] Careful patient selection and independent counselling for both the donors and recipients and their partners is clearly essential.

In order to understand the emotional and social effects of egg sharing, a survey of attitudes[903] was undertaken in 217/750 women who replied to an appeal in infertility support group magazines and who had experience of egg donation or were interested in donating or receiving eggs. They found that: donating or sharing eggs is a social issue with 94% of respondents having discussed it with partners/family/friends; 86% of egg share donors and 79% of egg share donor enquirers felt that helping the childless was as important as having a chance of IVF themselves. The treatment procedure caused the most anxiety for egg donors. However, 65% of respondents with prior experience of egg sharing would do it again (63% of donors, 72% of recipients). Counselling was highly valued with 84% of respondents agreeing that patients, donors and recipients should have time to talk over egg donation issues with a counsellor.

Recommendations:

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

Oocyte recipients and donors should be offered independent counselling regarding the physical and psychological implications of treatment for themselves and children resulting from donated and undonated oocytes. [GPP]

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

18.4 Oocyte donation in older women

Women may become pregnant after the age of natural menopause by means of IVF of donated oocytes. Whilst oocyte donation for women with premature menopause has become widely accepted within the United Kingdom, the use of oocyte donation to achieve pregnancy after natural menopause remains controversial. Most advocate an age 'cut off'

of 45 years or 50 years for oocyte donation treatment, whilst a few centres accept older women into their programmes.

One study[904] assessed whether menopausal women aged 50-59 years could be prepared for pregnancy with oocyte donation. Of 18 patients with a mean age of 52.2 years screened initially, 14 couples were entered into the study. Oocytes were donated by fertile women (mean age 28.1 years). There were 22 donor follicle aspirations which resulted in 21 embryo transfers to 14 recipients. Pregnancies were established in nine women; one pregnancy ended in a preclinical loss. The ratio of clinical pregnancies per transfer attempt was 38%, with an implantation rate per transferred embryo of 19%. Of the eight clinical pregnancies, one spontaneous abortion occurred at seven weeks' gestation; three women delivered (two at 35 weeks by emergency caesarean section and one at 37 weeks after a normal vaginal birth), four pregnancies were continuing to progress normally beyond the second trimester.

One study[905] described the reproductive and obstetric outcomes of 36 postmenopausal women aged 50-59 years attempting pregnancy using donor oocytes. Oocytes were provided by designated gamete donors. Forty-five aspirations resulted in 22 pregnancies (48.9%): three preclinical, two ending in spontaneous abortion, and 17 viable pregnancies (37.8%). The embryo implantation rate was 20.6%; 52.9% of pregnancies were multiple gestations. All pregnancies delivered beyond 32 weeks. Complications occurred in eight patients (gestational hypertension seven, preterm labour three, gestational diabetes two, andpre-eclampsia one). One infant was trisomy-21. In this study, patients ≥50 years experienced similar pregnancy rates after oocyte donation as younger women and were at equal risk for multiple gestation. Antenatal complications were experienced by the majority of patients, underscoring the importance of high risk obstetric surveillance and care.

Pregnancy rates after oocyte donation remain high in older recipients, with the major determinant of outcome being the age of the donor.[906] Miscarriage rates are correspondingly low. However, the incidence of maternal morbidity during pregnancy is less encouraging. A higher incidence of pregnancy-related diseases, including gestational

diabetes, hypertension, and moderate and severe pre-eclampsia have been reported.[907] If oocyte donation is to be offered to older post-menopausal women, they should be fully informed about the obstetric risks for themselves and their offspring. They should also be screened and investigated as accurately as possible for any existing medical contraindications to pregnancy.

Recommendations:

Women who are considering using donated oocytes beyond the age of natural menopause should be offered information regarding the welfare of potential offspring and the risks of pregnancy and labour (including risks associated with multiple pregnancy) in older women before starting such treatment. [C]

Women who are considering using donated oocytes beyond the age of natural menopause should be offered independent counselling regarding the physical and psychological implications of such treatment. [GPP]

Chapter 19 Cryopreservation

19.1 Information about cryopreservation in cancer treatment

Oncologists should be aware of conditions for which treatment is available and facilities for cryopreservation of gametes. A working party of the Royal College of Physicians and the Royal College of Radiologists[908] has recommended procedures to be followed before commencing chemotherapy or radiotherapy likely to affect fertility and the management of post-treatment infertility. [evidence level IV]

Although anticancer treatment can cause ovarian failure, cryopreservation of oocytes has had very limited success (see Section 18.1). However, cryopreservation of embryos is possible and another solution is oocyte donation followed by IVF.[879] Success following oocyte donation has been reported in women who had previously received chemotherapy or radiotherapy (see Section 18.1)

Semen cryopreservation should be considered in conditions that impair fertility or need treatment likely to impair fertility, such as malignancies of the genital tract (for example, testicular cancer and prostate cancer), or systemic malignancies (for example, non-Hodgkin's or Hodgkin's lymphoma, and leukaemia). Survival rates in men with these conditions (who are often young) are promising and likely to improve in the future. For patients about to receive chemotherapy or radiotherapy, and those about to undergo a surgical procedure, loss or impairment of fertility is an important issue and cryopreservation of semen in such patients has become a realistic option to preserve fertility. For males, sperm banking has become a standard accepted procedure to circumvent loss or damage to spermatozoa.

Semen quality is adversely affected by the presence of cancer[909] and current techniques in cryopreservation of human semen substantially decrease sperm quality. The particular

diagnosis of malignancy (for example, Hodgkin's disease) is not an adequate predictor of the effect of cryopreservation on human semen.[910;911] Some authors[912-914] encourage sperm banking at cancer diagnosis regardless of semen quality, before the initiation of specific medical treatment. Some patients may later decide that the specimens are not needed.[915] Successful outcomes with IUI and IVF following successful treatment for malignancy have been reported in one retrospective review.[916] Retrospective case series and case reports show that even poor quality (either pre-freeze or post-thaw) cryopreserved spermatozoa from cancer patients may provide successful results with techniques such as ICSI, irrespective of the length of storage.[913;916-918] An abstinence period of 24-48 hours can be recommended for sperm banking in cancer patients.[919] The offer of cryopreservation may be extended in the future to other diseases, such as cystic fibrosis.[920]

The possibilities for successful reproductive outcomes by means of sperm cryopreservation are encouraging for cancer patients whose complete loss of fertility could otherwise occur. Therefore, there should be facilities and opportunities to offer men with disease undergoing treatment likely to impair their fertility the possibility of sperm cryopreservation before undergoing treatment. Oncologists should be aware before commencing chemotherapy/radiotherapy of the procedures likely to affect fertility, and of the management of post treatment infertility. Local protocols between all health professionals involved will help with this. Many technical, legal, and ethical considerations remain.

