



# **Fertility**

assessment and  
treatment for people  
with fertility problems

**Clinical Guideline**  
February 2004

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# Fertility: assessment and treatment for people with fertility problems

National Collaborating Centre for Women's and Children's Health

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## Stakeholder organisations

ACeBabes  
Airedale Primary Care Trust

Association of British Health-Care Industries  
Association of Clinical Biochemists, The  
Association of Clinical Embryologists  
Association of the British Pharmaceuticals Industry  
British Andrology Society  
British Association of Art Therapists  
British Association of Perinatal Medicine  
British Dietetic Association  
British Fertility Society  
British In Vitro Diagnostics Association  
British Infertility Counselling Association  
British Medical Association  
British National Formulary  
British Psychological Society, The  
British Society for Paediatric Endocrinology and Diabetes  
BUPA  
CancerBACUP  
CARE  
CHILD, The National Infertility Support Network  
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Department of Health  
Faculty of Family Planning and Reproductive Health Care  
Faculty of Public Health  
Family Planning Association  
Ferring Pharmaceuticals Limited  
Fertility Friends  
Fertility Research Organising Group  
Fertility Working Party - Northern Region  
Fibroid Network Charity  
General Medical Council  
Human Fertilisation and Embryology Authority  
Independent Healthcare Association  
Infertility Network  
ISSUE: The National Fertility Association  
Long Term Medical Conditions Alliance  
Medicines and Healthcare Products Regulatory Agency  
NANCSH  
National Council for Disabled People, Black, Minority and Ethnic Community  
National Infertility Awareness Campaign  
National Public Health Service  
NHS Information Authority (PHSMI Programme)  
NHS Quality Improvement Scotland  
North Bristol NHS Trust  
North Tees and Hartlepool NHS Trust  
Organon Laboratories Limited  
Patient Involvement Unit for NICE  
Plymouth Hospitals NHS Trust  
Portex Ltd/Wallace IVF  
Prodigy  
Royal College of Anaesthetists  
Royal College of General Practitioners  
Royal College of General Practitioners Wales  
Royal College of Midwives  
Royal College of Nursing  
Royal College of Obstetricians and Gynaecologists  
Royal College of Paediatrics and Child Health

Royal College of Pathologists  
Royal College of Psychiatrists  
Royal Pharmaceutical Society of Great Britain  
Schering Health Care Ltd  
Scottish Intercollegiate Guidelines Network  
Serono Pharmaceuticals Ltd  
Sheffield Teaching Hospitals NHS Trust  
Society and College of Radiographers  
Society for Endocrinology  
The Daisy Network  
The Royal Society of Medicine  
The Survivors Trust  
UK Coalition of People Living with HIV & AIDS  
UK Pain Society  
UK Thalassaemia Society  
United Kingdom Association of Sonographers  
Welsh Assembly Government (formerly National Assembly for Wales)

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# Abbreviations

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AID	artificial insemination of donor
AIH	artificial insemination of husband's sperm
BMI	body mass index
BNF	British National Formulary
CBAVD	congenital bilateral absence of vas deferens
CC	clomiphene citrate
CI	confidence interval
COH	controlled ovarian hyperstimulation
DH	Department of Health
DNA	deoxyribonucleic acid
EIA	enzyme immunoassay
ELISA	enzyme-linked immunosorbent assay
ESHRE	European Society for Human Reproduction and Embryology
ERHCGSG	European Recombinant Human Chorionic Gonadotrophin Study Group
ET	embryo transfer
EUROCAT	European Registry of Congenital Anomalies and Twins
FAST	fallopian sperm transfer system
FCU	first-catch urine
FSH	follicle-stimulating hormone
FSP	fallopian tube sperm perfusion
GIFT	gamete intrafallopian transfer
GnRH	gonadotrophin-releasing hormone
GnRHa	gonadotrophin-releasing hormone agonist
GP	general practitioner
GRP	Guideline Review Panel
HFEA	Human Fertilisation and Embryology Authority
HIV	human immunodeficiency virus
hCG	human chorionic gonadotrophin
hMG	human menopausal gonadotrophin
HR	hazard ratio
HSG	hysterosalpingography
HyCoSy	hysterosalpingo-contrast-sonography
ICSI	intracytoplasmic sperm injection
IUI	intrauterine insemination
im	intramuscular
iv	intravenous
IVF	in vitro fertilisation
LCR	ligase chain reaction
LH	luteinising hormone
LSHTM	London School of Hygiene and Tropical Medicine
LUH	luteinised unruptured follicles
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
NPV	negative predictive value
NSAID	non steroidal anti-inflammatory drug
OHSS	ovarian hyperstimulation syndrome
OR	odds ratio
PCOS	polycystic ovary syndrome
PCR	polymerase chain reaction

PCT	primary care trust
PESA	percutaneous epididymal sperm aspiration
pGnRH	pulsatile gonadotrophin-releasing hormone
PPV	positive predictive value
PROST	pronucleate stage tubal transfer
QALY	quality-adjusted life year
RCOG	Royal College of Obstetricians and Gynaecologists
RCT	randomised controlled (clinical) trial
RD	risk difference
rhCG	recombinant human chorionic gonadotrophin
rFSH	recombinant follicle-stimulating hormone
RR	relative risk (or risk ratio)
sc	subcutaneous
SEM	standard error of the mean
SUZI	subzonal sperm injection
TEFNA	testicular fine needle aspiration
TESA	testicular sperm aspiration
TESE	testicular sperm extraction
uhCG	urinary human chorionic gonadotrophin
uFSH	urinary follicle-stimulating hormone
WHO	World Health Organization
ZIFT	zygote intrafallopian transfer

# Glossary of terms

---

<b>Assisted reproduction</b>	The collective name for treatments designed to lead to conception by means other than sexual intercourse. Assisted reproduction techniques include intrauterine insemination, in vitro fertilisation, intracytoplasmic sperm injection and donor insemination.
<b>Bias</b>	Influences on a study that can lead to invalid conclusions about a treatment or intervention. Bias in research can make a treatment look better or worse than it really is. Bias can even make it look as if the treatment works when it actually does not. Bias can occur by chance or as a result of systematic errors in the design and execution of a study. Bias can occur at different stages in the research process, e.g. in the collection, analysis, interpretation, publication or review of research data.
<b>Blinding or masking</b>	The practice of keeping the investigators or subjects of a study ignorant of the group to which a subject has been assigned. For example, a clinical trial in which the participating patients or their doctors are unaware of whether they (the patients) are taking the experimental drug or a placebo (dummy treatment). The purpose of 'blinding' or 'masking' is to protect against bias. See also Double-blind study.
<b>Case-control study</b>	A study that starts with the identification of a group of individuals sharing the same characteristics (e.g. people with a particular disease) and a suitable comparison (control) group (e.g. people without the disease). All subjects are then assessed with respect to things that happened to them in the past, e.g. things that might be related to getting the disease under investigation. Such studies are also called retrospective, as they look back in time from the outcome to the possible causes.
<b>Case report (or case study)</b>	Detailed report on one patient (or case), usually covering the course of that person's disease and their response to treatment.
<b>Case series</b>	Description of several cases of a given disease, usually covering the course of the disease and the response to treatment. There is no comparison (control) group of patients.
<b>Clinical trial</b>	A research study conducted with patients which tests out a drug or other intervention to assess its effectiveness and safety. Each trial is designed to answer scientific questions and to find better ways to treat individuals with a specific disease. This general term encompasses controlled clinical trials and randomised controlled trials.
<b>Cohort</b>	A group of people sharing some common characteristic (e.g. patients with the same disease), followed up in a research study for a specified period of time.
<b>Cohort study</b>	An observational study that takes a group (cohort) of patients and follows their progress over time in order to measure outcomes such as disease or mortality rates and make comparisons according to the treatments or interventions that patients received. Thus within the study group, subgroups of patients are identified (from information collected about patients) and these groups are compared with respect to outcome, e.g. comparing mortality between one group that received a specific treatment and one group which did not (or between two groups that received different levels of treatment). Cohorts can be assembled in the present and

followed into the future (a 'concurrent' or 'prospective' cohort study) or identified from past records and followed forward from that time up to the present (a 'historical' or 'retrospective' cohort study). Because patients are not randomly allocated to subgroups, these subgroups may be quite different in their characteristics and some adjustment must be made when analysing the results to ensure that the comparison between groups is as fair as possible.

**Confidence interval**

A way of expressing certainty about the findings from a study or group of studies, using statistical techniques. A confidence interval describes a range of possible effects (of a treatment or intervention) that is consistent with the results of a study or group of studies. A wide confidence interval indicates a lack of certainty or precision about the true size of the clinical effect and is seen in studies with too few patients. Where confidence intervals are narrow they indicate more precise estimates of effects and a larger sample of patients studied. It is usual to interpret a '95%' confidence interval as the range of effects within which we are 95% confident that the true effect lies.

**Control group**

A group of patients recruited into a study that receives no treatment, a treatment of known effect, or a placebo (dummy treatment), in order to provide a comparison for a group receiving an experimental treatment, such as a new drug.

**Controlled clinical trial (CCT)**

A study testing a specific drug or other treatment involving two (or more) groups of patients with the same disease. One (the experimental group) receives the treatment that is being tested, and the other (the comparison or control group) receives an alternative treatment, a placebo (dummy treatment) or no treatment. The two groups are followed up to compare differences in outcomes to see how effective the experimental treatment was. A CCT where patients are randomly allocated to treatment and comparison groups is called a randomised controlled trial.

**Cost benefit analysis**

A type of economic evaluation where both costs and benefits of healthcare treatment are measured in the same monetary units. If benefits exceed costs, the evaluation would recommend providing the treatment.

**Cost effectiveness**

A type of economic evaluation that assesses the additional costs and benefits of doing something different. In cost effectiveness analysis, the costs and benefits of different treatments are compared. When a new treatment is compared with current care, its additional costs divided by its additional benefits is called the cost effectiveness ratio. Benefits are measured in natural units, for example, cost per additional heart attack prevented.

**Cost utility analysis**

A special form of cost effectiveness analysis where benefit is measured in quality adjusted life years. A treatment is assessed in terms of its ability to extend or improve the quality of life.

**Crossover study design**

A study comparing two or more interventions in which the participants, upon completion of the course of one treatment, are switched to another. For example, for a comparison of treatments A and B, half the participants are randomly allocated to receive them in the order A, B and half to receive them in the order B, A. A problem with this study design is that the effects of the first treatment may carry over into the period when the second is given. Therefore a crossover study should include an adequate 'wash-out' period, which means allowing sufficient time between stopping one treatment and starting another so that the first treatment has time to wash out of the patient's system.

**Cross-sectional study**

The observation of a defined set of people at a single point in time or time period – a snapshot. (This type of study contrasts with a longitudinal study, which follows a set of people over a period of time.)

<b>Cryopreservation</b>	The freezing and storage of eggs, sperm and/or embryos that may be thawed for use in future in vitro fertilisation treatment cycles.
<b>Donor insemination</b>	The placement of donor sperm into the vagina, cervix or womb.
<b>Double blind study</b>	A study in which neither the subject (patient) nor the observer (investigator or clinician) is aware of which treatment or intervention the subject is receiving. The purpose of blinding is to protect against bias.
<b>Evidence based</b>	The process of systematically finding, appraising, and using research findings as the basis for clinical decisions.
<b>Evidence-based clinical practice</b>	Evidence-based clinical practice involves making decisions about the care of individual patients based on the best research evidence available rather than basing decisions on personal opinions or common practice (which may not always be evidence based). Evidence-based clinical practice therefore involves integrating individual clinical expertise and patient preferences with the best available evidence from research.
<b>Evidence table</b>	A table summarising the results of a collection of studies which, taken together, represent the evidence supporting a particular recommendation or series of recommendations in a guideline.
<b>Exclusion criteria</b>	see <b>Selection criteria</b> .
<b>Experimental study</b>	A research study designed to test whether a treatment or intervention has an effect on the course or outcome of a condition or disease, where the conditions of testing are to some extent under the control of the investigator. Controlled clinical trial and randomised controlled trial are examples of experimental studies.
<b>Gamete intrafallopian transfer</b>	A procedure in which eggs are retrieved from a woman, mixed with sperm and immediately replaced in one or other of the woman's fallopian tubes so that they fertilise inside the body.
<b>Gold standard</b>	A method, procedure or measurement that is widely accepted as being the best available.
<b>Gonadotrophins</b>	Hormones that stimulate the ovaries.
<b>Health economics</b>	A field of conventional economics that examines the benefits of healthcare interventions (e.g. medicines) compared with their financial costs.
<b>Heterogeneity</b>	Or lack of homogeneity. The term is used in meta-analyses and systematic reviews when the results or estimates of effects of treatment from separate studies seem to be very different, in terms of the size of treatment effects, or even to the extent that some indicate beneficial and others suggest adverse treatment effects. Such results may occur as a result of differences between studies in terms of the patient populations, outcome measures, definition of variables or duration of follow up.
<b>Homogeneity</b>	This means that the results of studies included in a systematic review or meta-analysis are similar and there is no evidence of heterogeneity. Results are usually regarded as homogeneous when differences between studies could reasonably be expected to occur by chance.
<b>Inclusion criteria</b>	see <b>Selection criteria</b> .
<b>Intervention</b>	Healthcare action intended to benefit the patient, e.g. drug treatment, surgical procedure, psychological therapy.
<b>Intracytoplasmic sperm injection</b>	A variation of in vitro fertilisation in which a single sperm is injected into the inner cellular structure of an egg.
<b>Intrauterine insemination</b>	Placement of sperm into the uterus of a woman.

<b>In vitro fertilisation</b>	A technique whereby eggs are collected from a woman and fertilised with a man's sperm outside the body. Usually, one or two resulting embryos are then transferred to the womb with the aim of starting a pregnancy.
<b>Longitudinal study</b>	A study of the same group of people at more than one point in time. (This type of study contrasts with a cross-sectional study, which observes a defined set of people at a single point in time.)
<b>Masking</b>	see <b>Blinding</b> .
<b>Meta-analysis</b>	Results from a collection of independent studies (investigating the same treatment) are pooled, using statistical techniques to synthesise their findings into a single estimate of a treatment effect. Where studies are not compatible e.g. because of differences in the study populations or in the outcomes measured, it may be inappropriate or even misleading to statistically pool results in this way. See also <b>Systematic review</b> and <b>Heterogeneity</b> .
<b>Non-experimental study</b>	A study based on subjects selected on the basis of their availability, with no attempt having been made to avoid problems of bias.
<b>Nulliparous</b>	Having never given birth to a viable infant.
<b>Number needed to treat (NNT)</b>	This measures the impact of a treatment or intervention. It states how many patients need to be treated with the treatment in question in order to prevent an event that would otherwise occur; e.g. if the NNT = 4, then four patients would have to be treated to prevent one bad outcome. The closer the NNT is to one, the better the treatment is. Analogous to the NNT is the number needed to harm (NNH), which is the number of patients that would need to receive a treatment to cause one additional adverse event. e.g. if the NNH = 4, then four patients would have to be treated for one bad outcome to occur.
<b>Observational study</b>	In research about diseases or treatments, this refers to a study in which nature is allowed to take its course. Changes or differences in one characteristic (e.g. whether or not people received a specific treatment or intervention) are studied in relation to changes or differences in other(s) (e.g. whether or not they died), without the intervention of the investigator. There is a greater risk of selection bias than in experimental studies.
<b>Odds ratio</b>	Odds are a way of representing probability, especially familiar for betting. In recent years odds ratios have become widely used in reports of clinical studies. They provide an estimate (usually with a confidence interval) for the effect of a treatment. Odds are used to convey the idea of 'risk' and an odds ratio of one between two treatment groups would imply that the risks of an adverse outcome were the same in each group. For rare events the odds ratio and the relative risk (which uses actual risks and not odds) will be very similar. See also <b>Relative risk</b> , <b>Risk ratio</b> .
<b>Oocyte donation</b>	The process by which a fertile woman donates her eggs to be used in the treatment of others or for research.
<b>Ovarian hyperstimulation syndrome</b>	A serious complication following stimulation of the ovaries with gonadotrophin drugs.
<b>Parous</b>	Having borne at least one viable offspring.
<b>Peer review</b>	Review of a study, service or recommendations by those with similar interests and expertise to the people who produced the study findings or recommendations. Peer reviewers can include professional, patient and carer representatives.
<b>Pilot study</b>	A small-scale 'test' of the research instrument. For example, testing out (piloting) a new questionnaire with people who are similar to the population of the study, in order to highlight any problems or areas of concern, which can then be addressed before the full-scale study begins.

<b>Placebo</b>	Placebos are fake or inactive treatments received by participants allocated to the control group in a clinical trial, which are indistinguishable from the active treatments being given in the experimental group. They are used so that participants are ignorant of their treatment allocation in order to be able to quantify the effect of the experimental treatment over and above any placebo effect due to receiving care or attention.
<b>Placebo effect</b>	A beneficial (or adverse) effect produced by a placebo and not due to any property of the placebo itself.
<b>Power</b>	see <b>Statistical power</b> .
<b>Prospective study</b>	A study in which people are entered into the research and then followed up over a period of time with future events recorded as they happen. This contrasts with studies that are retrospective.
<b>p value</b>	If a study is done to compare two treatments then the p value is the probability of obtaining the results of that study, or something more extreme, if there really was no difference between treatments. (The assumption that there really is no difference between treatments is called the 'null hypothesis'.) Suppose the p value was 0.03. What this means is that, if there really were no difference between treatments, there would only be a 3% chance of getting the kind of results obtained. Since this chance seems quite low we should question the validity of the assumption that there really is no difference between treatments. We would conclude that there probably is a difference between treatments. By convention, where the value of p is below 0.05 (i.e. less than 5%) the result is seen as statistically significant. Where the value of p is 0.001 or less, the result is seen as highly significant. p values just tell us whether an effect can be regarded as statistically significant or not. In no way do they relate to how big the effect might be, for which we need the confidence interval.
<b>Qualitative research</b>	Qualitative research is used to explore and understand people's beliefs, experiences, attitudes, behaviour and interactions. It generates non-numerical data, e.g. a patient's description of their pain rather than a measure of pain. In health care, qualitative techniques have been commonly used in research documenting the experience of chronic illness and in studies about the functioning of organisations. Qualitative research techniques such as focus groups and in-depth interviews have been used in one-off projects commissioned by guideline development groups to find out more about the views and experiences of patients and carers.
<b>Quantitative research</b>	Research that generates numerical data or data that can be converted into numbers, for example clinical trials or the National Census, which counts people and households.
<b>Random allocation or randomisation</b>	A method that uses the play of chance to assign participants to comparison groups in a research study, for example, by using a random numbers table or a computer-generated random sequence. Random allocation implies that each individual (or each unit in the case of cluster randomisation) being entered into a study has the same chance of receiving each of the possible interventions.
<b>Randomised controlled trial</b>	A study to test a specific drug or other treatment in which people are randomly assigned to two (or more) groups: one (the experimental group) receiving the treatment that is being tested, and the other (the comparison or control group) receiving an alternative treatment, a placebo (dummy treatment) or no treatment. The two groups are followed up to compare differences in outcomes to see how effective the experimental treatment was. (Through randomisation, the groups should be similar in all aspects apart from the treatment they receive during the study.)