Recommendations:

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. [D]

Men undergoing medical treatment that is likely to make them infertile should be offered information about semen cryostorage because the effectiveness of this procedure has been established. [B]

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 quickly and effectively. [C]

Men undergoing medical treatment that is likely to make them infertile should be offered independent counselling to help them cope with the stress and the potential physical and psychological implications for themselves, their partners and any potential children resulting from semen cryostorage. [GPP]

19.2 Cryopreservation of supernumerary embryos

Embryo cryopreservation allows any supernumerary embryos created after the initial egg collection and fertilisation to be stored for some time before a subsequent attempt at replacement either because the fresh embryo transfer has failed or because further children are desired. The ability to routinely preserve embryos has the added benefits of increasing the number of potential embryo replacement cycles without additional egg retrievals thereby improving the overall pregnancy rate and decreasing the risk to the patient of ovarian hyperstimulation syndrome by substituting frozen-thawed embryo transfer in unstimulated cycles (see Section 14.2). Embryo quality has the most significant impact on post-thaw survival.[921] Freezing poor quality embryos will lead to poor cryosurvival and implantation.[922] As with fresh embryos, pregnancy rates will be affected by factors such as patient age[922-925] and number of embryos transferred (see Section 14.2).[923-925] A beneficial outcome is also more likely if a pregnancy resulted from the original stimulation cycle from which the frozen embryos were derived.[924-926] The number of oocytes retrieved in the initial stimulation cycle and the number of embryos available for cryopreservation also affects outcome.[927] Methods of embryo freezing and culture conditions may affect outcome, but as these factors are likely to be addressed by

forthcoming guidelines to be issued by the Association of Clinical Embryologists they are not considered in this guideline.

The most recent data on live birth rates with frozen IVF cycles obtained from the HFEA are discussed in Chapter 14 (see Table 14.2).

Pregnancy rates from frozen embryo replacements

HFEA data from the year 1996/1997 report a clinical pregnancy rate of 13.3% and a live birth rate of 11.0% per treatment cycle in 4331 patients using their own gametes.[928] The French register of assisted reproduction outcomes included 15676 thawed embryo transfers between January 1987 and December 1995. During this period, the pregnancy rate per embryo transfer increased from 11.5% to 16.0%. Clinical pregnancy rates and pregnancy loss rates are similar whether the frozen embryos are obtained from oocytes fertilised by conventional IVF or from oocytes fertilised by ICSI.[929-931]

Cumulative pregnancy rates when frozen embryo replacements used in addition to fresh embryo transfer

A retrospective review[927] of experience with embryo cryopreservation over an eight year period (March 1984-December 1991) reviewed every freeze-thaw cycle excluding those following oocyte donation. Over this time period 4898 embryos were frozen and 3288 embryos were thawed. Those that survived (n=2002) were replaced in 897 cycles. Ninety-eight ongoing pregnancies were achieved resulting in an ongoing clinical pregnancy rate of 10.9%. This was comparable with an ongoing clinical pregnancy rate achieved with fresh IVF over the same time period of 13.3%. Overall, the cryopreservation of supernumerary embryos and subsequent thawing and transfer increased the overall pregnancy rate of their IVF/GIFT programme by 4%, increased the clinical pregnancy rate of women who had embryos cryopreserved by 7%, and increased the cumulative pregnancy rate in those who returned for frozen-thawed embryo transfer cycles by 11%.

A cohort study[932] followed 485 couples who started their first IVF attempt between January 1989 and February 1991 until June 1992. Tbis study found that a total of 1086 treatment

cycles were initiated, resulting in a take-home baby rate of 17.4% per cycle started. A total of 193 women had embryos cryopreserved in at least one IVF cycle and 88 completed at least one frozen embryo replacement cycle. Twenty-five deliveries/ongoing pregnancies resulted from these cycles meaning that the cryopreservation programme (within the limitations of Norwegian law, as frozen embryos can only be stored in Norway for 12 months) contributed a 5.2% increase in the take-home baby rate for women entering the IVF programme. Another study[933] reported a cumulative viable pregnancy rate of 40.7% following one fresh and two freeze-thaw embryo replacements (using two embryos only) in a series of 364 consecutive patients requesting IVF.

Perinatal and postnatal outcome from cryopreserved embryos

A retrospective study[934] compared 283 babies from 232 consecutive births from cryopreserved embryos with 961 babies from 763 births after conventional IVF. The incidence of twin and triplet births was similar in both groups as were mean gestational age and birthweight of singleton, twin and triplet births. No difference in perinatal mortality rates was found between the groups and the incidence of major congenital malformations was significantly lower in the cryopreserved group (1%) than in the IVF group (3%). One study[935] matched 255 children from cryopreserved embryos for maternal age, parity, single or twin pregnancy and date of delivery with 255 children born after standard IVF with fresh embryos and 252 children from spontaneous pregnancies. Growth, the incidence of major malformations and the prevalence of chronic diseases at 18 months were similar in all three groups.

Summary

The benefits of including embryo cryopreservation and frozen embryo replacement in an IVF or ICSI programme are clear as pregnancy rates are improved for a single oocyte stimulation and collection cycle. The outcome of children born from cryopreserved embryos seems to be normal. However, there is inevitably some loss of embryos during the freeze-thaw cycle.

Recommendations:

Cryopreservation of supernumerary embryos allows multiple embryo transfers from a single egg collection and improves the chances of a live birth. [B]

Embryo cryopreservation should be discussed with all couples considering assisted reproduction and should be offered if sufficient embryos of suitable quality for cryopreservation are available. [C]

19.3 Natural vs artificial replacement cycles

The replacement of frozen-thawed embryos can take place in either a natural cycle or in an artificial cycle where exogenous hormones with or without GnRH analogue are used to prepare the endometrium. Patients with anovulatory or irregular cycles will be easier to manage with a programmed cycle such as a GnRHa-hormone replacement therapy protocol.[936;937]

A prospective partly randomised study[936] assessed the relative efficacy of two strategies of patient management for the replacement of frozen-thawed embryos. One group (n=84) were treated with a GnRH analogue before receiving hormone replacement therapy (oral oestradiol valerate and intramuscular progesterone) for endometrial priming. The second group (n=78) had their frozen-thawed embryos replaced during their natural cycles. Women with regular menstrual cycles were randomised to either group, but some categories of patients were allocated to the GnRH-hormone replacement therapy group without randomisation. These included women with amenorrhoea, oligomenorrhoea, inadequate luteal function or previously unsuccessful frozen embryo replacement in a natural cycle. There was no difference between groups in terms of age, obstetric history, duration of infertility, number of oocytes retrieved or fertilised or the numbers of embryos frozen following ovarian stimulation in the initial cycle. Eighty embryos were replaced in the first group and 16 (20%) clinical pregnancies occurred. A similar pregnancy rate was achieved in the second group with 14 clinical pregnancies (20%) occurring after replacement of 70 embryos.

In a prospective, non-randomised series,[938] where 78 women had all their embryos electively cryopreserved to minimise the risk of developing OHSS, 125 frozen-thawed embryo replacements were subsequently undertaken. These took place in either a GnRHa and hormone replacement therapy cycle (n=93) or a natural cycle (n=32) according to the choice made by couples based on their individual circumstances. The pregnancy rates in natural cycles and GnRHa/hormone replacement therapy cycles were not significantly different (RR 0.65, 95% CI 0.29, 1.42).