<b>Relative risk</b>	A summary measure which represents the ratio of the risk of a given event or outcome (e.g. an adverse reaction to the drug being tested) in one group of subjects compared to another group. When the 'risk' of the event is the same in the two groups the relative risk is 1. In a study comparing two treatments, a relative risk of 2 would indicate that patients receiving one of the treatments had twice the risk of an undesirable outcome than those receiving the other treatment. Relative risk is sometimes used as a synonym for risk ratio.
<b>Reliability</b>	Reliability refers to a method of measurement that consistently gives the same results. For example, someone who has a high score on one occasion tends to have a high score if measured on another occasion very soon afterwards. With physical assessments it is possible for different clinicians to make independent assessments in quick succession and if their assessments tend to agree then the method of assessment is said to be reliable.
<b>Retrospective study</b>	A retrospective study deals with the present and past and does not involve studying future events. This contrasts with studies that are prospective.
<b>Risk ratio</b>	Ratio of the risk of an undesirable event or outcome occurring in a group of patients receiving experimental treatment compared with a comparison (control) group. The term relative risk is sometimes used as a synonym of risk ratio.
<b>Sample</b>	A part of the study's target population from which the subjects of the study will be recruited. If subjects are drawn in an unbiased way from a particular population, the results can be generalised from the sample to the population as a whole.
<b>Screening</b>	The presumptive identification of an unrecognised disease or defect by means of tests, examinations or other procedures that can be applied rapidly. Screening tests differentiate apparently well persons who may have a disease from those who probably have not. A screening test is not intended to be diagnostic but should be sufficiently sensitive and specific to reduce the proportion of false results, positive or negative, to acceptable levels. Persons with positive or suspicious findings must be referred to the appropriate healthcare provider for diagnosis and necessary treatment.
<b>Selection criteria</b>	Explicit standards used by guideline development groups to decide which studies should be included and excluded from consideration as potential sources of evidence.
<b>Sensitivity</b>	In diagnostic testing, this refers to the chance of having a positive test result given that you have the disease. 100% sensitivity means that all those with the disease will test positive, but this is not the same the other way around. A patient could have a positive test result but not have the disease – this is called a 'false positive'. The sensitivity of a test is also related to its 'negative predictive value' (true negatives) – a test with a sensitivity of 100% means that all those who get a negative test result do not have the disease. To fully judge the accuracy of a test, its specificity must also be considered.
<b>Specificity</b>	In diagnostic testing, this refers to the chance of having a negative test result given that you do not have the disease. 100% specificity means that all those without the disease will test negative, but this is not the same the other way around. A patient could have a negative test result yet still have the disease – this is called a 'false negative'. The specificity of a test is also related to its 'positive predictive value' (true positives) – a test with a specificity of 100% means that all those who get a positive test result definitely have the disease. To fully judge the accuracy of a test, its sensitivity must also be considered.
<b>Statistical power</b>	The ability of a study to demonstrate an association or causal relationship between two variables, given that an association exists. For example, 80%

power in a clinical trial means that the study has a 80% chance of ending up with a p value of less than 5% in a statistical test (i.e. a statistically significant treatment effect) if there really was an important difference (e.g. 10% versus 5% mortality) between treatments. If the statistical power of a study is low, the study results will be questionable (the study might have been too small to detect any differences). By convention, 80% is an acceptable level of power. *See also p value.*

**Systematic review**

A review in which evidence from scientific studies has been identified, appraised and synthesised in a methodical way according to predetermined criteria. May or may not include a meta-analysis.

**Validity**

Assessment of how well a tool or instrument measures what it is intended to measure.

**Variable**

A measurement that can vary within a study, e.g. the age of participants. Variability is present when differences can be seen between different people or within the same person over time, with respect to any characteristic or feature that can be assessed or measured.

**Zygote intrafallopian transfer**

A process in which eggs are fertilised outside the body and then transferred into the fallopian tubes.



# 1. Introduction

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## 1.1 Aim of the guideline

Clinical guidelines have been defined as ‘systematically developed statements that assist clinicians and patients in making decisions about appropriate treatment for specific conditions’.

The aim of this guideline is to offer best practice advice on the care of people in the reproductive age group who perceive that they have problems in conceiving. 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. This guideline is based on those RCOG guidelines and takes into account a new review of the research evidence; it also covers the diagnostic, medical and surgical management of people throughout all stages of their care in primary-, secondary- and tertiary-care settings.

Infertility can be primary, in couples who have never conceived, or secondary, in couples who have previously conceived. It is estimated that infertility affects one in seven couples in the UK. A typical primary care trust, health board or strategic health authority may therefore expect to see around 230 new consultant referrals (couples) per 250 000 head of population per year. 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 cause of infertility is not identified in 30% of couples. In a further 27% of couples the cause is attributed to ovulatory disorders; in 14% of couples tubal damage. A low sperm count or quality is thought to contribute to infertility in 19% of couples.<sup>1,2</sup> However, the presence of disorders in both the man and the woman has been reported to occur in about 39% of cases.<sup>3</sup> The guideline includes advice for couples with a known reason for their fertility problems; for example, prior treatment for cancer or human immunodeficiency virus (HIV).

National Health Service (NHS) funding for investigation of fertility problems is generally available but there is wide variation and often limited access to NHS-funded treatment, particularly assisted reproduction techniques. There are three main types of fertility treatment: medical treatment (such as 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; in vitro fertilisation (IVF);\* embryo transfer;\* intrauterine insemination (IUI); donor insemination;\* intracytoplasmic sperm injection (ICSI);\* gamete intrafallopian transfer (GIFT); zygote intrafallopian transfer (ZIFT); pronucleate stage tubal transfer (PROST);\* cryopreservation\* and other related procedures.<sup>4</sup> Those procedures which involve the handling of embryos or donated gametes (indicated by \* above) are regulated by the Human Fertilisation and Embryology Authority (HFEA). There is concern about the impact on health and health services resources of multiple births resulting from fertility treatment, particularly triplet births in England and Wales.

This guideline includes recommendations about the optimal age range for IVF treatment, the number of cycles of IVF treatment, and the number of embryos to be transferred in any one cycle of IVF treatment.

## 1.2 Areas outside the remit of the guideline

The guideline does not address primary prevention of fertility or the management of pregnancies resulting from fertility treatment (for example, the management of multiple births). It is also beyond the scope of this guideline to address the effective management and treatment of conditions or comorbidities that are not directly related to the treatment of subfertility, such as endometriosis or sexual dysfunction.

Infertility is defined as failure to conceive after frequent unprotected sexual intercourse for one to two years in couples in the reproductive age group. This guideline does not include the management of people who are outside this definition, such as the initial management of sexual dysfunction, couples who are using contraception (for example, where one partner has been sterilised), non-heterosexual couples or couples outside the reproductive age range. If the problem persists despite appropriate treatment then their management is within the remit of the guideline. Embryo donation and surrogacy are outside the remit.

The guideline does not include preimplantation genetic diagnosis.

The guideline does not address laboratory standards or service configuration that may impact on the quality of care. It also does not include assessment of social criteria that might be relevant to access for fertility services funded by the NHS for example whether there are any existing children in the family.

## 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, GPs, counsellors and nurses
- those with responsibilities for commissioning and planning fertility services in primary care trusts and Health Commission Wales
- couples seeking advice and treatment for possible infertility.

A version of this guideline for people with fertility problems, their families and the public is available, entitled *Assessment and treatment for people with fertility problems. Understanding NICE guidance – information for people with fertility problems, their partners, and the public* (reproduced in Appendix A). This version can be downloaded from the National Institute for Clinical Excellence (NICE) website ([www.nice.org.uk](http://www.nice.org.uk)) or ordered via the NHS Response Line (0870 1555 455; quote reference number N0466 for an English version and N0467 for an English and Welsh version).

## 1.4 Who has developed the guideline?

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

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

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

All Guideline Development Group 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 NICE.

## 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*, available from the NICE website ([www.nice.org.uk](http://www.nice.org.uk)).

### 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 3, 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 October 2003), EMBASE (Ovid version for the period between 1988 to October 2003), the Cumulative Index to Nursing and Allied Health Literature, the British Nursing Index and PsychInfo were also searched, as was the Database of Abstracts and Reviews of Effectiveness.

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

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

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

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

### Outcome measures

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

Primary outcomes considered in the guideline include:

- live birth
- patient satisfaction
- anxiety/depression
- multiple births
- fetal abnormalities
- ectopic pregnancy
- 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
- 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
- improved sexual function.

### Clinical effectiveness

For all subject areas, evidence from the study designs least subject to bias was included. Where possible, the highest levels of evidence were used, but all papers were reviewed using established guides.<sup>5-11</sup> Published systematic reviews or meta-analyses were used where available. For subject areas where neither was available, other appropriate experimental or observational studies were sought.

Identified articles were assessed methodologically and the best available evidence was used to form and support the recommendations. The highest level of evidence was selected for each clinical question. The retrieved evidence was graded according to the evidence-level structure shown in Table 1.1.

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

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

**Table 1.1** Hierarchy of evidence

Level	Evidence
1a	Systematic review and meta-analysis of randomised controlled trials
1b	At least one randomised controlled trial
2a	At least one well-designed controlled study without randomisation
2b	At least one other type of well-designed quasi-experimental study
3	Well-designed non-experimental descriptive studies, such as comparative studies, correlation studies or case studies
4	Expert committee reports or opinions and/or clinical experience of respected authorities

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

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

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

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

## 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 their cost effectiveness. The aim is to produce guidance that uses scarce health service resources efficiently, that is providing the best possible care within resource constraints.

### *Cost effectiveness of assisted reproduction*

The approach to presenting the economic evidence on assisted reproduction was to model the cost effectiveness of assisted reproduction under different assumptions and conditions. There were several reasons for adopting this approach. First, decision analysis is an important step towards understanding the cost effectiveness of different treatment pathways that a couple may be offered. Second, the approach allows for the synthesis of clinical effectiveness evidence, alongside the estimated costs of diagnosis and treatment and the consequences of treatment that relate to the 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.<sup>12,13</sup> The most recent review<sup>12</sup> identified 2547 studies. From these, 30 economic evaluations, 22 cost studies and five 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 of the systematic reviews reported high levels of variability in the costs of treatment, 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 women and their families) were incorporated.

The earlier review<sup>13</sup> was undertaken to complement the RCOG clinical guidelines for infertility services in the UK. A high proportion of studies were not relevant to the UK setting and did not reflect the true cost of treatment in the UK.<sup>13</sup>

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

Key topics for the economic analysis in the guideline were determined by the Guideline Development Group 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
- a review of the current literature on the cost impact of reducing the number of embryos transferred during IVF treatment.

### *Valuing the cost of assisted reproduction*

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

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

### *Representation of the consequences of assisted reproduction: quality-adjusted life years*

Ethical and moral arguments relating to the value of live births resulting from assisted reproduction are not addressed in the economic analysis because they go beyond the issues that can be addressed in a clinical guideline. The primary outcome considered in the economic models is a live birth and not a measure of life years. There is an important debate about whether the outputs of assisted reproduction can be incorporated into a measure that can be compared with other uses of the same resources. It is not logical to try to derive a quality-adjusted life-year (QALY) measure from live births arising from IVF. It has been argued that:<sup>14</sup>

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

Another review<sup>15</sup> stated that:

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

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

### *Forming and grading recommendations*

The Guideline Development Group 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 Group worked on an informal consensus basis. Formal consensus methods (the nominal group technique) were employed when required (e.g. grading recommendations and agreeing audit criteria).

**Table 1.2** Strength of evidence corresponding to each level of recommendation

Grade	Strength of evidence
A	Directly based on level 1 evidence
B	Directly based on level 2 evidence or extrapolated recommendation from level 1 evidence
C	Directly based on level 3 evidence or extrapolated recommendation from either level 1 or 2 evidence
D	Directly based on level 4 evidence or extrapolated recommendation from either level 1, 2 or 3 evidence
Good practice point (GPP)	The view of the Guideline Development Group
NICE Technology Appraisal	Recommendation taken from a NICE Technology Appraisal

The strength of evidence corresponding to each level of recommendation is shown in Table 1.2. The grading of recommendations follows that outlined in the Health Technology Assessment ‘How to develop cost conscious guidelines’.<sup>16</sup>

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

#### *External review*

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 drafts were reviewed by an independent Guideline Review Panel established by NICE and by the NICE Executive and the Patient Involvement Unit for NICE.

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

# 2. Summary of recommendations and practice algorithms

## 2.1 Summary of recommendations

### Chapter 3 Initial advice to people concerned about delays in conception

#### 3.1 Natural conception

People who are concerned about their fertility should be informed that about 84% of couples in the general population will conceive within 1 year if they do not use contraception and have regular sexual intercourse. Of those who do not conceive in the first year, about half will do so in the second year (cumulative pregnancy rate 92%).

D

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

C

#### 3.2 Frequency and timing of sexual intercourse

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

C

#### 3.3 Alcohol

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

D

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

GPP

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

B

#### 3.4 Smoking

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

B

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

A

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

B

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

#### 3.5 Caffeinated beverages

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

B

### 3.6 Body weight

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

B

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

B

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

A

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

C

Women who have a body mass index of less than 19 and who have irregular menstruation or are not menstruating should be advised that increasing body weight is likely to improve their chance of conception.

B

### 3.7 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-fitting underwear improves fertility.

B

### 3.8 Occupation

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

B

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

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

B

### 3.10 Complementary therapy

People who are concerned about their fertility should be informed that the effectiveness of complementary therapies for fertility problems has not been properly evaluated and that further research is needed before such interventions can be recommended.

GPP

### 3.11 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 0.4 mg per day. For women who have previously had an infant with a neural tube defect or who are receiving anti-epileptic medication, a higher dose of 5 mg per day is recommended.

A

### 3.12 Susceptibility to rubella

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

D

### 3.13 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 to women who are concerned about their fertility. Cervical screening should be offered in accordance with the national cervical screening programme guidance.

GPP

### 3.14 Defining infertility

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

D

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

GPP

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

GPP

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

GPP

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

GPP

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

GPP

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

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

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

C

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

GPP

#### 4.2 Psychological effects of fertility problems

Couples should be informed that stress in the male and/or female partner can affect the couple's relationship and is likely to reduce libido and frequency of intercourse which can contribute to fertility problems.

C

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

GPP

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

C

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

GPP

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

GPP

#### 4.3 Specialist and generalist care

People who experience fertility problems should be treated by a specialist team because this is likely to improve the effectiveness and efficiency of treatment and is known to improve patient satisfaction.

D

## Chapter 5 Investigation of fertility problems and management strategies

### 5.1 Semen analysis

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

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

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

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

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

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

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

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

### 5.2 Assessing ovulation

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

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

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

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

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

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

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

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

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C

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

C

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

B

### 5.3 Screening for *Chlamydia trachomatis*

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

B

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

C

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

GPP

### 5.4 Assessing tubal damage

Women who are not known to have comorbidities (such as pelvic inflammatory disease, previous ectopic pregnancy or endometriosis) should be offered hysterosalpingography (HSG) to screen for tubal occlusion because this is a reliable test for ruling out tubal occlusion, and it is less invasive and makes more efficient use of resources than laparoscopy.

B

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

A

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

B

### 5.5 Assessing uterine abnormalities

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

B

### 5.6 Postcoital testing of cervical mucus

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

A

## Chapter 6 Medical and surgical management of male factor fertility problems

### 6.1 Medical management

Men with hypogonadotrophic hypogonadism should be offered gonadotrophin drugs because these are effective in improving fertility.

B

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

A

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

A

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

A

### 6.2 Surgical management

Where appropriate expertise is available, men with obstructive azoospermia should be offered surgical correction of epididymal blockage because it is likely to restore

C

patency of the duct and improve fertility. Surgical correction should be considered as an alternative to surgical sperm recovery and in vitro fertilisation.

C

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

A

### 6.3 Management of ejaculatory failure

Treatment of ejaculatory failure can restore fertility without the need for invasive methods of sperm retrieval or the use of assisted reproduction procedures. However, further evaluation of different treatment options is needed.

C

## Chapter 7 Ovulation induction

### 7.1 Antioestrogens

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

A

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

B

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

A

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

GPP

### 7.2 Metformin

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

A

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

GPP

### 7.3 Ovarian drilling

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

A

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

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

A

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

A

### 7.5 Gonadotrophin use during in vitro fertilisation treatment

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

A

**7.6 Gonadotrophin-releasing hormone analogues in ovulation induction therapy**  
Women with polycystic ovary syndrome who are being treated with gonadotrophins should not be offered treatment with gonadotrophin-releasing hormone agonist concomitantly because it does not improve pregnancy rates, and it is associated with an increased risk of ovarian hyperstimulation.

A

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

A

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

A

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

A

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

B

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

A

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

A

**7.11 Monitoring ovulation induction during gonadotrophin therapy**  
Women who are offered ovulation induction with gonadotrophins should be informed about the risk of multiple pregnancy and ovarian hyperstimulation before starting treatment.

C

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

C

**7.12 Other risks and side effects associated with ovulation induction agents**  
Women who are offered ovulation induction should be informed that a possible association between ovulation induction therapy and ovarian cancer remains uncertain. Practitioners should confine the use of ovulation induction agents to the lowest effective dose and duration of use.

C

## Chapter 8 Tubal and uterine surgery

**8.1 Tubal microsurgery and laparoscopic tubal surgery**  
For women with mild tubal disease tubal surgery may be more effective than no treatment. In centres where appropriate expertise is available it may be considered as a treatment option.