A retrospective study[939] evaluated the results of 149 consecutive frozen-thawed embryo replacement cycles. In the natural cycle group, 77 women with proven ovulation had embryo transfer following a positive LH surge and confirmation of ovulation by ultrasonography. The artificial cycle group included 72 women that were anovulatory, oligomenorrhoiec or older. GnRHa administration was followed by oestradiol valerate supplementation. Progesterone was started after adequate endometrial development was seen on ultrasonography, and embryo transfer was performed two days after progesterone initiation. Pregnancy rates per cycle (26% and 25%) and delivery rates (20.8% in both groups) were similar regardless of whether the cycle was natural or artificial.

Another study[923] performed a similar retrospective evaluation. From January 1987 to December 1993, 521 women aged less than 40 years underwent 628 thawed embryo transfers. Transfer was performed in a natural cycle two days after the LH peak or on day 17 of a programmed cycle using a GnRH agonist and hormone replacement therapy protocol. Similar pregnancy rates were seen in the natural cycles (28%) and the artificial cycles (30%).

Another retrospective study[940] analysed 236 women undergoing 381 consecutive frozen-thawed embryo transfers and evaluated the implantation and clinical pregnancy rates according to the endometrial preparation protocol. There were no differences in implantation rates or clinical pregnancy rates (16.9%, 16.5%, and15.6%) between the three different protocols used (spontaneous cycles, artificial preparation, and ovarian stimulation cycles).

One study[941] compared two types of endometrial preparation in women with normal ovulatory function. Natural cycle replacement was compared with controlled preparation of the endometrium using exogenous oestrogen and progesterone without the use of a GnRH analogue. Pregnancy rates, ongoing pregnancy rates and implantation rates were similar in both groups but the controlled cycles were more convenient.

Another study[942] found that pregnancy rates did not differ significantly between spontaneous cycles (16.1%), an ovarian stimulation protocol (11.4%) and oestrogen/progesterone replacement therapy (9.5%) when frozen-thawed embryos were replaced.

If artificial, programmed cycles are used, the addition of prior GnRH analogue suppression is not necessary. One study[943] compared the outcome of frozen-thawed embryo transfer cycles using micronised 17 beta-oestradiol and micronised vaginal progesterone preparations with and without the concomitant use of a GnRH analogue. One hundred and six women were randomly divided into two groups of 53. The two groups did not differ in age, number of embryos transferred per patient, day of progesterone initiation or endometrial thickness on day of progesterone initiation. None of the women had any follicular development and only one cycle in the non GnRH analogue group had to be cancelled because of premature progesterone secretion. The pregnancy rate per embryo transfer was comparable in both groups (GnRHa used: 26.4%, no GnRHa: 21.1%).

Three other non-randomised studies also suggested that the use of a GnRH agonist was not necessary for artificial replacement cycles. A prospective case series[944] of 91 women using oestradiol valerate and progesterone administered vaginally resulted in 57 embryo transfer cycles. Three cycles were cancelled because of an elevated progesterone level and in 31 cycles no embryo survived thawing. One hundred and sixteen embryos were transferred in the 57 cycles and 10 pregnancies (17.5%) with 5 (8.8%) live births resulted. A retrospective study[945] analysed pregnancy outcomes after 366 consecutive frozen

embryo transfers in one of three types of artificial replacement cycle: the first group used GnRHa and transdermal oestradiol patches; the second group used GnRHa and oral micronised oestradiol; and the third group used oral micronised oestradiol only. The clinical pregnancy rates were not different between the three regimens (13.7% with GnRHa and transdermal oestradiol patches vs 11.4% with GnRHa and oral micronised oestradiol vs 13.5% with oral micronised oestradiol only). Another retrospective analysis of 199 artificial cycles without initial GnRHa suppression using transdermal oestradiol and intramuscular progesterone[946] also found that GnRHa suppression was not necessary in order to achieve an acceptable pregnancy rate of 29.2 % with an ongoing pregnancy or delivery rate of 16.1%.

A matched follow-up study[947] of 122 cycles of cryopreserved embryo transfer showed that parenteral or sublingual progesterone administration were equally effective in preparing the endometrium for implantation of cryopreserved embryos.

Recommendation:

In women who have regular ovulatory cycles, the likelihood of live birth after replacement of frozen-thawed embryos is similar whether natural or artificial replacement cycles are used. [B]

Chapter 20 Follow-up of children born as a result of assisted reproduction

Genetic risks and congenital malformations

The ability of assisted reproduction to circumvent natural barriers to conception has led to concerns about the safety of ICSI and IVF, including their potential to transmit genetic aberrations to the next generation and the long-term consequences on later development of children born after IVF/ICSI. To date, there have been no adequate prospective RCTs of sufficient power to assess the efficacy and safety of assisted reproduction.

A 1995 world report showed that each year more than 40,000 babies were born worldwide after IVF treatment.[948] A study published in 1997 reported that more than 150,000 children had been born worldwide through IVF,[949] and another study published in 2000 reported that more than 20,000 had been born following the use of ICSI.[950]

A systematic review of available literature found 30 cohort and case series studies reporting the outcome of ICSI pregnancies on five clinical outcomes:

- congenital malformations;
- growth disturbances;
- neurological development disturbances;
- chromosomal abnormalities; and
- transmission of sub-fertility to male offspring.

Overall there was no increased risk of major birth defects including chromosomal abnormalities (OR 1.13, 95% CI 1.00 to 1.29, p=0.06) in offspring resulting from treatment of severe male infertility with ICSI. Available data do not indicate increased risk of any

particular malformation. Whether ICSI treatment of infertile couples with normal karyotypes increases the occurrence of chromosomal abnormalities in the offspring is currently not clarified. Sons of infertile males with Y chromosome microdeletions will inherit the same abnormality and are therefore probably infertile. Males with no known genetic cause for severely compromised sperm quality may also father sons with Y chromosome microdeletions. Theoretical models indicate that ICSI will not result in any substantial increase in male infertility. ICSI offspring do not seem to have any increase in neurological or psychomotor disabilities compared with offspring conceived by standard IVF treatment. Current data are inconclusive regarding pre- or postnatal growth disturbances. It is not known whether the ICSI method per se, or factors related to the infertile couples, increase the risk of birth and other developmental defects.[951] [evidence level IIb–III]

Recently attention has focused on reports of imprinting disorders, such as the Beckwith-Wiedermann syndrome. The reports on Beckwith-Wiedermann syndrome suggest a six-fold increase in risk against a background prevalence of around 1.3 per 100 000 new-born infants.{DeBaun et al. 2003; Maher et al. 2003} [evidence level ?]

Psychological and educational development

A case-control study found that developmental indices were positively correlated to gestational age, birth weight and head circumference at birth. IVF infants were within normal range of these indices and did not differ from their matched controls.[952] [evidence level III]

A cohort study found no significant difference at 3 years in psychomotor development of IVF children compared with children born after ovarian stimulation without IVF and children conceived naturally.[953] [evidence level IIb]

Another cohort study compared families with children conceived through assisted reproduction (including IVF treatment and donor insemination) with families with naturally conceived children.[954] [evidence level IIb] This study found that the quality of parenting in

families with children conceived through assisted reprodctuion was better than that shown by families with a naturally conceived child. However, no significant differences in children's emotions, behaviour or relationships with parents were found between the two groups.

A survey of 743 IVF children over the age of 4 years showed no significant increase in the rate of behavioural or psychological problems compared with a control group. Neither males nor females from multiple gestation pregnancies had a statistically increased incidence of problems compared with same sex singletons births among the IVF children, or compared with the control group.{Montgomery 1999} [evidence level III]

20.1 Risk of cancer

A cohort study found that cancer incidence at age 5 years among 2507 children born as a result of assisted reproduction undertaken between 1978 and 1991 did not differ significantly from that in the general population of the United Kingdom, with 2.0 cancers identified compared with 3.5 cancers expected (standardised incidence ratio 57, 95% CI 7 to 206). However this analysis lacked statistical power and a larger sample size would be required to detect a difference in the incidence of a rare condition like cancer. The mean follow-up time was 8.6 years.[955] [evidence level IIb]

A retrospective cohort study in Sweden found no increase in childhood cancer among 5586 IVF children when compared with babies born in the general population, with 4 children developing cancers compared with an expected number of 3.6. However, this study had limited power to compare cancer incidence.[956] [evidence level III]

Another retrospective study in Australia showed no significant increase of cancer in children conceived using IVF and related procedures, compared with a population-based cancer registry (6 observed cases vs 4.33 expected cases, standardised incidence ratio

1.39, 95% CI 0.62 to 3.09). The medium follow-up time was 3 years and 9 months.[957] [evidence level III]

A cohort study found no increased risk for childhood malignancies between children conceived by IVF or related techniques and children conceived naturally by mothers who were diagnosed with subfertility (16 observed cases in both groups vs 15.5 expected cases, standardised incidence ratio 1.0, 95%CI 0.6 to 1.7). A direct comparison between IVF children and non-IVF children showed a RR of 0.8 (95% CI 0.3 to 2.3). The average follow-up time was 6 years.[958] [evidence level IIb]

A recent report on childhood cancer from the Netherlands suggested an increased risk of childhood retinoblastoma.{Moll et al. 2003} [evidence level ?] This study reported a RR in the range 4.9-7.2 after assisted reproduction, against a background incidence of 2.6 cases per 100 000 children in the first year of life, and 0.9 per 100 000 in children aged 1-4 years.

Recommendation:
Couples contemplating assisted reproduction should be given up-to-date information about the health of resulting children. [C]

Research recommendation:

Long-term longitudinal follow-up of children resulting from assisted reproduction is important, and such follow-up should be co-ordinated on a national basis.

Appendix A Economic models

A.1 Aim of the economic models

The purpose of the economic modelling was to synthesise the estimates of the costs and clinical effectiveness of assisted reproduction for couples seeking treatment for fertility problems after initial investigation. The assisted reproduction techniques for which sufficient data were available to construct models were IVF alone and IVF with ICSI. The economic analysis focused on the effect of age on the cost-effectiveness of IVF and ICSI, and the cost-effectiveness of these treatments according to the number of previous unsuccessful cycles. Different scenarios were explored using sensitivity analysis since a published evidence reported a range of estimates for several important parameters.

A.2 Structure of the economic models

A.2.1 In vitro fertilisation treatment

Two separate models were constructed in order to estimate age-specific and cycle-specific costs per live birth. The models had to be structured differently because different forms of data were available in relation to age and number of cycles.

Age-specific model

The model based on age was structured so that couples were offered up to six fresh cycles of IVF treatment. This model was based on age-specific success rates obtained from the HFEA (see Tables 14.1 to 14.5). The lowest age used in the economic mode was 24 years because below this age there were fewer than 100 treatment cycles (see Table 14.1). For each unsuccessful fresh cycle, couples would be offered up to two attempts at frozen embryo transfer. It is assumed that, on average, one-third of couples whose fresh IVF treatment cycles are unsuccessful will have enough viable embryos for two attempts at frozen embryo transfer. This model also assumed that live birth rates were constant for

each treatment cycle. The structure of the model is presented in Figure A.1, which for the purposes of illustration shows only one of the six potential fresh cycles of IVF treatment. The potential outcomes of each (fresh or frozen) IVF cycle are: a live birth (in which case treatment ceases); an ectopic pregnancy; a miscarriage; or no pregnancy. The options for couples without a live birth are: to discontinue treatment; to attempt a frozen embryo transfer; or to proceed straight to the next fresh cycle of IVF treatment if there are no embryos suitable for frozen embryo transfer. The model assumed that no couples would choose to discontinue treatment until they has used up all embryos suitable for frozen embryo transfer.

The model also allowed for the possibility of OHSS, but it was assumed that having OHSS would not affect the outcome of IVF treatment. A detailed description of the clinical effectiveness data used in this model is presented in Table A.1. The discontinuation rates used in the model were estimated in studies based on experience in the independent sector, which may be higher than those that would occur if couples were not paying for treatment themselves.

There is very little robust clinical evidence to determine whether any long-term adverse outcomes are associated with IVF treatment, and so long-term consequences of treatment were not included in our models. Such consequences would include the potential costs to people with fertility problems in terms of psychological ill-health relating to waiting for treatment and the stress associated with assisted reproduction, irrespective of the outcome of treatment.

Figure A.1 Structure of the in vitro fertilisation treatment model for deriving age-specific cost per live birth [included as a separate file]

Table A.1 Clinical effectiveness data used in the in vitro fertilisation treatment model for deriving age-specific cost per live birth

Outcome	Cycle	Rate (%)	Source
Live birth	All fresh cycles	Age-specific rates used	HFEA data 1995–99 (see Table 14.1)

	All frozen cycles	Age-specific rates used	HFEA data 1995–99 (see Table 14.2)
Ectopic pregnancy	All cycles	Age-specific rates used	HFEA data 1995–99 (see Table 14.4)
Miscarriage	All cycles	Age-specific rates used	HFEA data 1995–99 (see Table 14.5)
Discontinuation	All fresh cycles	40–50% including pregnancy 20% without pregnancy	FIVNAT 1998[619]
	All fresh cycles, under 30 years All fresh cycles, 38–40 years	17.7% 50.0%	Mardesic et al. 1984[620]
Ovarian hyperstimulation syndrome	All cycles	0.2–1.0%	Various[435-437]

Cycle-specific models

The models based on the number of cycles were structured so that couples were offered up to four fresh cycles of IVF treatment and no frozen embryo transfers. Two models were used because two data sets with different structures were available.