D

**8.2 Tubal catheterisation or cannulation**

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

B

**8.3 Uterine surgery**

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

C

**Chapter 9 Medical and surgical management of endometriosis****9.1 Medical management (ovarian suppression)**

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

A

**9.2 Surgical ablation**

Women with minimal or mild endometriosis who undergo laparoscopy should be offered surgical ablation or resection of endometriosis plus laparoscopic adhesiolysis because this improves the chance of pregnancy.

A

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

A

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

B

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

A

**Chapter 10 Intrauterine insemination**

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

A

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

A

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

A

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

A

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

A

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

A

**Chapter 11 Factors affecting the outcome of in vitro fertilisation treatment****11.1 Surgery for hydrosalpinges before in vitro fertilisation treatment**

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

A

### 11.2 Female age

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

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

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

C

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

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

C

### 11.4 Number of previous treatment cycles

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

C

### 11.5 Pregnancy history

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

C

### 11.6 Alcohol, smoking and caffeine consumption

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

C

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

C

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

C

### 11.7 Body weight

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

B

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

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

GPP

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

GPP

**11.9 Gamete intrafallopian transfer and zygote intrafallopian transfer**

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

A

**Chapter 12 Procedures used during in vitro fertilisation treatment****12.1 Medical assessment and screening**

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

B

**12.2 Management of couples with viral infections**

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

D

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

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

A

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

B

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

A

**12.4 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. Consideration should be given to minimising cost when prescribing.

A

**12.5 Monitoring of stimulated cycles**

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

C

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

A

**12.6 Ovarian hyperstimulation syndrome**

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

GPP

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

A

**12.7 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.

D

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

A

*12.8 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 available.

C

*12.9 Assisted hatching*

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

A

*12.10 Embryo transfer techniques*

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

A

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

B

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

B

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

A

*12.11 Luteal support*

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

A

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

A

**Chapter 13 Intracytoplasmic sperm injection**

*13.1 Indications for intracytoplasmic sperm injection*

The recognised indications for treatment by intracytoplasmic sperm injection include:

- severe deficits in semen quality
- obstructive azoospermia
- nonobstructive azoospermia.

B

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.

*13.2 Genetic issues and counselling*

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

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

B

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

B

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

B

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

GPP

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

C

chromosome involved in the regulation of spermatogenesis, and couples should be informed of this.

C

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

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

A

## **Chapter 14 Donor insemination**

### *14.1 Indications for donor insemination*

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

B

- obstructive azoospermia
- nonobstructive azoospermia
- infectious disease in the male partner (such as HIV)
- severe rhesus isoimmunisation
- severe deficits in semen quality in couples who do not wish to undergo intracytoplasmic sperm injection.

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

### *14.2 Information and counselling*

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

C

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

C

### *14.3 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 counselling from someone who is independent of the treatment unit regarding the implications for themselves and their genetic children, including any potential children resulting from donated semen.

GPP

### *14.4 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 after three cycles if treatment has been unsuccessful.

GPP

### *14.5 Intrauterine insemination versus intracervical insemination*

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

A

### *14.6 Unstimulated versus 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

### *14.7 Timing of donor insemination*

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

C

*14.8 Maximum number of cycles*

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

GPP

**Chapter 15 Oocyte donation**

*15.1 Indications for oocyte donation*

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

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

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

C

*15.2 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

*15.3 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 counselling from someone who is independent of the treatment unit regarding the physical and psychological implications of treatment for themselves and their genetic children, including any potential children resulting from donated oocytes.

GPP

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

GPP

**Chapter 16 Applications of 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 and adolescent boys preparing for medical treatment that is likely to make them infertile should be offered semen cryostorage because the effectiveness of this procedure has been established.

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 sensitively and effectively.

C

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

C

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

D

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

GPP

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

GPP

### Chapter 17 Follow-up of children born as a result of assisted reproduction

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

C

## 2.2 Future research recommendations

- Further research is needed to evaluate the access for people from ethnic minority groups to investigation and treatment of fertility problems.
- Further research is needed to assess the long-term psychological impact of investigation and treatment of people who perceive problems with their fertility, both in people who subsequently achieve a live birth and people who do not.
- Further research is needed to determine whether women with raised serum prolactin should have macroprolactin excluded.
- Further research is needed to ascertain the value of fertiloscopy and falloposcopy in the investigation of couples who experience problems with fertility.
- Further randomised controlled trials are needed to evaluate the potentially therapeutic effects of tubal flushing with water-soluble media.
- The role of pelvic ultrasound in women who are not suspected to have pelvic pathology requires further evaluation.
- Antioxidants, alpha blockers and mast-cell blockers need further evaluation before they can be considered in the treatment of men with semen abnormalities.
- Randomised controlled trials are needed to compare the effectiveness of surgery for varicoceles and in vitro fertilisation treatment in men with abnormal semen quality.
- Further research is needed to evaluate the effect of ovarian drilling on the formation of adhesions and the long-term health consequences of this procedure.
- Further research is needed to compare the clinical effectiveness (including patient satisfaction) and the cost effectiveness of 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 research is needed to evaluate the clinical and cost effectiveness of tubal surgery compared with no treatment and other treatment options, particularly in vitro fertilisation. This research should include consideration of any adverse consequences of treatment, such as ectopic pregnancy.
- Randomised controlled trials are needed to evaluate any benefits of surgical treatment of leiomyoma on improving the chance of live birth.
- Further research is needed to evaluate any benefit on live birth rates of surgical resection of uterine septum in women with fertility problems.
- Research is needed to define semen quality criteria for assisted reproduction 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 intrauterine insemination in couples with unexplained fertility problems.
- Further randomised controlled trials evaluating the effectiveness of in vitro fertilisation in comparison with no treatment are needed for different durations and causes of fertility problems.
- Further research is needed to determine the relative effectiveness of intrauterine 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 research is needed to improve embryo selection to facilitate single embryo transfers.

- Further randomised controlled trials are needed to evaluate the effectiveness of assisted reproduction procedures in relation to female body mass index.
- Further research is needed to determine whether prophylactic albumin treatment administered at the time of egg collection is effective. This research should include issues related to timing and dose.
- Further research is needed to evaluate the effect of general anaesthesia on oocyte retrieval and outcome of in vitro fertilisation treatment, taking into account patient preference.
- Further research is needed to evaluate the effects of assisted hatching on live birth rates and long-term consequences for children born as a result of assisted hatching.
- Further research is needed to evaluate the effect of cleavage (day 2 or 3) and blastocyst (day 5 or 6) stage methods of embryo transfer on live birth rates.
- Further research is needed to evaluate the effects of different types of embryo transfer catheters on pregnancy rates.
- Further research is needed to compare the effectiveness (including patient satisfaction) of different drugs and routes of administration for luteal support during in vitro fertilisation using gonadotrophin-releasing hormone agonist cycles.
- Further research is needed to evaluate the effect of intracytoplasmic sperm injection on live birth or pregnancy rates in couples where the male partner has poor semen quality.
- Research is needed to evaluate the effectiveness of counselling in relation to oocyte donation and egg sharing in terms of the long-term psychological and social implications of these practices.
- Long-term longitudinal follow-up of children resulting from assisted reproduction is needed. This research should focus on physical, genetic, psychological and social development, and it should be co-ordinated on a national basis.

## 2.3 Algorithm

# Assessment and Treatment for People with Fertility Problems

## Initial advice for people concerned about delays in conception:

- Cumulative probability of pregnancy in general population:
  - 84% in first year
  - 92% in second year
- Fertility declines with a woman's age
- Lifestyle advice:
  - Sexual intercourse every 2–3 days
  - $\leq 1-2$  units alcohol/week for women;  $\leq 3-4$  units/week for men
  - Smoking cessation programme for smokers
  - Body mass index of 19–29
  - Information about prescribed, over-the-counter and recreational drugs
  - Information about occupational hazards
- Offer preconceptional advice:
  - Folic acid
  - Rubella susceptibility and cervical screening

## Infertility:

Failure to conceive after regular unprotected sexual intercourse for 2 years in the absence of known reproductive pathology. *This guideline does not include the management of people who are outside this definition, such as those with sexual dysfunction, couples who are using contraception and couples outside the reproductive age range.*

## Early investigation if:

History of predisposing factors (such as amenorrhoea, oligomenorrhoea, pelvic inflammatory disease or undescended testes); woman's age  $\geq 35$  years; people with HIV, hepatitis B and hepatitis C; prior treatment for cancer

## People preparing for cancer treatment:

- Follow Royal College of Physicians and Royal College of Radiologists guidance
- Cryostorage of gametes and/or embryos

## Principles of care:

- Couple-centred management
- Access to evidence-based information (verbal and written)
- Counselling from someone not directly involved in management of the couple's fertility problems
- Contact with fertility support groups
- Specialist teams

## Clinical investigation of fertility problems and management strategies

For people who have not conceived after 1 year of regular unprotected sexual intercourse

### Male

#### Semen analysis:

- ✓ Compare with WHO reference values:
  - Volume  $\geq 2.0$  ml
  - Liquefaction time within 60 minutes
  - pH  $\geq 7.2$
  - Sperm concentration  $\geq 20 \times 10^6$  per ml
  - Total sperm number  $\geq 40 \times 10^6$  spermatozoa per ejaculate
  - Motility  $\geq 50\%$  (grades a and b) or  $\geq 25\%$  with progressive motility (grade a) within 60 minutes of ejaculation
  - Vitality  $\geq 75\%$  live
  - White blood cells:  $< 10^6$  per ml
  - Morphology: 15% or 30%
- ✗ Screening for anti-sperm antibodies
- ✓ Ideally repeat after 3 months if abnormal or in as soon as possible if gross sperm deficiency

#### If abnormal

#### Hypogonadotropic hypogonadism:

- Gonadotrophins
- Obstructive azoospermia:
  - Surgery
  - Sperm recovery

#### If normal, see Unexplained infertility

#### Mild male factor fertility problems:

- Unstimulated intra-uterine insemination x 6 cycles

#### Ejaculatory failure:

- Drug therapy
- Sperm recovery

#### Varicoceles:

- ✗ Surgery

### Female

#### Assessment of ovulation:

- Check for frequency and regularity of menstrual cycles
- If irregular:
  - ✓ Day 21 serum progesterone if 28-day cycle or later in long cycle to confirm ovulation
  - ✓ Serum gonadotrophins (FSH and LH)
  - ✓ Serum prolactin unless galactorrhoea or pituitary tumour
  - ✗ Inhibin B
  - ✗ Thyroid function test unless symptoms of thyroid disease
  - ✗ Endometrial biopsy

#### Irregular ovulation

If regular ovulation, see Unexplained infertility

#### WHO group I (hypothalamic pituitary failure):

- Gonadotrophins with LH activity or pulsatile GnRH

#### WHO group II (hypothalamic pituitary dysfunction, mainly polycystic ovary syndrome):

- Clomifene citrate\* or tamoxifen\* (up to 12 months if ovulating) with ultrasound monitoring during at least the first cycle to adjust dose if ovulating but not pregnant after 6 months:

- Offer clomifene citrate\* plus intra-uterine insemination

- If no ovulation with clomifene citrate:
  - Metformin plus clomifene citrate\* or
  - hMG\*, uFSH\* or rFSH\* with ultrasound monitoring or
  - Ovarian drilling

#### Hyperprolactinaemia:

- Bromocriptine

\* Risk of OHSS and multiple pregnancy

#### Tests for tubal occlusion:

The results of semen analysis and assessment of ovulation should be known before a test for tubal patency is performed.

- ✓ Screening for *Chlamydia trachomatis* before uterine examination or offer prophylactic antibiotics
- ✓ HSG/hysterosalpingo-contrast-ultrasonography if no history of co-morbidity (endometriosis/ pelvic inflammatory disease/ ectopic pregnancy)
- ✓ Laparoscopy and dye if history of co-morbidity

#### If occlusion

#### Consider in vitro fertilisation

- Tubal surgery if mild tubal disease
- Tubal catheterisation or cannulation if proximal occlusion

#### Minimal/mild endometriosis:

- Surgical ablation or resection and adhesiolysis at laparoscopy

#### If no pregnancy:

- Stimulated intra-uterine insemination x 6 cycles with ultrasound monitoring with risk of OHSS and multiple pregnancy

#### Moderate/severe endometriosis:

- Surgery
- Endometriomas:
  - Laparoscopic cystectomy

#### If normal

#### Unexplained fertility problems

(Normal semen analysis, no ovulation disorders, no tubal occlusion):

- Clomifene citrate
- Unstimulated intra-uterine insemination x 6 cycles
- Fallopian sperm perfusion

# If no pregnancy with azoospermia, bilateral tubal occlusion or 3 years' infertility and the woman is aged 23–39 years, offer up to 3 stimulated cycles of in vitro fertilisation treatment

**Additional principles of care for people undergoing in vitro fertilisation treatment:** Access to evidence-based information (verbal and written) on risks/implications of assisted reproduction, including health of resulting children; genetic counselling; consideration of welfare of the child

## Factors affecting the outcome of in vitro fertilisation treatment:

- Salpingectomy before in vitro fertilisation treatment for women with hydrosalpinges
- Optimal woman's age is 23–39 years at time of treatment
- Increased success with previous pregnancy and/or live birth
- Ideal body mass index is 19–30
- Increased success with low alcohol/caffeine intake
- Increased success in non-smokers
- Consistent for first three cycles of treatment, effectiveness after three cycles is uncertain

## Procedures for in vitro fertilisation treatment:

### 1. Offer screening:

- ✓ HIV, hepatitis B, hepatitis C; specialist referral if positive

### 3. Embryo transfer:

- ✓ No more than two embryos to be transferred during any 1 cycle
- ✓ Offer cryostorage of supernumerary embryos if more than two embryos
- ✓ Frozen embryos to be transferred before further stimulated cycles
- ✓ Ultrasound-guided embryo transfer on day 2 or 3, or on day 5 or 6

### 4. Luteal support:

- ✓ Progesterone

### 2. Ovulation induction:

- ✓ Natural cycle
- ✓ Pituitary down-regulation with GnRH agonist long protocol
- ✓ GnRH agonist with gonadotrophins with consideration to minimising cost
- ✓ GnRH antagonists
- ✓ Growth hormone adjuvant
- ✓ Monitor follicular development with ultrasound: clinics should have protocols for management of OHSS
- ✓ Oocyte maturation with human chorionic gonadotrophins
- ✓ Oocyte retrieval: offer conscious sedation (follow Academy of Medical Royal Colleges guidance)
- ✓ Follicle flushing
- ✓ Assisted hatching

Women should be informed of the risks of OHSS and multiple pregnancy

## Management options associated with in vitro fertilisation treatment and other forms of assisted reproduction

### Intracytoplasmic sperm injection

- for couples with:
  - Severe semen quality deficits
  - Azoospermia
  - Poor in vitro fertilisation treatment response

### Screening:

Male karyotype

### Donor insemination

- for couples with:
  - Azoospermia
  - Genetic/infectious disease in male partner
  - Severe testis ischaemia
  - Severe semen deficits

### Screening of sperm donors:

- Follow British Andrology Society guidance
- Assessment of female partner.
- ✓ Confirm ovulation
- ✓ HSG if no pregnancy after 3 cycles

### Donor insemination:

- ✓ Time insemination with either urinary luteinising hormone or basal body temperature changes
- ✓ If regular ovulation, offer 6 unstimulated cycles

### Oocyte donation — for women with:

- Premature ovarian failure
- Gonadal dysgenesis including Turner syndrome
- Bilateral oophorectomy
- Ovarian failure following chemotherapy or radiotherapy
- Certain cases of in vitro fertilisation treatment failure
- Genetic disorder transmission to offspring

### Screening of oocyte donors:

- Follow Human Fertilisation and Embryology Authority guidance

### Oocyte donors:

- Risks of ovarian stimulation and oocyte collection
- Egg sharing: counselling

This algorithm should, where necessary, be interpreted with reference to the full guideline

**Key:** FSH follicle-stimulating hormone; GnRH gonadotrophin-releasing hormone; HIV human immunodeficiency virus; hMG human menopausal gonadotrophin; HSG hysterosalpingography; LH luteinising hormone; OHSS ovarian hyperstimulation syndrome; rFSH recombinant FSH; uFSH urinary FSH; WHO World Health Organization

# 3. Initial advice to people concerned about delays in conception

## 3.1 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 upon 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 man and the woman. 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 one), 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 seven days in the genital tract and sometimes even longer (see Section 3.2).<sup>17</sup>

In the general population (which includes people with fertility problems), it is estimated that 84% of women would conceive within one year of regular unprotected sexual intercourse. This rises cumulatively to 92% after two years and 93% after three years.<sup>18,19</sup>

Fertility may be measured as conception rate per menstrual cycle. This is known as fecundability. Natural female fertility declines with age,<sup>20</sup> [Evidence level 3] but reliable data on fecundability rates of specific age groups in fertile populations are limited. The decline with age in rates of conception is seen after 30 years of age and is more marked after age 35 years.<sup>21,22</sup> [Evidence level 3] 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 sexual intercourse than in fertile women receiving donor insemination.<sup>21,23</sup> The effect of age on male fertility is less clear.<sup>24</sup> [Evidence level 3]

Another important factor that can influence conception rates in the general population is coital frequency. Statistical estimates suggest that fecundability rises sharply with frequency of intercourse (see Section 3.2). With regular intercourse, 94% and 77% of fertile women aged 35 years and 38 years conceive after three years of trying.<sup>22,25</sup> [Evidence level 3]

Psychological stress can affect libido and coital frequency and hence fertility (see Section 4.2).

### RECOMMENDATIONS

People who are concerned about their fertility should be informed that about 84% of couples in the general population will conceive within 1 year if they do not use contraception and have regular sexual intercourse. Of those who do not conceive in the first year, about half will do so in the second year (cumulative pregnancy rate 92%).

D

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

C

## 3.2 Frequency and timing of sexual intercourse

Daily intercourse results in the highest probability of conception but is not the only factor influencing conception,<sup>26</sup> considering the viability of the egg and its short survival time. [Evidence level 3] Ejaculation eight times per week tends to reduce sperm parameters,<sup>27-30</sup> but not the fertility potential of the men.<sup>27</sup> The best sperm motility has been found in semen emission every three to four days on average.<sup>27</sup> [Evidence level 2b] Coitus every two to three days is likely to maximise the overall chance of natural conception, as spermatozoa survive in the female reproductive tract for up to seven days after insemination.<sup>17,30</sup> [Evidence level 3]

It has been observed that most pregnancies can be attributed to sexual intercourse during a six-day period ending on the day of ovulation,<sup>31,32</sup> with the highest estimated conception rates associated with intercourse two days before ovulation.<sup>33</sup> [Evidence level 3]

Six cohort studies that evaluated the use of basal body temperature or urinary luteinising hormone (LH) kits to time intercourse did not report improvement in the chance of natural conception.<sup>34-39</sup> [Evidence level 2b] Timed intercourse has been found to be an emotionally stressful intervention in the initial evaluation of infertility.<sup>40</sup> [Evidence level 3] However, for the minority of couples who find it difficult to have frequent sexual intercourse, the prediction of ovulation using LH kits can be useful.

### RECOMMENDATION

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

C

## 3.3 Alcohol

There is inconsistent evidence about the impact of alcohol intake on female fertility.<sup>41-46</sup> [Evidence level 2b] Excessive alcohol consumption is harmful to the fetus.<sup>47</sup> The Department of Health (DH) has recommended that women who are pregnant or trying to become pregnant should drink no more than one or two units of alcohol once or twice per week and should avoid episodes of intoxication.<sup>48</sup>

One cohort study showed that female wine drinkers (up to seven units per week) had slightly shorter waiting times to pregnancy than non-wine drinkers and drinkers of other alcoholic beverages, after adjusting for age, parity, smoking and body mass index (BMI).<sup>49</sup> [Evidence level 2b]

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.<sup>50-53</sup> [Evidence level 2b] The current recommended guidelines on safe drinking limits for men allow three to four units per day.<sup>54</sup>

### RECOMMENDATION

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

D

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

GPP

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

B

## 3.4 Smoking

There is a significant association between smoking and reduced fertility among female smokers.<sup>55,56</sup> [evidence level 2b] There is an association in men between smoking and reduced

semen parameters.<sup>51,57-62</sup> [Evidence level 2b] However, the relationship between male smoking habits and fertility is uncertain. Male and female exposure in utero is associated with reduced fertility later in life.<sup>63</sup> [Evidence level 2b]

It has been reported that passive smoking in women is associated with delayed conception.<sup>64</sup> [Evidence level 2b]

For women with fertility problems, basic information about the impact of smoking on fertility or a scripted three- to five-minute intervention with booklets specific to the woman's 'stage-of-change' smoking continuum, together with exhaled carbon monoxide monitoring, were highly effective in stopping smoking but not in improving pregnancy rates.<sup>65</sup> [Evidence level 1b] We found no studies that investigated the effect of the use of nicotine replacement therapy on infertility.

There are significant associations between maternal cigarette smoking in pregnancy and increased risks of small-for-gestational-age infants,<sup>66</sup> stillbirth<sup>67</sup> and infant mortality.<sup>68</sup> [evidence level 2b] For further information please refer to the Antenatal Care Guideline.<sup>1147</sup>

### RECOMMENDATIONS

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

**B**

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

**A**

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

**B**

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**

## 3.5 Caffeinated beverages

Caffeine is present in coffee, tea, colas and chocolate. The association between caffeine and female infertility is inconsistent.<sup>45,69-80</sup> [evidence level 2b] 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. However, the combination of coffee drinking with smoking diminished sperm motility and increased the proportion of dead sperm.<sup>51</sup> [evidence level 2b]

### RECOMMENDATIONS

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

**B**

## 3.6 Body weight

### Obesity

BMI is a measure of body fat calculated from an individual's weight and height (kg/m<sup>2</sup>). The internationally accepted range for BMI is from less than 18.5 kg/m<sup>2</sup> (underweight) to 30 kg/m<sup>2</sup> or over (obese).<sup>81</sup> Women with BMI over 30 kg/m<sup>2</sup> take longer to conceive, compared with women with lower BMI, even after adjusting for other factors such as menstrual irregularity.<sup>82-84</sup> [evidence level 2b] For infertile anovulatory women with BMI of over 29 kg/m<sup>2</sup>, there is evidence that a supervised weight loss programme or a group programme including exercise, dietary advice and support helps to reduce weight,<sup>85,86</sup> resume ovulation<sup>85</sup> and improve pregnancy rates.<sup>86</sup> [Evidence level 1b]

A BMI of 30 or over was reported to be an independent risk factor for spontaneous abortion in women who were oocyte recipients.<sup>87</sup> [evidence level 3]

An increased risk of miscarriage has been reported in moderately obese women (BMI 25–27.9 kg/m<sup>2</sup>) with polycystic ovary syndrome (PCOS; see Section 5.2) undergoing ovulation induction.<sup>88</sup> [Evidence level 2b]

An observational study reported an inverse relationship between BMI and the total number of normal-motile sperm cells. There was a significant reduced number of normal-motile sperm cells in men who were overweight (BMI 25–30) and obese (BMI greater than 30) when compared with men of normal weight (BMI 20–24).<sup>89</sup> [evidence level 3] A higher incidence of sperm DNA fragmentation has also been observed in men with a BMI of over 25.<sup>90</sup> [evidence level 3]

Obesity may have a deleterious effect on erectile function in men with existing vascular risk factors such as heart disease and diabetes.<sup>91</sup> [evidence level 2b]

### RECOMMENDATIONS

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

B

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

B

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

A

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

C

### Low body weight

Low body weight is recognised as an important cause of hypo-oestrogenic amenorrhoea. It is important that the subgroup of women who have anorexia nervosa are detected and managed appropriately. Many women with hypo-oestrogenic amenorrhoea 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.<sup>92</sup> Restoration of body weight may help to resume ovulation and restore fertility.<sup>93,94</sup> [Evidence level 2b]

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.<sup>95</sup> [Evidence level 2b]

### RECOMMENDATION

Women who have a body mass index of less than 19 and who have irregular menstruation or are not menstruating should be advised that increasing body weight is likely to improve their chance of conception.

B

## 3.7 Tight underwear for men

Increased scrotal temperature is closely associated with reduced semen quality in healthy populations.<sup>96–98</sup> [Evidence level 3] Important determinants of testicular temperature such as a sedentary work position and occupational heat exposure have been associated with abnormal semen quality (see Section 3.8).<sup>98,99</sup> [Evidence level 3] There is some evidence that, in a fertile population, wearing tight-fitting underwear can impair semen quality.<sup>100</sup> [Evidence level 1b] 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.<sup>101</sup> [Evidence level 2b]

**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-fitting underwear improves fertility.



**3.8 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.<sup>102</sup> Tables 3.1 and 3.2 summarise the main occupational agents implicated in the reduction of human fertility.<sup>103–109</sup> [Evidence level 2b–3] The lists of agents presented in the tables is not exhaustive.

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



**Table 3.1** Occupational agents and their effects on male fertility

Occupational agents	Occupational groups	Effects on male fertility
<i>Physical</i>		
Shift work/long working hours	Shift workers	No association <sup>110,111</sup>
Heat (increase in scrotal temperature)	Welders, bakers, drivers	Abnormal sperm parameters <sup>99</sup>
X-ray	Radiotherapists	Azoospermia, reduced sperm count, may be reversible <sup>112,113</sup>
Non-ionising radiation: electromagnetic fields	Metal workers	Inconsistent association <sup>114–116</sup>
Vibrations	Engine drivers, diggers	Oligozoospermia, asthenozoospermia <sup>117</sup>
<i>Chemical</i>		
Dibromochloropropane (pesticide)	Agricultural workers	Oligozoospermia and azoospermia, reversible in most cases, <sup>118–121</sup> reduced fertilisation rate <sup>122</sup>
Ethylene dibromide (pesticide)		Abnormal sperm parameters <sup>107</sup>
Carbaryl (pesticide)		No association <sup>123</sup>
Polychlorinated biphenyls	Agricultural workers	Abnormal sperm parameters <sup>124,125</sup>
Lead, cadmium, manganese	Metal workers, smelters, battery factory workers	Reduced fertility, mainly affecting female partners, <sup>126–131</sup> no association <sup>132</sup>
Mercury	Dental amalgam	No association <sup>133</sup>
Acetone, carbon disulphide, glycol ethers (solvents)	Chemists, laboratory workers, painters	Abnormal sperm parameters, <sup>135,136</sup> reduced fecundability, <sup>137</sup> oligospermia <sup>138</sup>
Toluene, styrene (solvents)	Plastic and printing industry	No association <sup>139,140</sup>
Anaesthetic gases	Dentists, anaesthetists	No association <sup>141,142</sup>

**Table 3.2** Occupational agents and their effects on female fertility

Occupational agents	Occupational groups	Effects on female fertility
<i>Physical</i>		
Shift work/intense physical work load/long working hours	Hospital workers	Reduced fecundability, <sup>143,144</sup> prolonged time to pregnancy, <sup>110,111</sup> no association <sup>111</sup>
Ionising radiation	Nuclear industry workers	Non-significant association <sup>145</sup>
Visual display units	Office workers	No association, <sup>146</sup> increased risk of infertility <sup>147</sup>
<i>Chemical</i>		
Pesticides	Agricultural workers	Inconsistent time to pregnancy <sup>148</sup>
Lead	Smelters	No association at low levels, <sup>149</sup> prolonged time to pregnancy <sup>150</sup>
Mercury, cadmium		prolonged time to pregnancy <sup>150</sup>
Anti-neoplastics (chemotherapy drugs)	Nurses, pharmacists	Increased self-reported infertility <sup>151</sup>
Antibiotics		Small risk of prolonged time to pregnancy <sup>152</sup>
Nitrous oxide	Anaesthetists, theatre nurses dental assistants	Reduced fecundability <sup>143,153,154</sup>
Chloroform, benzene		No association <sup>141</sup>
Mercury vapour	Lamp factory workers	No clear association, <sup>155</sup> reduced fecundability <sup>156</sup>
Solvents		Infertility <sup>147</sup>
Formaldehyde	Wood workers	Reduced fecundability <sup>157</sup>

### 3.9 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.<sup>158,159</sup> [Evidence level 1b] Immunosuppressive and anti-inflammatory drugs for rheumatic diseases may affect conception.<sup>160</sup> [evidence level 3] In a case-control study, women who had ever used thyroid replacement hormones, antidepressants, tranquilisers or asthma medication were reported to have elevated risks of anovulatory infertility.<sup>161</sup> [Evidence level 2b] Chemotherapy treatment with cytotoxic drugs can induce ovarian failure at different rates for various types of malignancies and treatment regimens.<sup>162,163</sup> [Evidence level 2b]

Medication such as cimetidine and sulphasalazine and long term-daily use of some antibiotics and androgen injections can affect semen quality and cause oligozoospermia.<sup>164–166</sup> The effect is generally reversible after three months following withdrawal of medication. Use of beta-blockers and psychotropic drugs may lead to impotence.<sup>167</sup> Chemotherapy treatment can induce azoospermia, which is permanent in most cases.<sup>168</sup> [Evidence level 3]

The effect of anti-psoriatic treatment for arthritis with methotrexate on male infertility is unclear.<sup>169</sup> [Evidence level 3]

#### Recreational drug use

The use of recreational drugs or drugs of abuse such as marijuana and cocaine can adversely affect ovulatory and tubal function.<sup>170</sup> The use of drugs such as anabolic steroids and cocaine can adversely affect semen quality.<sup>171–173</sup> [evidence level 2b–3] Overall, use of these recreational

drugs diminishes the fertility potential of the couple. We did not find any studies that assessed the effect of recreational drug use on pregnancy rates.

### RECOMMENDATION

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

B

## 3.10 Complementary therapy

We found four RCTs that evaluated the effects of various substances on semen quality,<sup>174,175</sup> ovulation and pregnancy rates.<sup>176,177</sup> Three of the RCTs<sup>174,176,177</sup> were of poor design with unclear methods of randomisation and clinical heterogeneity. The fourth RCT<sup>175</sup> compared oral selenium supplementation with selenium plus vitamins or placebo in a group of subfertile men. This RCT reported an improvement in sperm motility and pregnancy rates in the selenium group compared with the placebo group (11% with selenium versus 0% with placebo).<sup>175</sup> [Evidence level 1b]

An increase in pregnancy rates was observed in a preliminary trial assessing the effect of intercessory prayer on patients undergoing IVF treatment. However, there is no biological mechanism to explain such an effect.<sup>178</sup>

### RECOMMENDATION

People who are concerned about their fertility should be informed that the effectiveness of complementary therapies for fertility problems has not been properly evaluated and that further research is needed before such interventions can be recommended.

GPP

## 3.11 Folic acid supplementation

A systematic review<sup>119</sup> of four RCTs (n = 6425 women) showed that periconceptional folate supplementation reduced the incidence of neural tube defects (anencephaly and spina bifida) in children (RR 0.28, 95% CI 0.13 to 0.58). In all four RCTs, folic acid was taken before conception and up to 6–12 weeks of gestation. The dose assessed ranged from 0.36 to 4 milligrams. Multivitamins alone were not associated with prevention of neural tube defects and did not produce additional preventative effects when given in combination with folate.<sup>179</sup> [Evidence level 1a] An Expert Advisory Group to the DH recommended a dose of 0.4 milligrams of folic acid per day for women who have not had a previous infant with a neural tube defect and a dose of 5.0 milligrams per day for women who have previously had an infant with a neural tube defect and those who are receiving antiepileptic drugs. Supplementation should continue until 12 weeks into pregnancy.<sup>180</sup> The *British National Formulary* recommends that women taking anti-epileptic drugs wishing to become pregnant should be referred to an appropriate specialist to discuss the risk of teratogenicity.<sup>181</sup> The size of the effect for a given dose of folic acid was recently quantified and modelling has suggested that a reduced risk is associated with higher doses (i.e. 5 milligrams instead of 0.4 milligrams), The practical implication of an increased dose of folic acid has yet to be investigated.<sup>182,183</sup>

### 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 0.4 mg per day. For women who have previously had an infant with a neural tube defect or who are receiving antiepileptic medication, a higher dose of 5 mg per day is recommended.

A

### 3.12 Susceptibility to rubella

Rubella infection during pregnancy is associated with a significant teratogenic risk to the fetus, resulting in multiple congenital abnormalities.<sup>184</sup> [Evidence level 2b] 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%.<sup>185–188</sup> [Evidence level 3] The rubella vaccine is a live attenuated virus; thus, when vaccination is given conception should be deferred for one month.

#### RECOMMENDATION

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

D

### 3.13 Cervical cancer screening

The reported proportion of infertile women with abnormal cervical smears ranges from 5% to 13%.<sup>186,188</sup> [Evidence level 3] As part of the national screening programme, women between the age of 20 years and 64 years are offered cervical screening every three years or five years. Around 60% of health authorities invite women every three years and 15% have a mixed policy, inviting women every three to five years, depending upon their age.<sup>189</sup> Abnormal cervical cytology that is overlooked may lead to increased delay in fertility treatment<sup>186</sup> 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 to women who are concerned about their fertility. Cervical screening should be offered in accordance with the national cervical screening programme guidance.

GPP

### 3.14 Defining infertility

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’.<sup>190</sup> [Evidence level 4] Infertility should, therefore, be considered to be a disease process worthy of investigation and treatment.

Infertility has been defined as failure to conceive after frequent unprotected sexual intercourse for one or two years.<sup>1,3,191–213</sup> Diagnosis of infertility based on a failure to conceive within one 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.<sup>118,119</sup>

The prevalence of infertility in European countries is around 14%, affecting one in seven couples.<sup>1,3,193,196,197,201–205,208,210,212,214,215</sup> Data from historical populations estimate 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.<sup>216</sup>

The first consultation should include an assessment of the perceived fertility problem. For many couples, information about normal patterns of conception will provide reassurance that they are likely to have a good chance of conception. However, there should also be a specific enquiry about the medical, surgical, sexual, contraceptive and pregnancy history and a general physical examination to detect abnormalities, including measurement of height and weight to calculate BMI to identify couples who are likely to experience delays in conception.<sup>217</sup> Couples should be offered information about lifestyle such as smoking, alcohol intake, occupational factors and diet which may impact on their fertility.

### RECOMMENDATIONS

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

D

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

GPP

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

GPP

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

GPP

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

GPP

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

GPP

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

GPP

# 4. Principles of care

## 4.1 Information giving and couple-centred management

Seeking fertility treatment concerns both partners. Both the World Health Organization (WHO) and the HFEA strongly suggest that couples should be seen together.<sup>207,218</sup> [Evidence level 4] Two surveys have reported that women were more satisfied when seen with their partners at their infertility consultation.<sup>219,220</sup> [Evidence level 3] A further survey reported that couples were seen together in only 35% of clinics.<sup>221</sup> However, there was strong agreement among GPs that couples should be seen together as part of infertility management.<sup>222</sup> [Evidence level 3]

Couples want more information about their conditions, their treatment and outcomes.<sup>223</sup> Low levels of satisfaction about information given to people with fertility problems at consultation have been reported in patient surveys.<sup>220,224–228</sup> [Evidence level 3] Verbal as well as written information can improve understanding.<sup>229</sup> [Evidence level 2b] 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.<sup>230</sup> [Evidence level 3] Verbal information should be supported by written evidence-based guidance sensitive to the needs of individual patients.<sup>231</sup> A clear protocol that sets out the purpose of investigation and the proposed care plan should be designed.

For assisted reproduction, the HFEA Code of Practice stipulates that individuals seeking treatment should be given oral explanations, supported by relevant written materials, about the ‘medical, scientific, legal and psychological implications of their decision’. Individuals should be ‘encouraged to seek any further information that they may need, and all questions should be answered in as straightforward and comprehensive a way as possible’.<sup>218</sup> [Evidence level 4] Information leaflets about various aspects of assisted reproduction are available from the HFEA.<sup>232–242</sup>

Information and advice given in a manner that is culturally sensitive to the individuals concerned may improve acceptability of infertility management and care.<sup>243–245</sup> [Evidence level 3]

### RECOMMENDATIONS

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

C

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

C

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

GPP

### RESEARCH RECOMMENDATION

Further research is needed to evaluate the access for people from ethnic minority groups to investigation and treatment of fertility problems.