The first cycle-specific model was based on live birth rates by number of previous unsuccessful cycles obtained from the HFEA (see Table 14.6) This dataset included estimates for up to four fresh (not frozen) cycles of treatment (see Section 14.2). The dataset did not include miscarriage or ectopic pregnancy rates by number of previous unsuccessful cycles. However, overall miscarriage rates and ectopic pregnancy rates (irrespective of the number of previous treatment cycles) were available from the HFEA, and these were used in this model (see Tables 14.4 and 14,5, respectively). The structure of the model is presented in Figure A.2, which shows all four potential fresh cycles of IVF treatment. The potential outcomes of each IVF cycle are: a live birth (in which case treatment ceases); an ectopic pregnancy; a miscarriage; or no pregnancy. The options for couples without a live birth are: to discontinue treatment; or to proceed straight to the next fresh cycle of IVF treatment. A detailed description of the clinical effectiveness data used in this model is presented in Table A.2.

Figure A.2 Structure of the in vitro fertilisation treatment model for deriving cycle-specific cost per live birth [included as a separate file]

Table A.2 Clinical effectiveness data used in the first in vitro fertilisation treatment model for deriving cycle-specific cost per live birth

Outcome	Cycle	Rate (%)	Source
Live birth	Cycle 1 Cycle 2 Cycle 3 Cycle 4	18.2 17.2 18.8 19.4	HFEA data 1995–99 (see Table 14.6)
Ectopic pregnancy	All cycles	Overall rate (0.5%) used	HFEA data 1995–99 (see Table 14.4)
Miscarriage	All cycles	Overall rate (2.7%) used	HFEA data 1995–99 (see Table 14.5)
Discontinuation	All fresh cycles	40–50% including pregnancy 20% without pregnancy	FIVNAT 1998[619]
	All fresh cycles, under 30 years All fresh cycles, 38–40 years	17.7% 50.0%	Mardesic et al. 1984[620]

The second cycle-specific model was based on live birth rates by number of previous unsuccessful cycles obtained from the Oxford Fertility Unit (see Table 14.7) This dataset included estimates for up to three fresh (not frozen) cycles of treatment for two different age group (under 39 years vs 39 years and over; see Section 14.2). The dataset also included miscarriage rates, but not ectopic pregnancy rates. The possibility of ectopic pregnancy was, therefore, not included in this model. The structure of the model is similar to that presented in Figure A.2, except that only three fresh cycles of IVF treatment are modelled, and the possibility of ectopic pregnancy is not considered. A detailed description of the clinical effectiveness data used in this model is presented in Table A.3.

Table A.3 Clinical effectiveness data used in the second in vitro fertilisation treatment model for deriving cycle-specific cost per live birth

Outcome	Cycle	Rate (%)	Source
Live birth	Cycle 1 - under 39 years - 39 years and over Cycle 2 - under 39 years - 39 years and over Cycle 3 - under 39 years - 39 years and over	24.0 10.2 24.2 9.7 21.9 16.4*	Oxford Fertility Unit, 1995–2001 (see Table 14.7)
Miscarriage	Cycle 1 - under 39 years - 39 years and over Cycle 2 - under 39 years - 39 years and over Cycle 3 - under 39 years - 39 years and over	10.2 19.4 9.9 35.3 9.8 16.1	Oxford Fertility Unit, 1995–2001

Discontinuation	All fresh cycles	40–50% including pregnancy 20% without pregnancy	FIVNAT 1998[619]
	All fresh cycles, under 30 years All fresh cycles, 38–40 years	17.7% 50.0%	Mardesic et al. 1984[620]

* The live birth rate for women aged 39 years and over with two previous unsuccessful cycles is less reliable than the other rates because it is based on fewer cycles.

A.2.2 Intracytoplasmic sperm injection

We used one model to estimate the cost per live birth of IVF plus ICSI. This model had the same basic structure as the age-specific model for IVF treatment (that is, it included fresh and frozen treatment cycles; see Figure A.1). However, no data were available on the clinical effectiveness of ICSI, and so this model was based on overall (not age-specific) success rates for IVF treatment obtained from the HFEA (see Tables 14.1 to 14.5). A detailed description of the clinical effectiveness data used in this model is presented in Table A.4.

Table A.4 Clinical effectiveness data used in the intracytoplasmic sperm injection model for deriving overall cost per live birth

Outcome	Cycle	Rate (%)	Source
Live birth	All fresh cycles	Overall rate (17.6%) used	HFEA data 1995–99 (see Table 14.4)
	All frozen cycles	Overall rate (11.5%) used	HFEA data 1995–99 (see Table 14.2)
Ectopic pregnancy	All cycles	Overall rate (0.5%) used	HFEA data 1995–99 (see Table 14.4)
Miscarriage	All cycles	Overall rate (2.7%) used	HFEA data 1995–99 (see Table 14.5)
Discontinuation	All fresh cycles	40–50% including pregnancy 20% without pregnancy	FIVNAT 1998[619]
	All fresh cycles, under 30 years All fresh cycles, 38–40 years	17.7% 50.0%	Mardesic et al. 1984[620]
Ovarian hyperstimulation syndrome	All cycles	0.2–1.0%	Various[435-437]

A.3 Costs used in the economic models

Treatment costs were estimated using a variety of published and unpublished sources of data. Table A.5 summarises the cost data used in the model. NHS reference costs were used where no published research papers reporting specific costs could be identified. NHS reference costs are second best cost estimates since they show wide variation and are not derived from detailed bottom-up calculation of the true inputs into a service. The best cost data are derived from United Kingdom based economic evaluation studies that report resource use and unit costs as well as a cumulative mean cost estimates. Such data were not available for many of the estimates used in the model.

A range of estimates for the cost of an IVF cycle was obtained from different sources. A web-published review by the voluntary organisation, Fertility Confidential, reported in 2002 that the average charge for IVF treatment in the UK at the 71 fee-paying clinics was £1,737 per treatment cycle, with the lowest reported charge around £1000 and the highest around £2500. The HFEA reported on its website that the cost of an IVF cycle is around £1771 excluding drug costs. The HFEA also reported on its website that the cost of an ICSI cycle is £1936 (without drugs).

A United Kingdom study[959] reported the cost of a stimulated cycle of IVF to be around £4250 and a natural cycle to be around £898. An earlier study reported the cost per couple of IVF to range from £1786 to £5749, and a single cycle to cost £1100.[6] Another United Kingdom study undertaken earlier in the 1990s reported a cost of IVF to be £1005 for stimulated IVF.[572]

In our models we have explored the cost per live birth of IVF at the lower and higher ranges of cost estimates. We have also estimated the cost per live birth with and without the costs of IVF drugs since gonadotrophins can increase the cost per cycle by around £500-1000, depending on the drugs used. We used three costs in our models. The baseline cost was £2771 (£1771, which includes the costs associated with health services

use and counselling, plus £1000 for drugs); a lower value of £1771 (the cost without drugs); and a higher value of £3500 (£2500, which was the highest value reported in the Fertility Confidential survey, plus £1000 for drugs). The cost for an ICSI cycle in our model was £2936 (£1936, plus £1000 for drugs).