## 4.2 Psychological effects of fertility problems

The relationship between psychological stress and fertility problems is complex.<sup>246</sup> [Evidence level 3] Individual response to stress situations will vary. Three cohort studies have reported an

association between work-related stress and a lower probability of conception in women.<sup>247–249</sup> [Evidence level 2b] However, the association in men is less clear.<sup>250,251</sup> [Evidence level 2b] Psychological stress can affect a couple's relationship and libido, which may impact upon their chance of conception. A higher frequency of male sexual disturbances including loss of libido and a decrease in the frequency of sexual intercourse has been observed in couples undergoing fertility diagnostic and treatment procedures.<sup>252–254</sup> [Evidence level 3–4]

Infertility is regarded as an upsetting and difficult life experience for some women,<sup>255,256</sup> with a subpopulation of women reporting elevated levels of anxiety and depression in some studies;<sup>255,257–265</sup> however, another study<sup>266</sup> did not find such an association. 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 HIV.<sup>267</sup> 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 two years after tubal reconstructive surgery.<sup>268</sup> [Evidence level 3]

Two RCTs have shown that group psychological interventions such as cognitive behavioural therapy and support prevent distress<sup>269,270</sup> and improve pregnancy rates (55% in a cognitive behavioural therapy group versus 54% in a support group versus 20% in a routine care group)<sup>270</sup> in women with less than two years' duration of infertility. [Evidence level 1b]

Psychiatric morbidity was reported to be positively associated with the experience of infertility and the number of treatment cycles, affecting more women than men.<sup>265</sup> [Evidence level 3] 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.<sup>271</sup>

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.<sup>272</sup> [Evidence level 1b]

Four surveys have reported that most patients feel that access to a support group and counselling would be beneficial.<sup>226,263,273,274</sup> Some felt that psychological support should be available at all stages of infertility treatment and investigation.<sup>230</sup> An unpublished survey<sup>274</sup> found that few GPs offered counselling or identified methods of support, but two-thirds of couples attending an infertility clinic said they would accept psychological assistance if offered.<sup>263</sup> [Evidence level 3] In another study, 70% of patients said they would request counselling if it were available free of charge.<sup>228</sup> [Evidence level 3] Despite this, overall uptake of counselling is low at between 18% and 25%.<sup>226,230,275</sup> 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.<sup>276</sup> Two-thirds of patients undergoing IVF treatment reported reading newspaper or 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.<sup>277</sup> 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 3]

The emotional consequences of anxiety and stress can be reduced by adequate provision of clear information about all aspects of investigations and treatment, involving both partners as an integral part of the management plan. The impact of psychological stress should be acknowledged throughout the care of the couple with fertility problems with offers of counselling. 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 fertility 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.<sup>278</sup>

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.<sup>279</sup> People who experience problems with fertility are often very vulnerable.<sup>280</sup> 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.<sup>280</sup> [Evidence level 3]

The HFEA Code of Practice<sup>218</sup> 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 and anyone else affected by the donation or treatment.

Support counselling aims to give emotional support at times of particular stress, for example, when there is a failure to achieve a pregnancy. This may occur at any stage before, during and after donation or treatment.

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, or the use of gametes or embryos posthumously, must be given 'a suitable opportunity to receive proper counselling about the implications of taking the proposed steps' before they consent.<sup>218</sup> [Evidence level 4]

Counsellors should have professional counselling qualifications and the ability to work in accordance with the Human Fertility and Embryology 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 should be informed that stress in the male and/or female partner can affect the couple's relationship and is likely to reduce libido and frequency of intercourse which can contribute to fertility problems.

C

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

GPP

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

C

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

GPP

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

GPP

#### RESEARCH RECOMMENDATION

Further research is needed to assess the long-term psychological impact of investigation and treatment of people who perceive problems with their fertility, both in people who subsequently achieve a live birth and people who do not.

### 4.3 Specialist and generalist care

The impact of specialist as compared to non-specialist care on the management of fertility problems 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.<sup>281–283</sup> [Evidence level 2b–3] Training and expertise have been suggested as reasons for women achieving higher pregnancy rates after tubal surgery carried out by specialists rather than general gynaecologists.<sup>284</sup> [Evidence level 3]

In a survey, patients seeking fertility treatment were reported to be more satisfied with services provided in a specialist clinic than those provided in a general gynaecological clinic.<sup>220</sup> [Evidence level 3] Patients were dissatisfied with attending an infertility clinic which shared a waiting room with users of antenatal classes or was located in a place where parent craft classes took place.<sup>274</sup>

A review of treatments and services in the management of people with fertility problems 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.<sup>2</sup> [Evidence level 4]

### RECOMMENDATION

People who experience fertility problems should be treated by a specialist team because this is likely to improve the effectiveness and efficiency of treatment and is known to improve patient satisfaction.

D

# 5. Investigation of fertility problems and management strategies

## 5.1 Semen analysis

WHO criteria for assessing semen quality are based on populations of fertile men and are described as 'reference' values rather than 'normal' values (Table 5.1).<sup>285,287</sup> [Evidence level 4] In the detection of male factor fertility problems, basic semen analysis using the WHO criteria is a sensitive test (sensitivity of 89.6%, i.e. it is likely to detect nine out of ten men who have 'true' semen abnormality), but it has poor specificity (an abnormal test result does not always mean there is a true semen abnormality). 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%.<sup>286</sup> [Evidence level 2b] Definitions relating to semen quality are given in Table 5.2.

**Table 5.1** WHO reference values for semen analysis, 2000<sup>287</sup>

Criteria	Reference value
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* and 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

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

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

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

**Table 5.2** Definitions relating to semen quality

Term	Definition
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
Cryptozoospermia	Few spermatozoa recovered after centrifugation

Repeat semen measurements from the same individual will vary over time.<sup>28,29</sup> This has prompted the suggestion that two<sup>285</sup> or three semen samples<sup>29</sup> are needed in order to establish a reliable semen profile. However, as the WHO criteria provide a sensitive test (that is, the test is likely to identify most 'true' abnormalities), if the semen analysis is normal there is no need for a repeat analysis. To reduce false positives, it is suggested that a repeat semen analysis should be performed only if the result of the first analysis is abnormal.<sup>288</sup> Biologically, the optimal time for the second sample is at least three months after the initial sample because the cycle of spermatozoa formation takes about three months to complete.<sup>289</sup> [Evidence level 3] However, this delay may cause anxiety and the timing of the second sample should take into consideration the preferences of the man. If azoospermia or severe oligozoospermia is reported in the initial semen analysis, a repeat test should be undertaken within two to four weeks. If the repeat test is reported as normal the semen can be regarded as normal and no further test is needed. However, these men may need further assessment of semen quality if assisted reproduction is being considered.

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 individual or 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 criteria include assessment for the presence of autoimmune antisperm antibodies as a standard part of semen analysis.<sup>287</sup> [Evidence level 4] This analysis is performed using either an immunobead test or a mixed antiglobulin reaction test. However, opinions differ on the reliability of these tests and whether they should be used routinely in the initial investigation of fertility problems.<sup>290-293</sup> [Evidence level 3-4] Semen analysis should not include screening for antisperm antibodies because there is no effective treatment in terms of improving male fertility (see Section 6.1).

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.<sup>211,294</sup> [Evidence level 4]

The reliability of the WHO reference values, especially that for sperm concentration, in predicting the chance of conception has been questioned.<sup>295</sup> [Evidence level 3]

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.<sup>211,294</sup> [Evidence level 4]

In the UK, low sperm count or quality is found to be the only cause of infertility in about 20% of couples, and is a contributory factor in a further 25% of couples.<sup>1,2,296</sup> It is estimated that in between 30% and 50% of men with poor semen quality no cause for this will be identified.<sup>297,298</sup> Impaired semen quality, azoospermia and inadequate coitus are contributing factors in nearly 50% of infertile couples.

Abnormal semen characteristics are usually idiopathic (idiopathic oligoasthenoteratozoospermia). Idiopathic semen abnormalities occur in about 26% of infertile men.<sup>298</sup> The spermatozoa are mostly dysfunctional and unable to fertilise but a proportion are often functionally normal. Sperm function may also be impaired by anti-sperm antibodies.

Azoospermia may be due to hypothalamic-pituitary failure, primary testicular failure (nonobstructive azoospermia) or obstruction of the genital tract (obstructive azoospermia).

Hypogonadotrophic hypogonadism, which is a condition caused by hypothalamic or pituitary dysfunction, accounts for less than 1% of male factor fertility problems.<sup>296</sup> It results in a deficiency of LH and FSH, which is associated with failure of spermatogenesis and testosterone secretion.

Primary testicular failure is the most common cause of male infertility due to oligozoospermia and is the cause of nonobstructive azoospermia. Testicular failure may be due to cryptorchidism, torsion, trauma, orchitis, chromosome disorders (Klinefelter's syndrome, Y-chromosome microdeletions), systemic disease, radiotherapy or chemotherapy; however, 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 that cause infertility should be

offered the opportunity to cryopreserve semen (see Section 16.1). Alternatively, surgical sperm retrieval with assisted reproduction or donor sperm may be considered (see Section 12.8).

Obstructive azoospermia is uncommon with a prevalence of less than 2%.<sup>1</sup> 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).

Anejaculation is defined as the total failure of seminal emission into the posterior urethra. Retrograde ejaculation is the substantial propulsion of seminal fluid from the posterior urethra into the bladder.<sup>299</sup> Anejaculation is a relatively uncommon occurrence in the general population,<sup>300</sup> and retrograde ejaculation accounts for about 0.3–2.0% of male fertility problems. Anejaculation and retrograde ejaculation may result from spinal cord injury, transurethral prostatectomy, retroperitoneal lymph node dissection, diabetes mellitus, transverse myelitis, multiple sclerosis or psychogenic (idiopathic) disorders. For example, it has been reported that only 7% of men retained ejaculation after transurethral resection of the prostate.<sup>301</sup> [Evidence level 2b] With the advent of ICSI, since only a small number of motile spermatozoa is required for a successful fertilisation,<sup>302</sup> both ejaculation disorders can be considered as treatable conditions. [Evidence level 3]

A 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.<sup>303</sup> The mechanism by which varicoceles might impair fertility and spermatogenesis is not clear. Varicoceles may be associated with decreased ipsilateral testicular volume, elevated scrotal temperature and pain, as well as impaired semen quality.<sup>303–305</sup>

## RECOMMENDATIONS

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

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

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

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

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

GPP

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

GPP

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

B

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

GPP

## 5.2 Assessing ovulation

### Regularity of menstrual cycles

Regular menstrual cycles in the range 26 to 36 days are usually indicative of ovulation.<sup>306</sup> A review of patient-monitored basal body temperature charts showed that they were not sufficiently reliable for detection of ovulation (see Section 3.2).<sup>34–39</sup> Ovulation involves leutinisation of the mature follicle and release of the oocyte. Both are triggered by the LH surge. In practice, testing for release of the oocyte by observing follicle rupture is impractical so ovulation detection is based on the detection of circulating progesterone produced following leutinisation of the follicle. Urinary LH kits used by couples can suggest when ovulation is imminent. Ovulation can be confirmed retrospectively by measurement of serum progesterone in midluteal 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) and repeated weekly until the next menstrual cycle starts, unless the bleeds are so infrequent that ovulation induction therapy will be needed in any case. Values range from 16 to 28 nmol/l as the lowest limit indicative of ovulation.<sup>211,307–309</sup> [Evidence level 2b]

Anovulation and oligo-ovulation are ovulatory disorders that are estimated to cause 21% of female infertility.<sup>1</sup> The WHO classifies ovulation disorders into three groups.<sup>207</sup>

Group 1 Hypothalamic pituitary failure (hypothalamic amenorrhoea or hypogonadotropic hypogonadism)

This group of disorders is characterised by low gonadotrophins, normal prolactin and low oestrogen, and it accounts for about 10% of ovulatory disorders. Failed ovarian follicular development results in hypo-oestrogenic amenorrhoea in this group of disorders.

Group 2 Hypothalamic pituitary dysfunction

This group, which is characterised by gonadotrophin disorder and normal oestrogen, accounts for about 85% of ovulatory disorders. This group of disorders results in anovulatory oligo/amenorrhea, predominately involving women with polycystic ovaries. Polycystic ovaries are present in about 80–90% of women with oligomenorrhoea and 30% of women with amenorrhoea.<sup>310</sup> In women who have polycystic ovaries, where there are associated clinical symptoms (such as menstrual cycle disturbances, obesity and hyperandrogenism presenting as hirsutism, acne or androgen-dependent alopecia), this is referred to as PCOS. About 30% of the PCOS population is of normal weight.<sup>311</sup>

Over many years, the diagnostic criteria for polycystic ovaries and PCOS have been evolving and different researchers have used differing definitions. An international consensus definition of PCOS, which includes a new definition of the polycystic ovary, provides the possibility that future research will be based on a consistent definition. The new definition for the diagnosis of a polycystic ovary (which is usually obtained from an ultrasound scan) requires the presence of at least 12 follicles measuring 2–9 mm in diameter and/or an ovarian volume in excess of 10 cm<sup>3</sup>.<sup>312–314</sup> [Evidence level 3–4] The new definition for the diagnosis of PCOS requires the presence at least two of the following three criteria:<sup>312,313</sup> [Evidence level 3–4]

- oligo- and/or anovulation
- clinical and/or biochemical hyperandrogenism
- polycystic ovaries, with the exclusion of other aetiologies.

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 (see Section 3.6).<sup>86</sup> [Evidence level 1b]

Group 3 Ovarian failure

This group, which is characterised by high gonadotrophins with hypogonadism and low oestrogen, accounts for about 4–5% of ovulatory disorders.

**RECOMMENDATIONS**

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

**B**

Women with regular menstrual cycles and more than 2 years' infertility can be offered a blood test to measure serum progesterone in the midluteal phase of their cycle (day 21 of a 28-day cycle) to confirm ovulation.

**B**

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

**GPP**

The use of basal body temperature charts to confirm ovulation does not reliably predict ovulation and 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**

**Prolactin measurement**

Hyperprolactinaemia is an endocrine disorder caused by an increased secretion of prolactin from the pituitary gland, resulting in galactorrhoea, irregular menstruation and possible infertility. The incidence of raised prolactin in infertile but ovulatory women ranges from 3.8% to 11.5%.<sup>315–317</sup> [Evidence level 3] There is no significant association between prolactin, progesterone levels and cumulative conception rates in ovulatory women.<sup>318,319</sup> [Evidence level 3] Estimation of prolactin levels should be reserved for women with symptoms of an ovulatory disorder, galactorrhoea or a pituitary tumour.

It has recently been proposed that hyperprolactinaemia attributable to macroprolactin, rather than prolactin, may be associated with fertility problems.<sup>320–322</sup> [Evidence level 3] However, further research is needed to determine whether women with raised serum prolactin should have macroprolactin excluded.

**RECOMMENDATION**

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

**C**

**RESEARCH RECOMMENDATION**

Further research is needed to determine whether women with raised serum prolactin should have macroprolactin excluded.

**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.<sup>323</sup> It would be valuable if reliable estimates of ovarian reserve could be obtained before embarking on fertility therapy such as ovulation induction and IVF in women over the age of 35 years.<sup>324,325</sup> [Evidence level 3–4]

Indirect measurements using endocrine markers, such as day-three basal serum follicle-stimulating hormone (FSH) and clomifene citrate challenge test, correlate well with the probability of conception in these populations: women in the infertile population,<sup>326,327</sup> women undergoing complex ovulation induction and women participating in assisted reproductive technology cycles.<sup>328–331</sup>

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.<sup>332</sup> [Evidence level 3]

An elevated basal day-three 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% versus 42%)<sup>328</sup> when compared with women with normal ovarian reserve. [Evidence level 2b–3] Poor pregnancy rate after assisted reproduction (2.7%) and high rate of pregnancy loss (71.4%) were also reported in women with elevated basal day-three FSH, regardless of age.<sup>333</sup> [Evidence level 3]

A cohort study of 344 women undergoing IVF following pituitary desensitisation showed that basal FSH was a better predictor of cycle cancellation rates and of the number of oocytes collected than age, although age and not basal FSH was independently associated with pregnancy rate.<sup>334</sup> Another cohort study of 1045 cycles of women undergoing IVF reported 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 versus 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.<sup>335</sup> [Evidence level 2b]

A cohort study of 547 women reported that those with poor response to ovarian stimulation and raised basal FSH were more likely to have poor reproductive performance and more likely to experience menopause before the age of 45 years compared with normal responders.<sup>336</sup> [Evidence level 2b]

It has been reported that direct measures of ovarian function such as inhibin B correlate inversely with age and FSH levels<sup>337</sup> and that inhibin B levels are reduced in women with diminished ovarian reserve.<sup>338</sup> However, the role of inhibin B in predicting pregnancy outcome is unclear<sup>339,340</sup> and needs further evaluation. [Evidence level 3]

One study reported that none of these markers accurately reflected ovarian reserve.<sup>341</sup> This study 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.<sup>341</sup> [Evidence level 3]

It has been reported that pregnancy rates decline significantly as day-three FSH rises above 15 mIU/ml. Very few pregnancies were reported when FSH exceeded 25 mIU/ml.<sup>329</sup> [Evidence level 3] 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.<sup>342</sup> [Evidence level 4]

Tests of ovarian reserve do not currently have the necessary sensitivity or specificity for general application.<sup>325</sup>

### RECOMMENDATIONS

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

C

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

C

### Thyroid function tests

Thyroid dysfunction can lead to menstrual and ovulatory disorder associated with infertility.<sup>343,344</sup> 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.<sup>345</sup> Abnormal thyroid function test measurements have been reported in 1.3–5.1% of infertile women.<sup>316,346–349</sup> [Evidence level 3] It has been estimated that subclinical hypothyroidism occurs in 0.88–11.3% of women with ovulation disorders.<sup>347,348</sup> [Evidence level 3]

#### RECOMMENDATION

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

C

#### 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.<sup>350</sup> The defect is estimated to affect 3–20% of the infertile population and 23–60% of women with recurrent miscarriage.<sup>351</sup> [Evidence level 3]

There is no consensus of opinion about the diagnosis or effective treatment of luteal-phase defect, and its role as a cause of infertility has been questioned.<sup>352,353</sup> The benefit of treatment for luteal-phase defect on pregnancy rates has not been established.<sup>354,355</sup> [Evidence level 1b–3]

Traditionally, luteal-phase defect is diagnosed by a timed endometrial biopsy based on a standard set of criteria,<sup>356</sup> repeated on at least two occasions. [Evidence level 2b] It has been suggested that diagnosis of luteal-phase defect based on histological dating of endometrial biopsy could be a chance event.<sup>355</sup>

#### RECOMMENDATION

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

B

### 5.3 Screening for *Chlamydia trachomatis*

*Chlamydia trachomatis* is present in 11% of the sexually active population aged 19 years or less.<sup>357</sup> It is a major cause of pelvic inflammatory disease, leading to chronic abdominal pain, ectopic pregnancy and tubal factor infertility.<sup>358,359</sup> Asymptomatic chlamydial infection may go unrecognised and untreated. Although the prevalence of *C. trachomatis* among subfertile women in the UK is only 1.9%,<sup>360</sup> uterine instrumentation carried out routinely as part of the infertility investigation may reactivate or introduce upper tract dissemination of endocervical chlamydial infection, resulting in iatrogenic pelvic inflammatory disease. [Evidence level 2b]

Clinical pelvic infection following hysterosalpingography (HSG) has been reported in up to 4% of cases and in 10% of patients with tubal disease.<sup>361</sup> [Evidence level 3] Prophylactic antibiotics are effective in reducing this and should be considered.<sup>360,362</sup> [Evidence level 3] Both doxycycline and azithromycin are effective prophylaxis and treatment for chlamydia.<sup>363</sup> [Evidence level 1b]

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.<sup>364</sup> [Evidence level 1b] The Chief Medical Officer's Expert Advisory Group on Chlamydia has called for action to reduce the prevalence and morbidity of chlamydial infection. It recommends that consideration be given to screening couples attending fertility clinics and women undergoing procedures requiring instrumentation of the uterus.<sup>365</sup> [Evidence level 4] 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.<sup>366–368</sup> [Evidence level 2b]

Chlamydial infection has been implicated in male infertility<sup>369</sup> 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.<sup>365</sup> [Evidence level 4]

### RECOMMENDATIONS

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

B

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

C

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

GPP

## 5.4 Assessing tubal damage

It is estimated that tubal factors account for 14% of the causes of subfertility in women.<sup>1</sup> Tubal blockage involves the proximal part (which is closest to the uterus), the mid part or the distal part (which is furthest from the uterus). Proximal (uterotubal) obstruction occurs in 10–25% of women with tubal disease.<sup>370</sup> The results of semen analysis and assessment of ovulation should be known before a test for tubal patency is performed.

Tubal disease includes tubal obstruction and pelvic adhesions due to infection, endometriosis and previous surgery. Endometriosis accounts for about 5% of female infertility.<sup>1</sup> It is defined as the presence of endometrial tissue occurring outside the uterine cavity which causes peritoneal lesions, adhesions and ovarian cysts 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,<sup>371</sup> 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.<sup>372,373</sup>

An ideal (or 'gold standard') test for tubal disease would correctly identify all women with tubal disease. It would be a sensitive test (i.e. all true positives would be identified by a positive test result and a negative test result would rule out disease in all those without disease) and it would also be specific (i.e. the test result 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. HSG and laparoscopy are both invasive procedures but HSG is less so. 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.<sup>374</sup> However, the detection and treatment of pathology missed by HSG did not increase live birth rates.<sup>374</sup> [Evidence level 2b]

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.<sup>375</sup> 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 to 0.78) and 0.83 (95% CI 0.77 to 0.88), respectively.<sup>375</sup> [Evidence level 2b] It is estimated that tubal damage accounts for 14% of fertility problems,<sup>1</sup> which suggests that when HSG suggests the presence of tubal obstruction this will be confirmed by laparoscopy in only 38% of women.

Thus, HSG is 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<sup>306</sup> 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.<sup>376</sup> [Evidence level 2b] Considerable interobserver variability in interpretation of HSGs has been reported, depending on the type of pathology being assessed.<sup>377,378</sup> Women with possible comorbidity 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.<sup>379</sup> [Evidence level 3] 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).<sup>379</sup> [Evidence level 3] 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).<sup>379</sup> [Evidence level 3] 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 enzyme-linked immunosorbent assay (ELISA), immunofluorescence or microimmunofluorescence is comparable to that of HSG in the diagnosis of tubal pathology.<sup>380</sup> [Evidence level 2b] Elevated titres of chlamydial antibodies in women were significantly associated with tubal disease.<sup>381</sup> The titre of chlamydial antibodies has also been reported to be more accurate in predicting severe tubal pathology than unspecified tuboperitoneal abnormalities.<sup>382</sup> 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.<sup>383</sup> [Evidence level 3]

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.<sup>384</sup> [Evidence level 2b] 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.<sup>385</sup> [Evidence level 2b]

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

Evaluative studies of hysterosalpingo-contrast-sonography (HyCoSy) showed good statistical comparability and concordance with HSG and laparoscopy combined with dye.<sup>386</sup> [Evidence level 1b] HyCoSy is well-tolerated and can be a suitable alternative outpatient procedure.<sup>387</sup> [Evidence level 1b] HyCoSy using contrast agent Infuson® appears to be more efficient than saline solution in detecting tubal obstruction.<sup>388</sup> [Evidence level 1b]

### *Fertiloscopy and fallopscopy*

Fertiloscopy is a relatively new procedure, defined as the combination in one investigation of transvaginal hydropelviscopy, dye test, optional salpingoscopy and hysteroscopy performed under local anaesthesia or neuroleptanalgesia.<sup>389</sup> Diagnostic fertiloscopy has also been used to identify tubal pathology as an alternative to laparoscopy.<sup>389</sup> [Evidence level 3] However, the procedure is not without risk, and bowel<sup>390</sup> and rectal injuries<sup>389</sup> following fertiloscopy have been reported. [Evidence level 3] The diagnostic accuracy of fertiloscopy in comparison to HSG and laparoscopy needs further evaluation.

Fallopscopy is defined as transvaginal microendoscopy of the fallopian tubes and direct visualisation of the entire fallopian tube lumen.<sup>391</sup> It has been suggested that it may be a more discriminatory test of tubal pathology because women with normal fallopian tubes at

fallopscopy achieve higher spontaneous pregnancy rates (27.6%) than those with mild or severe endotubal lesions (11.5% to 0%).<sup>392</sup> In another study, the management plan was changed in 90% of women following fallopscopy and 24% conceived naturally.<sup>393</sup> [Evidence level 3] However, further diagnostic evaluation studies are required, and technical problems with fallopscopy limit the use of the procedure in routine clinical practice.<sup>394,395</sup>

### 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.<sup>396</sup> [Evidence level 1a] 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 versus water media only.<sup>396</sup> [Evidence level 1a] There were no trials assessing tubal flushing with water-soluble media versus no treatment.

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

### RECOMMENDATIONS

Women who are not known to have comorbidities (such as pelvic inflammatory disease, previous ectopic pregnancy or endometriosis) should be offered hysterosalpingography (HSG) to screen for tubal occlusion because this is a reliable test for ruling out tubal occlusion, and it is less invasive and makes more efficient use of resources than laparoscopy.

**B**

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

**A**

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

**B**

### RESEARCH RECOMMENDATIONS

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

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

## 5.5 Assessing uterine abnormalities

Uterine abnormalities such as adhesions, polyps, submucous leiomyomas and septae have been found in 10% to 15% of women seeking treatment for fertility problems.<sup>398</sup> Compared with HSG, hysteroscopy is recognised as the 'gold standard' test for identifying uterine abnormalities as it allows direct visualisation of the uterine cavity.<sup>399</sup> [Evidence level 2b]

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.<sup>400</sup> [Evidence level 2b] In women undergoing assisted reproduction, the presence of uterine leiomyoma is associated with a reduced chance of clinical pregnancy or delivery.<sup>401,402</sup> [Evidence level 2b–3] However, the effectiveness of surgical treatment of uterine abnormalities to enhance pregnancy rates is not established.

### Ultrasound of the pelvis

Compared with bimanual pelvic examination, transvaginal ultrasound enables pelvic anatomy to be identified with more accuracy and reliability. Ultrasound can be used in the evaluation of pelvic pathology, such as endometriosis, endometrioma, cysts, polyp, leiomyoma, adnexal and ovarian abnormality, where such abnormalities are present.<sup>403–405</sup> [Evidence level 2b–3]

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 5.2).

#### RECOMMENDATION

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

**B**

#### RESEARCH RECOMMENDATION

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

## 5.6 Postcoital testing of cervical mucus

The value of postcoital testing of cervical mucus for the presence of motile sperm is controversial and is a subject of continuing debate.<sup>406–411</sup>

It has been reported that the postcoital test is an effective predictor of conception where defined female causes of infertility are absent and duration of infertility is less than three years.<sup>412</sup> [Evidence level 3] However, a systematic review of 11 observational studies (n = 3093 women) showed that the postcoital test has poor predictive power of fertility and lacks validity.<sup>413</sup> [Evidence level 3] One RCT (n = 444) compared cumulative pregnancy rates between couples offered a postcoital test versus 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 versus 48%, 95% CI 42% to 55% in the control group). The couples offered postcoital tests in this RCT also had more tests and treatments than those in the control group.<sup>414</sup> [Evidence level 1b]

It has been suggested that results of postcoital 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.<sup>410</sup> [Evidence level 4]

#### RECOMMENDATION

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

**A**

## 5.7 Strategies for management of fertility problems

The investigation of people with fertility problems will lead to a number of possible diagnostic categories. 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 importance of psychological support and counselling applies at every stage of the management strategy and process (see Section 4.2). Diagnostic categories and their corresponding management strategies are described below, and the individual techniques are described in subsequent chapters.

### Male factor fertility problems

Techniques for managing ejaculatory failure (anejaculation and retrograde ejaculation) are discussed in Section 6.3.

Semen quality can be marginally improved by lifestyle or medical measures (see Chapters 3 and 6) but natural pregnancy is rare because the spermatozoa remain predominantly dysfunctional.

Endocrine therapy for hypothalamic–pituitary failure and reconstructive surgery in selected cases of obstructive azoospermia may restore fertility by returning functional spermatozoa to the semen and natural pregnancy is feasible (see Chapter 6). In nonobstructive azoospermia there are foci of spermatogenesis in about 50% of cases but there is little potential for restoring fertility. However, in some cases lifestyle measures (see Chapter 3) may return sperm to the ejaculate and thereby avoid the need for surgical sperm recovery. Cases of irreversible obstructive azoospermia and nonobstructive azoospermia are managed by surgical sperm recovery from the epididymis or testis (see Section 12.8) followed by ICSI (see Chapter 13) because of the immaturity of the recovered sperm.

Leucocytospermia has been associated with adverse effects on semen parameters and function.<sup>415,416</sup> Antibiotics have been considered in the treatment of leucocytospermia (see Chapter 6).

Surgical treatment for varicocele is discussed in Section 6.2.

A specific male factor should be identified and corrected where possible to try to initiate natural pregnancy. As this is seldom feasible, the man's sperm is normally used for assisted reproduction, to avoid the need to consider sperm donation. However, an improvement in semen quality may reduce the complexity, costs and potential risks of future assisted reproduction for both partners and any resulting children.

Assisted reproduction methods are indicated by the quantity and quality of spermatozoa that can be isolated by semen preparation techniques. While IUI (see Chapter 10) or IVF (see Chapter 11) are feasible in mild–moderate oligozoospermia, ICSI (see Chapter 13) is usually required to achieve fertilisation, especially in moderate–severe oligozoospermia, asthenozoospermia or teratozoospermia. 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.

If only nonviable spermatozoa are isolated from the semen, surgical sperm recovery from the testis may be required to obtain viable sperm for IVF and/or ICSI (see Section 12.8). Alternatively, assisted reproduction uses sperm isolated from the semen or urine following physical methods involving vibration or electrostimulation to induce ejaculation (see Section 12.3).

Donor insemination (see Chapter 14) is an alternative treatment option for male factor subfertility, and is the principal option for the one in 200 of infertile men (and their partners) who have no sperm because of anorchia or complete germ-cell aplasia.

### World Health Organization Group I ovulation disorders

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 3.6). Otherwise, treatment for this group of women has included GnRH, a hypothalamic hormone which, if given in pulses, induces the appropriate release of the pituitary gonadotrophin hormones FSH and LH (see Section 7.9). Alternatively, women can be treated with gonadotrophins (see Section 7.4).

### World Health Organization Group II ovulation disorders

Treatment strategies in women with WHO Group II ovulation disorders, such as 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 discussed in detail in Chapter 7.

### **World Health Organization Group III ovulation disorders**

Ovarian failure and its management by oocyte donation are discussed in Chapter 15.

### **Hyperprolactinaemia**

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.<sup>417</sup> 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 Section 7.10).

### **Tubal disease**

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 8. The management of tubal disease by IVF does not generally differ from the use of IVF for other indications (see Chapter 11).

### **Endometriosis**

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 below). Medical management, in the absence of pelvic pain, is no longer thought to be an appropriate strategy (see Section 9.1). Surgical management by the ablation of endometriotic lesions and the removal of endometriomas is an established approach (see Section 9.2) but many women with endometriosis of all severities choose to have IVF treatment (see Chapter 11).

### **Uterine abnormalities**

Uterine abnormalities such as adhesions, polyps, submucous leiomyomas and septae may be associated with infertility but their role in causing infertility is not clear. Surgical approaches to management of uterine abnormalities are discussed in Chapter 8.

### **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<sup>418</sup> and 8–28% of infertility in couples.<sup>1,3</sup> In couples with unexplained infertility, the chance of spontaneous conception will relate to the duration of infertility (see Section 3.1). The spontaneous cumulative pregnancy rate has been estimated to lie between 33% and 60% at three years<sup>419,420</sup> and 36% at seven years, although this will be influenced by other known prognostic factors such as the age of the woman.<sup>421–425</sup> [Evidence level 2b–3] Data based on follow-up studies showed that the prognosis for pregnancy remained high without treatment until after three years duration of unexplained infertility. With longer duration of infertility, the prognosis falls by 25% per year and the prognosis is much poorer in women aged 35 years or over.<sup>422</sup>

Many couples who have unexplained fertility problems will be managed expectantly initially and further management is essentially empirical and arises mainly from the time factor.<sup>426</sup> Anti-oestrogens (usually clomifene citrate; see Section 7.1) and IUI (see Chapter 10) are usually used as intermediate options, with the final stage of management being IVF treatment (see Chapter 11). There is no evidence to suggest that ICSI improves pregnancy rates above those achieved with IVF in unexplained fertility problems (see Section 13.3).

Four further treatments that have been used in the management of unexplained infertility are tubal flushing (see Section 5.4), medical treatment with danazol or bromocriptine (see Section 7.10) and fallopian sperm perfusion (see Section 10.5).

# 6 Medical and surgical management of male factor fertility problems

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## 6.1 Medical management

### Gonadotrophin therapy for hypogonadotrophic hypogonadism

We found no RCTs that evaluated gonadotrophin treatment for hypogonadotrophic hypogonadism. Two case series suggest that treatment with human chorionic gonadotrophin (hCG) and hMG increases sperm counts within the normal range in men with hypogonadotrophic hypogonadism of postpubertal onset,<sup>427,428</sup> except in men who also have cryptorchidism.<sup>429</sup> [Evidence level 3]

In one case series, it was suggested that gonadotrophin (hCG and hMG) treatment may improve fertility (92%) in men with hypogonadotrophic hypogonadism.<sup>430</sup> [Evidence level 3] 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.<sup>431</sup> [Evidence level 2b]

Pulsatile GnRH may be as effective as hCG and hMG in enhancing sperm production in men with hypogonadotrophic hypogonadism.<sup>432-434</sup> [Evidence level 2b]

### Gonadotrophin therapy for idiopathic male factor fertility problems

Two RCTs showed no significant difference in pregnancy rates between gonadotrophin treatment when compared with placebo (n = 65, 5.8% with recombinant FSH versus 0% with placebo)<sup>435</sup> or no treatment (n = 136, 44.8% with FSH versus 37.2% with no treatment) in couples with idiopathic male infertility.<sup>436</sup> [Evidence level 1b]

### Anti-oestrogens (clomifene and tamoxifen)

A systematic review of ten RCTs examined the effect of anti-oestrogens in pregnancy rates.<sup>438</sup> It did not detect 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. [Evidence level 1a]

### 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.<sup>439</sup> [Evidence level 1a]

### 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.<sup>440</sup> Nonsignificant results were also reported in an additional RCT (9.6% versus 14%).<sup>441</sup> [Evidence level 1a]

### 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.<sup>442</sup> [Evidence level 1a] We did not identify any new trials since this review was published.

### Antioxidants

Two placebo-controlled RCTs found that vitamin E has a beneficial effect on semen parameters in infertile men,<sup>443,444</sup> but improvement in pregnancy rates was only shown in one trial (n = 87, 21% versus 0%).<sup>444</sup> Another RCT showed no significant improvement in semen parameters with vitamins C and E versus placebo and there was no pregnancy in either group.<sup>445</sup> [Evidence level 1b] Selenium is also an antioxidant, and selenium supplementation has been reported to improve sperm motility and pregnancy rate in subfertile men (see Section 3.10).<sup>175</sup>

Glutathione was found to have a significant positive effect on sperm motility and morphology in one RCT but pregnancy rate was not reported.<sup>446</sup> [Evidence level 1b]

### 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% versus 6.7%).<sup>447</sup> [Evidence level 1b]

### Mast-cell blockers

One RCT (n = 46) found that treatment with mast-cell blocker (tranilast) significantly improved semen parameters and pregnancy rate at one year (28.6% versus 0%) when compared with placebo in men with severe oligozoospermia.<sup>448</sup> [Evidence level 1b]

### Corticosteroid treatment of antisperm antibodies

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.<sup>296</sup>

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.<sup>449–451</sup> One RCT (n = 60) showed a significant increase in pregnancy rate with prednisolone versus placebo (27% versus 7%).<sup>452</sup> Another RCT (n = 77) showed a significant increase in pregnancy rate with low-dose prednisolone versus no treatment (18% versus 3%).<sup>453</sup> All these trials have small sample sizes. [Evidence level 1b] A significant incidence and severity of side effects (including dyspepsia, facial flushing, weight gain and rare complications such as aseptic necrosis of the hip) were reported.<sup>449,454–456</sup> [Evidence level 3]

### Antibiotic treatment of leucocytospermia

An RCT in men with leucocytospermia assigned patients to antibiotic treatment, antibiotic with frequent ejaculation, frequent ejaculation at one month or no treatment. The effect of these interventions on pregnancy rates is not clear; however, treatment groups showed resolution of leucocytospermia (40% versus 68% versus 32% versus 4%).<sup>457</sup> The resolution was sustained at two and three months only in those who took antibiotics and frequently ejaculated.<sup>457</sup> [Evidence level 1b]

Two other RCTs showed that treatment with antibiotics did not improve semen parameters in patients with leucocytospermia,<sup>459</sup> nor resolution of leucocytospermia.<sup>460</sup> [Evidence level 1b] Pregnancy outcomes were not assessed in these trials.