The costs of miscarriage and ectopic pregnancy after IVF treatment could not be estimated from the published literature, and so we used NHS reference costs relating to miscarriage and upper genital tract (intermediate procedures) for ectopic pregnancy.

A detailed description of the cost data used in this model is presented in Table A.5.

Table A.5 Cost data used in the in vitro fertilisation treatment models

Procedure/event	Baseline estimate	Source of data	Range of estimates found in published studies/other sources	Source of data
IVF without drugs per fresh cycle	£1771	HFEA Internet Site 2002	£1500-2500 £1786 (stimulated IVF) £1786-5749	Upper and lower limits of private clinic costs reported by Fertility Confidential Nargund et al, 2001[959] (UK) Phillips et al, 2000[6] (UK)
IVF per frozen cycle	£666	HFEA Internet Site 2002	£300-760	Private clinic costs published on the Internet 2003
IVF drugs per attempt: Urinary FSH HMG	Range £320-£490		Menogon £10.64 per 75 units 30 doses £319 35 doses £372 Menopur £14.75 per 75 units 30 doses £420 35 doses £490 Merional £13.95 per 75 units 30 doses £419 35 doses £488	BNF March, 2003[236]

Recombinant FSH	Range £790-£1100		Gonal –F £26.25 30 doses £788 35 doses £919 Puregon £20.00 30 doses £900 35 doses £1050	
Ovarian hyperstimulation syndrome	£800	Daya et al, 2001{?} (Canada)		
Frozen embryo transfer	£666	HFEA Internet Site 2002		
Cost of ICSI	£1936	HFEA Internet Site 2002	££2664-5278 £3121	Phillips et al 2000 (UK)[6] Granberg 1996[960] (Sweden)
Ectopic pregnancy	£769	NHS reference cost 2001		NHS reference cost for upper genital tract (intermediate procedures; nearest relevant cost)
Miscarriage	£233.64	NHS reference cost 2001		

A.4 Sensitivity analysis

Sensitivity analyses were undertaken to explore the effects on the total cost and cost per live birth of changing the following parameters in the models:

the cost (without drugs) per cycle of IVF/ICSI;

the number of couples who would choose to discontinue treatment rather than starting a new fresh cycle;

the rate of OHSS per fresh cycle of IVF/ICSI; and

the source of clinical effectiveness data (HFEA or Oxford Fertility Unit).

A.5 *Results*

A.5.1 In vitro fertilisation treatment

Age-specific model

Age-specific costs per live birth using the three cost estimates (baseline, lower and upper) for IVF treatment and an OHSS incidence rate of 0.2% are shown in Figure A.3. The figure shows that the costs per live birth are very similar for ages 24 years to 33 years, after which they rise steeply with increasing age. Detailed tables of costs for three specific ages (24 years, 35 years and 39 years) using the baseline cost of IVF treatment (£2771) are presented in Tables A.6, A.7 and A.8, respectively. The tables show that the costs per live birth were £11,917 at 24 years, £12,931 at 35 years, and £20,056 at 39 years. The total costs after three cycles of treatment based on 1000 couples at the start of treatment and using the baseline cost of IVF treatment and a discontinuation rate of 17.7% were £6.2 million in women aged 24 years, £6.3 million in women aged 35 years, and £6.8 million in women aged 39 years. The percentage of couples who achieved a live birth after three cycles of treatment were 52% at 24 years, 49% at 35 years, and 34% at 39 years.

The sensitivity analyses using lower and higher costs for IVF treatment (£1771 and £3500, respectively) resulted in costs per live birth of £8,103 and £14,697 at 24 years, £8,800 and £15,943 at 35 years, and £13,723 and £24,673 at 39 years. The sensitivity analyses using the baseline cost of IVF treatment and the higher discontinuation rate (50%) resulted in total costs after three cycles of IVF treatment based on 1000 couples at the start of treatment of £4.9 million for women aged 24 years, £5.0 million for women aged 35 years, and £5.3 million for women aged 39 years.

Cycle-specific models

Cycle-specific costs per live birth using the baseline cost estimate for IVF treatment and HFEA clinical effectiveness data are shown in Table A.9. The cost per live birth in the first cycle of IVF treatment was £15,281. The corresponding costs for the second, third and fourth cycles of IVF treatment were £16,169, £14,793, and £14,336. These costs reflect the varying live birth rates by number of previous unsuccessful IVF cycles (see Table 14.6). The total cost at the end of three cycles based on 1000 couples at the start of treatment was £5.9 million, with 38% of couples achieving a live birth.

The sensitivity analyses using the lower costs for IVF treatment (£1,771) resulted in costs per live birth of £9,787 for the first cycle, £10,356 for the second cycle, £9,474 for the third cycle, and £9,181 for the fourth cycle. The corresponding costs per live birth using the higher cost for IVF treatment (£3,500) were £19,287, £20,408, £18, 671 and £18,094. The sensitivity analyses using the baseline cost of IVF treatment and the higher discontinuation rate (50%) resulted in a total cost after three cycles of IVF treatment based on 1000 couples at the start of treatment of £4.4 million, with 28% of couples achieving a live birth.

Cycle-specific costs per live birth using the baseline cost estimate for IVF treatment and Oxford Fertility Unit clinical effectiveness data are shown in Tables A.10 (women aged less than 39 years) and A.11 (women aged 39 years and over). For women aged less than 39 years, the cost per live birth in the first cycle of IVF treatment was £11,694. The corresponding costs for the second and third cycles of IVF treatment were £11,548 and £12,758. For women aged 39 years and over, the costs per live birth were £27,611 for the first cycle of treatment, £28,938 for the second cycle of treatment, and £12,835 for the third cycle of IVF treatment. These costs reflect the varying live birth rates by number of previous unsuccessful IVF cycles (see Table 14.7), and the cost per live birth for the third cycle of treatment is not very reliable because of the small number of cycles on which the live birth rate was based. For women aged less than 39 years, the total cost at the end of three cycles based on 1000 couples at the start of treatment was £5.6 million, with 48% of couples achieving a live birth. For women aged 39 years and over, the total cost at the end of three cycles based on 1000 couples at the start of treatment was £6.4 million, with 29% of couples achieving a live birth. These costs are consistent with those obtained using the HFEA clinical effectiveness data, reflecting the differences in live birth rates according to the woman's age, rather than variations in live birth rates between clinics.

International comparison

The cost-effectiveness ratios (cost per live birth) presented here can be compared with cost-effectiveness ratios reported for other countries using RCT clinical effectiveness evidence. A recent review of this evidence shows far higher cost-effectiveness ratios (cost of IVF per delivery) in the United States (as might be expected), but similar results in

Scandinavian countries.{Granberg et al. 1998} The data reported below are for the year 1994.