In an RCT (n = 23) patients with male accessory gland infection (epididymo-prostato-vesiculitis), antibiotic treatment compared with placebo was shown to have no significant effect on pregnancy rates or sperm parameters (10% with antibiotics versus 8% with placebo).<sup>461</sup> Another RCT (n = 122) showed significant improvement with antibiotics in sperm parameters at three months and pregnancy rates (28.2% with antibiotics versus 5.4% with no treatment).<sup>462</sup>

[Evidence level 1b] Treatment with antibiotics did not affect pregnancy rates in couples with mycoplasma-related infertility.<sup>463</sup> [Evidence level 1b]

One RCT (n = 120) found that treatment with antibiotics and kallikrein improved sperm motility and pregnancy rates (32% with kallikrein plus antibiotics versus 17% with antibiotics alone; RR 1.84, 96% CI 0.95 to 3.56) in infertile men with genital tract infections.<sup>464</sup> [Evidence level 1b]

### RECOMMENDATIONS

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

B

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

A

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

A

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

A

### RESEARCH RECOMMENDATION

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

## 6.2 Surgical management

### Surgical treatment of obstructive azoospermia

A case-series study of 370 men with obstructive azoospermia showed that epididymovasostomy with postinfective caudal block gave a patency rate of 52% and pregnancy rate of 38%, respectively. Postinfective 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).<sup>465</sup> [Evidence level 3] Another case series of 44 men found that 58% achieved patency and 23% of couples achieved a pregnancy following surgery for ejaculatory duct obstruction.<sup>466</sup> [Evidence level 3] 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.<sup>467</sup> [Evidence level 3] 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 12.8). Sperm should be evident within 6 to 12 months of successful surgery and so it may be reasonable to discuss assisted reproduction with men whose partners have not conceived 12 to 18 months after surgery. Alternatively, men with congenital bilateral absence of vas deferens (CBAVD) may be offered surgical retrieval of spermatozoa for use in assisted reproduction (see Section 16.8).

### Surgical treatment of varicoceles

A systematic review of seven RCTs compared pregnancy rates of varicocele repair in men with normal semen (two RCTs), subclinical varicoceles (three RCTs) and clinical varicoceles with abnormal semen (two RCTs).<sup>468</sup> [Evidence level 1a] The review found that varicocele repair did not improve pregnancy rates in couples with male fertility problems or unexplained fertility problems (61 pregnancies among 281 treated couples versus 50 pregnancies among 259 controls; 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). Subgroup analysis showed that varicocele treatment was not effective in RCTs restricted to male subfertility with clinical varicoceles or in those that included men with subclinical varicoceles or normal semen analysis.<sup>469</sup> [Evidence level 1a] The trials reviewed were of varying sizes with no clear description of allocation concealment; there

was clinical heterogeneity in the subjects selected. Mean age of the male partners and duration of subfertility differed between the RCTs<sup>470,471</sup> which considered clinical varicoceles with abnormal semen and both of these studies had high drop-out rates. Meta-analysis of these two RCTs showed no improvement in pregnancy rate with varicocele repair (pooled RR 2.33; 95% CI 0.47 to 11.6 using a random effects model; RR 1.47; 95% CI 0.87 to 2.50 using a fixed effects model), although a significantly higher pregnancy rate was reported in one of the RCTs (RR 6.0, 95% CI 1.55 to 23.2).<sup>470</sup> This was a report from one of 12 centres involved in a WHO-sponsored multicentre RCT that started in 1984. The systematic review excluded three further publications relating to the multicentre trial<sup>472-474</sup> because they were only reported in abstract or summary form. The exclusion could have made a difference to the conclusions of the systematic review. Of the three additional publications, two showed a significant two-fold relative improvement in pregnancy rates following varicocele repair in men with abnormal semen.<sup>472,474</sup> However, the definitive WHO trial remains unpublished and the results are, therefore, not available to secondary researchers. Until such time as a full report of the WHO multicentre trial is published, the effectiveness of varicocele repair in men with abnormal semen will remain uncertain. Further primary research to clarify this issue seems unlikely, given the advances in alternative treatments such as ICSI. However, research comparing the effectiveness of varicocele treatment and in vitro fertilisation, taking into consideration patient preference and cost effectiveness would be useful.<sup>475,476</sup> [Evidence level 4]

### RECOMMENDATIONS

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

C

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

A

### RESEARCH RECOMMENDATION

Randomised controlled trials are needed to compare the effectiveness of surgery for varicocele and in vitro fertilisation treatment in men with abnormal semen quality.

## 6.3 Management of ejaculatory failure

We identified a systemic review that assessed treatment options for anejaculation and retrograde ejaculation in men with ejaculatory disorders or in men undergoing fertility treatment.<sup>299</sup> [Evidence level 1b–3] This review included 88 studies assessing treatment of anejaculation (n = 2346 patients) and 132 studies assessing treatment of retrograde ejaculation (n = 342 patients). The designs of these studies ranged from RCT (n = 1) to observational or small case studies.

Medical treatment of anejaculation has included the use of alpha-agonistic drugs such as imipramine, pseudoephedrine or parasympathomimetic and neostigmine. The systematic review found that treatment with alpha-agonistics had significantly lower success rates than treatment with parasympathetic drugs in the reversal of anejaculation (19% with alpha-agonists versus 51% with parasympathomimetics). Considerable adverse effects such as headache, nausea and vomiting were reported. Medical treatment of anejaculation is not generally recommended as treatment of first choice.

Medical treatment of retrograde ejaculation aims to increase sympathetic tone of the bladder or decrease parasympathetic activity using alpha-agonistic or anticholinergic and antihistamine drugs such as imipramine, milodrin, chlorpheniramine or brompheniramine. The systematic review found no significant differences between the different medical treatments in the reversal of retrograde ejaculation and spontaneous or assisted reproduction pregnancies (ranged from 56% to 79%), irrespective of the underlying diagnosis. Adverse effects such as dizziness, restlessness, dry mouth and nausea were reported. If medical treatment of retrograde ejaculation fails, the use of penile electrovibration stimulation and sperm recovery from the urine can be considered.

Penile electrovibration stimulation initiates reflex spinal cord activity, causing ejaculation. The systematic review reported pregnancy rates of between 42% and 89% following IUI, IVF, ICSI and GIFT in partners of men who underwent electrovibration stimulation for reversal of anejaculation.

Transrectal electroejaculation stimulates the nerves responsible for ejaculation. The systematic review reported pregnancy rates of between 16% and 80% following IUI, IVF, ICSI and GIFT in partners of men who underwent electroejaculation for reversal of anejaculation.

Urine is known to have a deleterious effect on sperm quality and alkalinisation of urine pH (a buffer) may be necessary for the retrieval of the retrograde ejaculate from the bladder. The systematic review reported pregnancy rates of between 50% and 100% following IUI, IVF, ICSI and GIFT in partners of patients who underwent sperm retrieval from the urine for reversal of retrograde ejaculation.

Due to the heterogeneous nature of the studies included in the review, such as in the different equipment and techniques used, dosage, outcomes measurement and study design, it remains questionable which modality offers the best chances for men with ejaculatory failure. RCTs comparing different treatment options are urgently needed.

Although sperm quality in men with anejaculation or retrograde ejaculation is often impaired, spermatozoa obtained with electrovibratory stimulation were reported to have better quality and a higher patient preference when compared with electroejaculation.<sup>477</sup> [Evidence 1b] However, the quality of semen obtained by electroejaculation was not reported to be significantly different from sperm obtained naturally after successful electroejaculation in a group of men with ejaculatory disorder.<sup>478</sup> [Evidence level 3] If only spermatozoa of poor quality can be retrieved, IVF/ICSI should be considered as first choice of treatment, whereas ICSI is a viable alternative for anejaculatory men in whom IUI or IVF failed.<sup>479,480</sup> [Evidence level 3] The combination of ICSI and electroejaculation may improve the fertility chances of patients with psychogenic anejaculation resistant to conventional treatment modalities.<sup>481</sup> [Evidence level 3]

Fertilisation and pregnancy rates in ICSI of cryopreserved sperm from transrectal electroejaculation are comparable to those of freshly obtained sperm in patients with psychogenic anejaculation.<sup>482</sup> [Evidence level 3]

If no viable spermatozoa can be retrieved with these treatment modalities, surgical sperm retrieval together with IVF and ICSI provides a good alternative option (see Section 12.8). A case study 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.<sup>483</sup> [Evidence level 3]

Anxiolytic drugs and/or sildenafil may also be helpful in cases of ejaculation failure associated with erectile dysfunction caused by psychogenic disorders.<sup>484</sup> [Evidence level 1a]

The relative merits of electroejaculation and surgical sperm retrieval remain uncertain.

### RECOMMENDATIONS

Treatment of ejaculatory failure can restore fertility without the need for invasive methods of sperm retrieval or the use of assisted reproduction procedures. However, further evaluation of different treatment options is needed.

C

# 7. Ovulation induction

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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 10 and 11, respectively.

## 7.1 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, increasing gonadotrophins and so stimulating the ovary to produce more follicles. The evidence relating to anti-oestrogens predominantly involves clomifene citrate. The adverse effects of anti-oestrogens such as clomifene citrate include hot flushes, ovarian hyperstimulation, abdominal discomfort and multiple pregnancy.<sup>181</sup>

### Anti-oestrogens in women with ovulatory disorders

A systematic review of four crossover RCTs that compared clomifene citrate with placebo in patients with amenorrhoea/oligomenorrhoea, 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).<sup>485</sup> [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 versus 15% with clomifene citrate; RR 1.45, 95% CI 0.58 to 3.63) and ovulation (44% with tamoxifen versus 45% with clomifene citrate) in anovulatory women with infertility.<sup>486</sup> [Evidence level 1b] Similar results were found in three other studies, including a quasi-randomised study.<sup>487–489</sup> [Evidence level 1b]

One RCT showed that tamoxifen/clomifene citrate combination therapy did not improve pregnancy rate per cycle (8.6% with tamoxifen/clomifene citrate versus 4.8% with clomifene citrate; RR 1.80, 95% CI 0.20 to 16.21).<sup>490</sup> [Evidence level 1b]

About 70% of anovulatory women ovulate in response to clomifene citrate treatment,<sup>491,492</sup> and they do so at a dose of 50–100 mg,<sup>493</sup> the maximum dose being 250 mg. Anovulatory women who do not ovulate while receiving the 150 mg dose of clomifene citrate are considered to be resistant to the drug.<sup>494</sup> In anovulatory women, there is a significant association between clomifene citrate treatment failure and increased BMI (BMI greater than 27.2 kg/m<sup>2</sup> or greater than 30.6 kg/m<sup>2</sup>).<sup>495,496</sup> [Evidence level 2b] A weight loss programme may improve ovulation and pregnancy outcomes in women who are obese and infertile for all forms of fertility treatment, including ovulation induction, IUI and IVF (see Sections 3.6 and 11.7).<sup>497,498</sup> [Evidence level 2b] Advice on weight reduction may improve response to clomifene citrate treatment; a modest weight reduction of 5% of initial body weight can result in improvement in endocrine and ovulatory function of obese women with PCOS.<sup>499</sup> Lifestyle modification may improve insulin sensitivity and restore ovulation in women with PCOS.<sup>500</sup> [Evidence level 2b]

Although the *British National Formulary* recommends a maximum of six cycles of clomifene citrate,<sup>181</sup> 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.<sup>495,501</sup> [Evidence level 2b] 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).<sup>502</sup> [Evidence level 3] 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.<sup>503</sup> [Evidence level 1a] The seventh trial was excluded from the systematic review because it used alternation rather than randomisation to allocate treatment. Allocation based on alternation may be predictable and this could bias the findings. In women with unexplained infertility, clomifene citrate treatment compared with no treatment increased clinical pregnancy rates per woman (OR 2.37, 95% CI 1.22 to 4.62) and per treatment cycle (OR 2.5, 95% CI 1.35 to 4.62).<sup>503</sup> 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 woman and per cycle in the clomifene citrate group compared with the no treatment group.<sup>504</sup>

### RECOMMENDATIONS

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

A

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

B

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

A

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

GPP

## 7.2 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.<sup>505</sup> The earlier review is of poorer quality and includes 12 RCTs and a number of observational studies.<sup>506</sup> 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<sup>2</sup>, metformin as a single agent was not found to increase clinical pregnancy rate when compared with placebo. However, treatment with both metformin and clomifene citrate did increase clinical pregnancy rate compared with clomifene citrate alone (OR 4.88; 95% CI 2.46 to 9.67). Metformin as a single agent was found to induce ovulation when compared with placebo (OR 3.88; 95% CI 2.25 to 6.69). Metformin in combination with clomifene citrate was also effective in inducing ovulation compared with clomifene citrate alone (OR 4.41; 95% CI 2.37 to 8.22). Metformin has significant adverse side effects such as nausea, vomiting and gastrointestinal disturbances.<sup>505</sup> [Evidence level 1a] Metformin can be used as an adjuvant to general lifestyle improvements (see Sections 3.6 and 5.2).

Metformin treatment of women with clomifene citrate-resistant PCOS undergoing IVF significantly improved clinical pregnancy rates.<sup>507</sup> [Evidence level 1b–2b]

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

**RECOMMENDATIONS**

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

A

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

GPP

**7.3 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.<sup>508</sup> [Evidence level 1a] 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.<sup>508</sup> [Evidence level 1a]

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 versus 88% with a thick needle, RR 0.59, 95% CI 0.39 to 0.91) in laparoscopic ovarian drilling in patients with PCOS.<sup>509</sup> [Evidence level 1b]

A retrospective study showed that three punctures per ovary appeared to be the plateau dose for laparoscopic ovarian diathermy.<sup>510</sup> [Evidence level 3]

Laparoscopic ovarian diathermy can impose technical problems and anaesthetic risks in obese women with PCOS.<sup>511</sup> There are no data on the long-term health consequences of ovarian drilling or the formation of adhesions.

**RECOMMENDATION**

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

A

**RESEARCH RECOMMENDATION**

Further research is needed to evaluate the effect of ovarian drilling on the formation of adhesions and the long-term health consequences of this procedure.

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

For women with WHO Group I ovulation disorders, treatment with hMG, which includes FSH and LH, was reported to be more effective in improving ovulation than FSH alone.<sup>512</sup> [Evidence level 2a]

For women with PCOS who do not respond to clomifene citrate, gonadotrophins have been used as ovulation induction agents.<sup>513</sup> Human menopausal gonadotrophin is a purified extract from human postmenopausal 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 as a recombinant peptide produced by cultured cells.

A systematic review of 14 RCTs found no significant differences between hMG (both FSH and LH) and urinary FSH (uFSH) in terms of 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).<sup>513</sup> [Evidence level 1a] No significant differences on the above outcomes were found between the use of subcutaneous pulsatile and intramuscular injection of gonadotrophins;<sup>513</sup> daily and alternate day administration; or step-up' and standard regimens.<sup>513</sup> [Evidence level 1a]

A systematic review of four RCTs compared recombinant FSH (rFSH) and 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).<sup>514</sup> [Evidence level 1a] No significant differences were shown in these outcomes between administering rFSH as a chronic low dose or conventional regimen.<sup>514</sup>

## RECOMMENDATIONS

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

A

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

A

## 7.5 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.<sup>515</sup> 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.<sup>516</sup> [Evidence level 1a]

### Urinary-derived gonadotrophins versus recombinant follicle-stimulating hormone

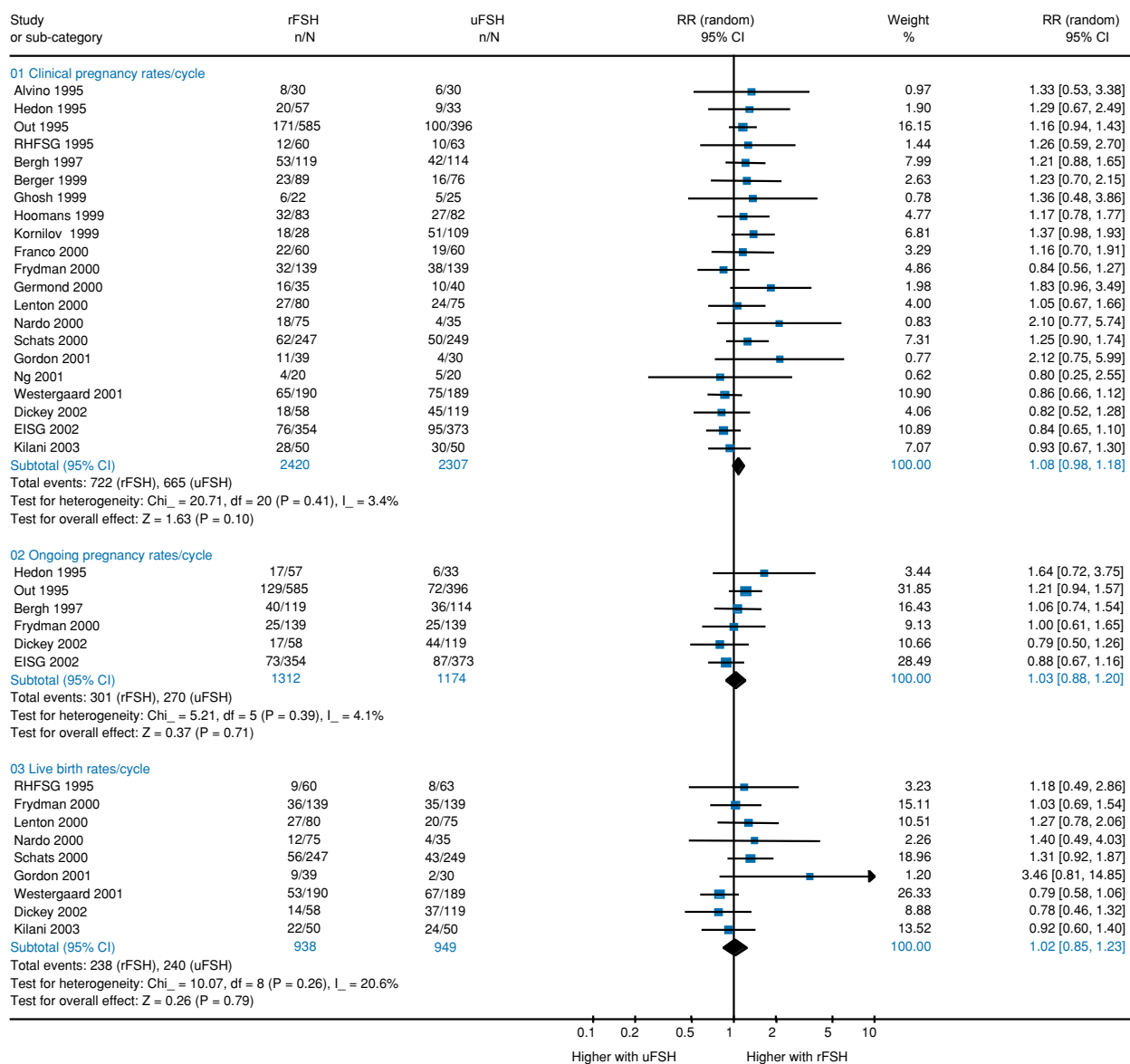
Four meta-analyses involving a total of 26 RCTs were identified. There was some overlap between the trials included in the different meta-analyses, with each meta-analysis using different inclusion and exclusion criteria for the intervention.<sup>517-520</sup> [Evidence level 1a] The first systematic review (18 RCTs) included only trials comparing uFSH with rFSH.<sup>517</sup> [Evidence level 1a] The second systematic review (20 RCTs) included trials comparing urinary gonadotrophins (including hMG, FSH-P and FSH-HP) versus rFSH.<sup>518</sup> [Evidence level 1a] The third systematic narrative review of eight RCTs included in the second systematic review provided no clear assessment of selection, quality and validity of included studies.<sup>519</sup> [Evidence level 1b-2a] The fourth systematic review (eight RCTs) included only trials comparing hMG versus rFSH.<sup>520</sup> [Evidence level 1a]