Sweden	£10,295
Denmark	£11,858
Norway	£13,413
Finland	£11,211
Iceland	£7,400

A.5.2 Intracytoplasmic sperm injection

The cost per live birth for couples undergoing ICSI using the baseline cost of ICSI treatment (£2,936) and an OHSS incidence rate of 0.2% is presented in Table A.12. The table show that the cost per live birth was £14,029. The total cost after three cycles of ICSI treatment was £6.5 million, with 48% of couples achieving a live birth. At a lower cost per ICSI treatment (£1936, which excludes drugs) the cost per live birth was £9,056. The sensitivity analysis for exploring the effect of a higher OHSS incidence rate (1.0%) resulted in a cost per live birth of £14,029, which is almost the same as the cost per live birth at the lower rate.

Figure A.3 Age-specific cost per live birth using three cost estimates for a cycle of in vitro fertilisation treatment

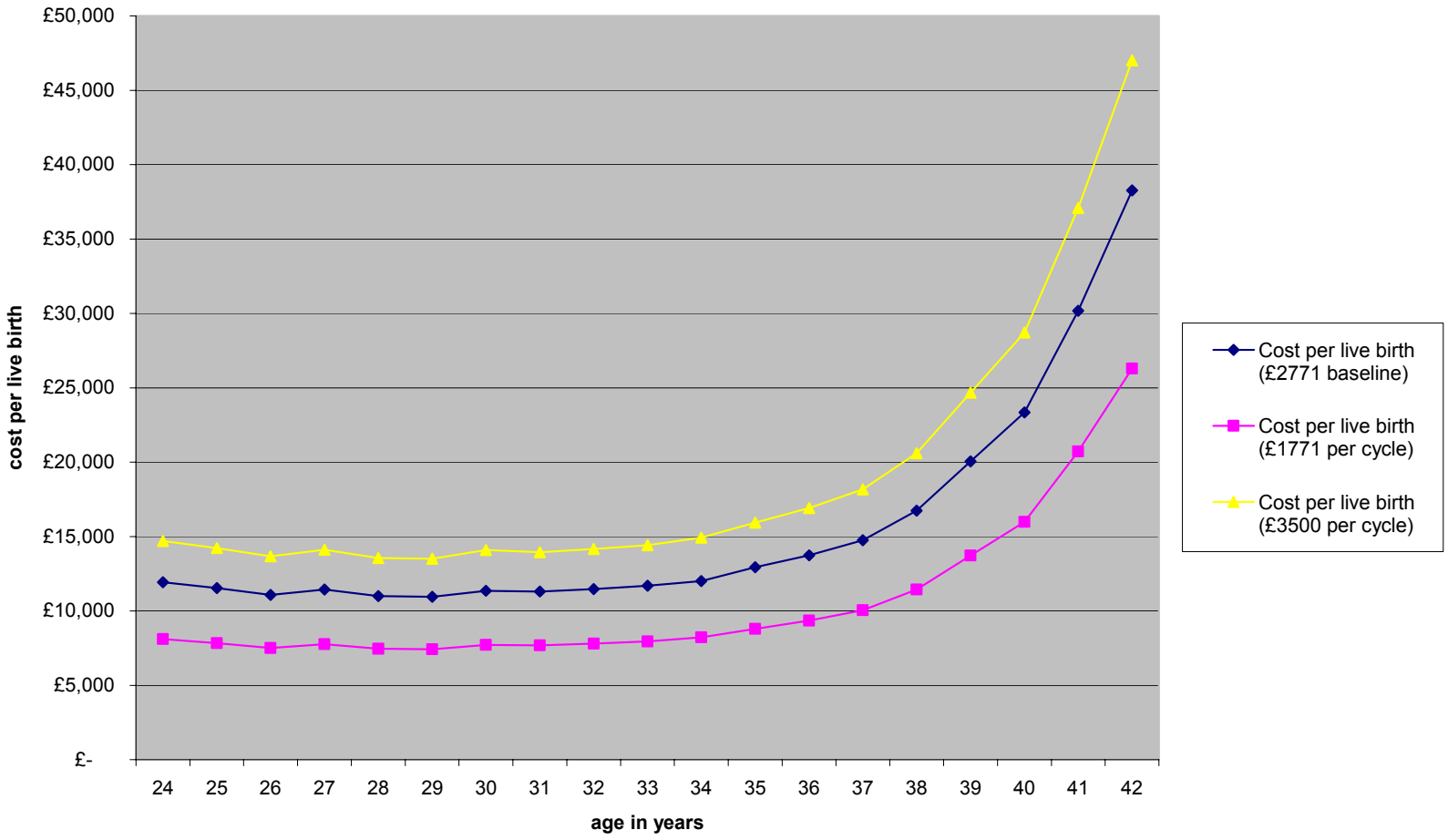

Table A.6 Cost per live birth for women aged 24 years using baseline cost for a cycle of in vitro fertilisation treatment

Age	**24 years**		**Live birth rate (fresh)**	**20.68%**		
Cost	**£2,771**		**Ectopic preg. rate**	**1.09%**		
Discontinuation Rate	**17.7%**		**Miscarriage rate**	**1.93%**		
OHSS rate	**0.2%**		**Live birth rate (frozen)**	**11.1%**		
	cycle 1	cycle 2	cycle 3	cycle 4	cycle 5	cycle 6
Cumulative No. Fresh Cycles	1000	1607	1976	2200	2336	2414
Cum. frozen ET	499	803	987	1099	1167	1208
Cum. Couples with baby	262	421	518	577	612	634
Difference	262	159	97	59	35	22
Cum. Ectopic	11	21	27	30	33	34
Cum. Miscarriage	29	47	57	64	68	70
Cum. OHSS	2.00	3.21	3.95	4.40	4.67	4.84
Discontinuation	131	79	48	29	18	61
Cum. Discontinuation	138	210	258	287	305	366
Total cost per cycle for 1000 couples	£ 3,108,098	£ 1,897,323	£ 1,152,053	£ 699,525	£ 424,937	£ 258,534
Cum. cost per cycle for 1000 couples	£ 3,108,098	£ 5,005,420	£ 6,157,473	£ 6,856,998	£ 7,281,935	£ 7,540,469
Cost per live birth	£ 11,917					
(all cycles)						

Table A.7 Cost per live birth for women aged 35 years using baseline cost for a cycle of in vitro fertilisation treatment

Age	**35 years**		**Live birth rate (fresh)**	**18.61%**		
Cost	**£2,771**		**Ectopic preg. rate**	**0.44%**		
Discontinuation Rate	**17.7%**		**Miscarriage rate**	**2.89%**		
OHSS rate	**0.2%**		**Live birth rate (frozen)**	**10.9%**		
	cycle 1	cycle 2	cycle 3	cycle 4	cycle 5	cycle 6
Cumulative No. Fresh Cycles	1000	1624	2013	2256	2407	2502
Cum. frozen ET	513	833	1033	1157	1236	1284
Cum. Couples with baby	242	393	487	546	582	605
Difference	242	151	94	59	36	23
Cum. Ectopic	4	9	11	13	14	14
Cum. Miscarriage	44	71	88	99	105	110
Cum. OHSS	2.00	3.25	4.03	4.51	4.81	5.0
Discontinuation	134	84	52	33	20	72
Cum. Discontinuation	138	218	270	303	323	395
Total cost per cycle for 1000 couples	£ 3,108,713	£ 1,952,383	£ 1,217,917	£ 759,750	£ 474,383	£ 297,152
Cum. Cost per cycle for 1000 couples	£ 3,108,713	£ 5,061,096	£ 6,279,013	£ 7,038,763	£ 7,513,146	£ 7,810,298
Cost per live birth	£ 12,931					
(all cycles)						
			Live birth	17.60%		

Table A.8 Cost per live birth for women aged 39 years using baseline cost for a cycle of in vitro fertilisation treatment

Age	**39 years**		**Live birth rate (fresh)**	**10.73%**		
Cost	**£2,771**		**Ectopic preg. rate**	**0.34%**		
Discontinuation Rate	**17.7%**		**Miscarriage rate**	**3.03%**		
OHSS rate	**0.2%**		**Live birth rate (frozen)**	**8.9%**		
	cycle 1	cycle 2	cycle 3	cycle 4	cycle 5	cycle 6
Cumulative No. Fresh Cycles	1000	1693	2173	2506	2737	2899
Cum. frozen ET	569	963	1236	1425	1559	1651
Cum. Couples with baby	158	267	343	396	430	455
Difference	158	109	76	53	34	26
Cum. Ectopic	3	7	10	11	13	14
Cum. Miscarriage	48	81	103	119	130	138
Cum. OHSS	2.00	3.39	4.35	5.01	5.47	5.80
Discontinuation	149	103	72	50	35	136
Cum. Discontinuation	138	252	324	374	408	545
Total cost per cycle for 1000 couples	£ 3,126,080	£ 2,194,692	£ 1,521,039	£ 1,054,161	£ 732,231	£ 512,101
Cum. cost per cycle for 1000 couples	£ 3,126,080	£ 5,320,772	£ 6,841,811	£ 7,895,972	£ 8,628,202	£ 9,140,303
Cost per live birth	**£ 20,056**					
(all cycles)						

Table A.9 Cost per live birth by cycle of in vitro fertilisation treatment using baseline cost estimate and Human Fertilisation and Embryology Authority clinical effectiveness rates

Human Fertilisation and Embryology Authority			cycle 1	cycle 2	cycle 3	cycle 4
No. cycles starting with 1000 couples			1000	673	459	307
No. births			182	116	86	59
No. ectopic pregnancies (0.5%)			5	3	2	2
No. miscarriages (2.7%)			27	18	12	8
No. couples discontinuing treatment			145	99	66	0
Discontinuation rate		17.7%				
Cumulative births			182	298	384	444
Cum. miscarriages			27	45	58	66
Cum. no. discontinuing			145	243	309	309
Cum. no. cycles			1000	1673	2132	2439
Cost per cycle	£ 2,771					
Cost of ectopic pregnancies	£ 769					
Cost of miscarriages	£ 234					
Total cost per cycle for 1000 couples			£ 2,781,153	£ 1,872,311	£ 1,275,875	£ 852,637
Mean cost per live brith			£ 15,281	£ 16,169	£ 14,793	£ 14,336
Cum. cost per cycle for 1000 couples			£ 2,781,153	£ 4,653,465	£ 5,929,340	£ 6,781,977
Cum. % couples with a baby			18%	30%	38%	44%

Table A.10 Cost per live birth by cycle of in vitro fertilisation treatment for women aged less than 39 years using baseline cost estimate and Oxford Fertility Unit clinical effectiveness rates

Oxford Fertility Unit				
Less than 39 years		cycle 1	cycle 2	cycle 3
No. cycles starting with 1000 couples		1000	626	391
No. births		239	152	86
No. miscarriages		102	62	38
No. of couples discontinuing treatment		135	84	n/a
Discontinuation rate	17.7%			
Cumulative births		239	391	476
Cum. miscarriages		102	164	202
Cum. no. discontinuing		135	219	n/a
Cum. no. cycles		1000	1626	2017
Cost per cycle	£ 2,771			
Cost of miscarriages	£ 234			
Total cost per cycle for 1000 couples		£ 2,794,831	£ 1,750,305	£ 1,091,601
Mean cost per live birth		£ 11,694	£ 11,548	£ 12,758
Cum. cost per cycle for 1000 couples		£ 2,794,831	£ 4,545,136	£ 5,636,737
Cum. % couples with a baby		23.9%	39.1%	47.6%

Table A.11 Cost per live birth by cycle of in vitro fertilisation treatment for women aged 39 years and over using baseline cost estimate and Oxford Fertility Unit clinical effectiveness rates

Oxford Fertility Unit				
39 years and over		cycle 1	cycle 2	cycle 3
No. cycles starting with 1000 couples		1000	739	549
No. births		102	72	120
No. miscarriages		194	261	88
No. of couples discontinuing treatment		159	0	n/a
Discontinuation rate	18%			
Cumulative births		102	174	294
Cum. miscarriages		194	455	543
Cum. no. discontinuing		159	159	n/a
Cum. no. cycles		1000	1739	2288
Cost per cycle	£ 2,771			
Cost of miscarriages	£ 234			
Total cost per cycle for 1000 couples		£ 2,816,326	£ 2,074,529	£ 1,542,610
Mean cost per llive birth		£ 27,611	£ 28,938	£ 12,825
Cum. cost per cycle for 1000 couples		£ 2,816,326	£ 4,890,855	£ 6,433,465
Cum. % couples with a baby		10.2%	17.4%	29.4%

Table A.12 Cost per live birth using baseline cost for intracytoplasmic sperm injection

All ages			**Live birth (fresh)**	**17.60%**		
Cost	**£ 2,936**		**Ectopic preg. rate**	**0.50%**		
Discontinuation Rate	**17.7%**		**Miscarriage rate**	**2.70%**		
OHSS rate	**0.2%**		**Live birth rate (frozen)**	**11.5%**		
	cycle 1	cycle 2	cycle 3	cycle 4	cycle 5	cycle 6
Cumulative No. Fresh Cycles	1000	1629	2025	2274	2431	2530
Cum frozen ET	518	843	1048	1177	1260	1311
Cum. Couples with baby	236	384	477	536	572	595
Difference	236	148	93	59	36	23
Cum. Ectopic	5	10	13	15	16	17
Cum. Miscarriage	41	67	83	93	100	104
Cum. OHSS	2.00	3.26	4.05	4.55	4.86	5.06
Discontinuation	135	85	54	34	21	76
Cum. Discontinuation rate	138	220	274	308	329	405
Total cost per cycle for 1000 couples	£ 3,136,015	£ 2,074,920	£ 1,305,436	£ 821,315	£ 517,516	£ 327,892
Cum. cost per cycle for 1000 couples	£ 3,136,015	£ 5,210,935	£ 6,516,371	£ 7,337,686	£ 7,855,202	£ 8,183,093
Cost per live birth	**£ 14,002**					
(all cycles)						