We conducted a systematic review of RCTs that compared rFSH to any urinary-derived FSH (for example, HP-hMG, uFSH, hMG) after GnRH agonist downregulation using a long protocol in normogonadotrophic women. After an exhaustive search of databases for studies comparing rFSH and urinary-derived FSH, 29 published RCTs were identified. Of these 29 RCTs, we excluded three studies in which a GnRH agonist protocol was not used,<sup>522,523,1148</sup> two studies in which a short GnRH agonist protocol was used,<sup>524,525</sup> one study in which a quasi-randomisation method was used,<sup>526</sup> one study published only as an abstract in which no data were presented,<sup>527</sup> and one other study published only as an abstract that we were unable to obtain a copy of.<sup>528</sup>

We found three RCTs<sup>529,530,1148</sup> that had not been included in any of the published systematic reviews. The total number of RCTs in our review was, therefore, 21 (4727 women).<sup>529-549</sup> All outcomes considered were dichotomous therefore relative risks with 95% confidence intervals were calculated using the random effects model. The results of the meta-analysis are presented as a forest plot in Figure 7.1. Nine RCTs reported live birth rates per cycle (1887 women), but there was no difference between rFSH and urinary-derived FSH (RR 1.02, 95% CI 0.85 to 1.23). Six RCTs reporting ongoing pregnancy rates per cycle (2486 women) did not show any difference between rFSH and urinary-derived FSH (RR 1.03, 95% CI 0.88 to 1.20). Twenty-one trials reporting clinical pregnancy rates per cycle showed no difference between rFSH and urinary-derived FSH (RR 1.08, 95% CI 0.98 to 1.18). [Evidence level 1a]

A recent RCT (n = 191) reported a significantly higher convenience score and less rFSH used with self injection by IVF patients with a pen device when compared with a conventional syringe.<sup>550</sup> [Evidence level 1b]

Comparison: Urinary-derived FSH versus recombinant FSH  
Outcome: Clinical pregnancy, ongoing pregnancy and live birth rates



**Figure 7.1** Comparison between urinary follicle-stimulating hormone and recombinant follicle-stimulating hormone showing clinical pregnancy, ongoing pregnancy and live birth rates

### 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.<sup>551,552</sup> [Evidence level 1a] The conclusions of the most recent review were that the use of rFSH compared to uFSH in IVF treatment increased the total number of ongoing pregnancies at 12 weeks of gestation (OR 1.20, 95% CI 1.02 to 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 high purity uFSH/hMG. This RCT did not detect a difference between the different gonadotrophins (OR 1.19, 95% CI 0.90 to 1.58).<sup>553</sup> [Evidence level 1b] However, in their economic model, in spite of the fact that there was no difference detected between the groups they used these estimates to predict a cumulative pregnancy rate after three cycles of 57% for rFSH and 44% for both high purity uFSH (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.<sup>518</sup> Overall, the pregnancy rates with rFSH and uFSH-HP/hMG are not different (OR 1.07 95% CI 0.94 to 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 minimising costs when prescribing.

A UK economic evaluation of urinary gonadotrophins (highly purified hMG or HP-hMG) compared with rFSH was undertaken recently.<sup>554</sup> This study was based on an RCT that found no difference in pregnancy rate or ongoing pregnancy at ten 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-F® (Serono) (rFSH) 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*<sup>181</sup> 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 or 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, urinary follicle-stimulating hormone and recombinant follicle-stimulating hormone are equally effective in achieving a live birth when used following pituitary down-regulation as part of in vitro fertilisation treatment. Consideration should be given to minimising cost when prescribing.

A

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

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

A systematic review of three RCTs comparing pretreatment with GnRH analogue (GnRHa) 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).<sup>555</sup> [Evidence level 1a] One further RCT with pretreatment with GnRHa and FSH compared with FSH alone did not improve the pregnancy rate (0% versus 50%) or the ovulation rate (20% versus 90% RR 0.22; 95% CI 0.06 to 0.78).<sup>556</sup> [Evidence level 1b] When gonadotrophins were used concomitantly with GnRHa, 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.<sup>513</sup> [Evidence level 1a]

### RECOMMENDATIONS

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

A

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

GnRH agonists are most often 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 versus no gonadotrophin-releasing hormone agonist protocol

A meta-analysis of 17 RCTs showed an increase in 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.<sup>557</sup> [Evidence level 1a] There was a reduction of cycle cancellation with the use of GnRH agonist protocols (OR 0.33, 95% CI 0.25 to 0.44).<sup>557</sup> [Evidence level 1a] There were no 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 live birth rates or OHSS rates.<sup>557</sup> [Evidence level 1a]

### Gonadotrophin-releasing hormone agonist protocols: long versus short versus ultrashort

In long protocols, GnRH agonists are started either in the midluteal phase or in the early follicular phase to achieve pituitary down-regulation in about 8 to 21 days after which gonadotrophins are commenced. The duration of GnRH agonist administration is about 10 to 14 days in short protocols and about three days in ultrashort protocols. Both short and ultrashort protocols take advantage of the increased secretion of gonadotrophins resulting from the initial direct stimulation of the pituitary gland by GnRH agonist before desensitisation. A 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 ultrashort GnRH agonist protocols. The pooled OR for clinical pregnancy rate per cycle in long versus short GnRH agonist protocol was 1.27 (95% CI 1.04 to 1.56) and in long versus ultrashort GnRH agonist protocols was 1.47 (95% CI 1.02 to 2.12).<sup>558</sup> [Evidence level 1a]

An earlier meta-analysis of 17 RCTs included quasi-randomised trials and is therefore excluded from this review.<sup>557</sup>

### **Gonadotrophin-releasing hormone agonist protocols: depot versus daily dose**

There are two types of GnRH agonist used in the long protocol: short-acting given in daily doses (buserelin, nafarelin nasal spray) or higher long-acting (depot) doses (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).<sup>559</sup> However, the use of depot GnRH agonist increased gonadotrophin requirements and duration of ovarian stimulation when compared with daily GnRH agonist.<sup>559</sup> [Evidence level 1a]

A meta-analysis of nine RCTs found no significant differences between intranasal GnRH agonist versus other GnRH agonist protocols in clinical pregnancy rate per embryo transfer (32% with intranasal GnRH agonist versus 30% with other GnRH agonists; common OR 0.93, 95% CI 0.57 to 1.51) and in cycle cancellation rate (5% versus 6%; common OR 0.88, 95% CI 0.44 to 1.79). There were no data on pregnancy rate per cycle.<sup>560</sup> [Evidence level 1a]

### **Gonadotrophin-releasing hormone antagonists versus 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 (less than one 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 women.

A systematic review of five RCTs showed that the use of GnRH antagonist resulted in reduced clinical pregnancy rates per woman (pooled OR 0.79, 95% CI 0.63 to 0.99) when compared with long protocol GnRH agonist.<sup>561</sup> [Evidence level 1a] There were no significant differences between these two protocols in terms of multiple pregnancy rates (pooled OR 0.74, 95% CI 0.48 to 1.16), incidence of severe OHSS (pooled OR 0.47, 95% CI 0.18 to 1.25), miscarriage rates (pooled OR 1.03, 95% CI 0.52 to 2.04) or cycle cancellation rates (pooled OR 0.88, 95% CI 0.56 to 1.40).<sup>561</sup> [Evidence level 1a] Patient satisfaction was not considered in this systematic review.

A second systematic review<sup>562</sup> included six RCTs, five of which were considered in the review discussed above, and a non-randomised study. The results of this review were similar to those of the above review.

Five further RCTs were identified. One RCT (n = 142)<sup>564</sup> compared GnRH agonist and GnRH antagonist protocols combined with rFSH for ovarian stimulation in women undergoing IVF treatment. There was no significant difference in pregnancy rates between the two groups (OR 0.91, 95% CI 0.39 to 2.14).<sup>564</sup> [Evidence level 1b] Three other RCTs [abstracts] (n = 586 cycles, n = 54 cycles and n = 19 cycles) reported no significant differences in clinical pregnancy rates or implantation rates between GnRH agonist and GnRH antagonist protocols for pituitary downregulation in IVF treatment.<sup>565-567</sup> [Evidence level 1b] A further RCT [abstract] (n = 27) found no significant difference in clinical pregnancy rate with GnRH antagonists compared with GnRH agonists for pituitary downregulation in IVF treatment (OR 3.24, 95% CI 0.69 to 15.2).<sup>568</sup> [Evidence level 1b]

The RCTs discussed above did not report on patient satisfaction or preference for treatment (reduction of adverse effects, shorter duration of treatment). The effect of antagonists in reducing the dose of gonadotrophins also needs to be quantified. Further RCTs are needed to assess the clinical (and economic) benefit of the use of GnRH antagonists in pituitary downregulation in IVF patients.

### Relative cost of agonists and antagonists in ovulation induction

The comparison of cost of ovulation induction using antagonists or agonists is determined by the difference in cost of these drugs, the cost of gonadotrophins and the number of days of treatment with these drugs. The exact regimen prescribed will depend upon the woman's responsiveness to treatment and the drugs that are used will vary between clinics. The costs reported below are based on typical drug and dose regimens for ovulation induction (see Table B.13, page 172). The drug costs, which were obtained from the *British National Formulary*,<sup>181</sup> may overestimate the prices charged to individual clinics, since these are negotiated on a clinic-by-clinic basis.

The cost of antagonists for a five-day treatment schedule is around £120 and the cost of agonists for a much longer schedule (24 to 31 days) is £111. The cost of agonists increases with longer schedules of treatment from around £88 for a shorter schedule to around £111 for a longer schedule. This could be an underestimate if a woman requires a few more doses of agonists, which may only be available in 30-dose or 60-dose units.

The cost of gonadotrophins is the same for both treatments since it typically involves around ten days of treatment. The total cost of gonadotrophins (using BNF prices) is around £544 for a low-dose schedule for women who are expected to respond well to ovulation induction and around £1,050 for a high dose schedule.

The overall cost of a schedule of ovulation induction with antagonists is between £645 and £1,170 per cycle of treatment. The cost of agonists is between £623 and £1,138 per cycle of treatment. In practice, the cost of the antagonist schedule is likely to be toward the lower end of the cost range as the higher doses are for women who have particular risk factors that predispose them to less successful ovulation induction. The agonist schedule of treatment is likely to cost toward the higher end of the range since women tend to use the drug for longer periods of time before starting gonadotrophins. Therefore, it is likely that the agonist schedule is less costly than antagonist schedule.

Evidence from robust economic studies is required to ascertain whether there is a true difference in cost between the two regimens as well as any other differences in resource use in order to determine their relative cost-effectiveness.

### RECOMMENDATIONS

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

A

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

A

### RESEARCH RECOMMENDATION

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

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

For women with clomifene citrate-resistant PCOS, co-treatment with recombinant human growth hormone plus GnRHa, or growth hormone plus hMG has no significant effect on the amount and duration of hMG used, ovulation (93% versus 93%; 88% versus 100%, respectively) and pregnancy rates (26% versus 20%; 25% versus 13%) when compared with GnRHa and hMG alone.<sup>569</sup> [Evidence level 1b] It has been suggested that co-treatment with growth hormone may improve ovarian responses to exogenous gonadotrophins, thus reducing the overall gonadotrophin requirement.<sup>570</sup>

### RECOMMENDATIONS

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

A

## 7.9 Pulsatile gonadotrophin-releasing hormone

In case series studies, pulsatile GnRH induces ovulation, achieving cumulative pregnancy rates of up to 82% in women 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.<sup>571–573</sup> [Evidence level 3]

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 women with clomifene citrate-resistant PCOS when compared with other ovulatory agents (hMG, FSH, with and without pretreatment with GnRHa).<sup>574</sup> [Evidence level 1a]

A study comparing hMG with pulsatile GnRH reported no difference in multiple gestation rates (14.8% versus 8.3%) but a lower rate of triplets in the pulsatile GnRH group.<sup>575</sup> [Evidence level 2b]

### RECOMMENDATIONS

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

B

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

A

## 7.10 Dopamine agonists

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 versus 52% and 48% with bromocriptine, respectively).<sup>576,577</sup> [Evidence level 1b] However, the manufacturer advises discontinuation of cabergoline at least one month before pregnancy.<sup>181</sup> [Evidence level 4]

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 versus placebo in couples with unexplained infertility.<sup>578</sup> [Evidence level 1a]

### RECOMMENDATION

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

A

## 7.11 Monitoring ovulation induction during gonadotrophin therapy

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,<sup>579–581</sup> in helping to reduce multiple pregnancy

rates, especially in women with PCOS<sup>571</sup> when compared with oestrogen monitoring. [Evidence level 2b] Oestrogen monitoring provides no additional information compared with ovarian ultrasound.<sup>579</sup> [Evidence level 2b] 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.<sup>582</sup> [Evidence level 3] An observational study reported that follicular sonography performed during ovarian stimulation predicted 88% of cycle decisions.<sup>583</sup> [Evidence level 3]

### Ovarian hyperstimulation syndrome

The aim of ovulation induction therapy is to stimulate the ovaries to produce more than one egg. This carries the risk of overstimulation and OHSS. OHSS is a potentially fatal condition when many follicles are stimulated, leading to ascites, pleural and pericardial effusion, haemoconcentration and coagulopathy.<sup>584</sup>

The exact incidence of severe OHSS when fertility drug therapy is used has not yet been determined. Available data suggest an incidence of 3% of cycles when hMG is used,<sup>585</sup> and in 0.2% to 1.0% of all assisted reproduction cycles.<sup>586–588</sup> Results generated by the European Society for Human Reproduction and Embryology (ESHRE) on assisted reproductive technology in Europe in 1999 reported an incidence of OHSS of 0.9% (range 0.3 % to 2.7%; 1083 cases of OHSS after 114,628 cycles).<sup>589</sup> [Evidence level 3]

Clinics that provide ovarian stimulation should have protocols in place for the prevention, diagnosis and management of OHSS (see Section 12.8).

### Multiple pregnancy

Prevention of iatrogenic multifetal gestation involves judicious use of ovulation induction drugs and monitoring with ultrasound to chart follicular development. It is best carried out in a specialist clinic.

There is a strong correlation between the initial number of embryos, the final number and the risks of pregnancy loss and prematurity.<sup>590,591</sup> [Evidence level 3] Multiple gestations are high-risk pregnancies associated with higher obstetric complications, perinatal, neonatal and infant mortality,<sup>592</sup> as well as significant financial<sup>593,594</sup> and psychological<sup>595</sup> consequences. [Evidence level 3] However, assisted reproduction multiple pregnancies do not appear to be at any more risk of poor obstetric and neonatal outcomes than those conceived spontaneously.<sup>596,597</sup> [Evidence level 3] Recent surveys have suggested that multiple pregnancies may not be viewed as an adverse outcome by women with fertility problems.<sup>598–602</sup> [Evidence level 3–4]

The exact numbers of multiple pregnancies arising from ovarian stimulation, with or without IUI, are unknown, as there are no national registers that record the outcome of controlled ovarian stimulation,<sup>603</sup> as there are with IVF and ICSI, such as the register monitored by the HFEA. Multiple pregnancy occurs in 2–13% of women with all causes of infertility taking clomifene citrate.<sup>604</sup> This compares with a spontaneous multiple pregnancy rate of about 1–2% of women in the North American and European populations.<sup>605,606</sup> Women with clomifene citrate-resistant PCOS treated with conventional regimens of gonadotrophins have a 36% multiple pregnancy rate.<sup>607</sup> [Evidence level 3] A one-year survey of triplets and higher-order pregnancies in the UK found that 31% of the triplet pregnancies were spontaneous, 34% were from various methods of ovulation stimulation and 35% were from IVF/GIFT. Triplet pregnancies accounted for 56% of all pregnancies attributable to clomifene citrate.<sup>608</sup> [Evidence level 3]

The issue of multiple pregnancies arising from IVF is discussed In Chapter 11, Section 11.2.

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.<sup>590</sup> [Evidence level 4] For any initial number of embryos, reduction to twins has the highest survival rate.<sup>591</sup> [Evidence level 3] Reduction to singletons rather than twins is associated with a higher gestational age at delivery but a lower survival rate.<sup>590</sup> [Evidence level 3]

## RECOMMENDATIONS

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

C

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

C

## 7.12 Other risks and adverse 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.<sup>609</sup> 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).<sup>502</sup> [Evidence level 3] 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).<sup>502</sup> [Evidence level 3]

Case reports and epidemiological studies examining ovarian cancer risk in relation to the use of fertility drugs have shown conflicting results, which may in part be explained by methodological problems such as low study power and misclassification bias. Reviews of these studies found insufficient evidence to support a direct causal relationship.<sup>610–614</sup> 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.<sup>615–620</sup> 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 UK found no evidence for a link between ovarian stimulation and increased cancer incidence, although this needs to be interpreted with caution because of methodological limitations.<sup>621</sup> [Evidence level 3]

A survey of women attending an infertility clinic reported that 67% of women knew of a possible relationship between ovulation induction 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 fertility treatment outweighed the risks.<sup>622</sup> A survey of reproductive endocrinologists reported that 83% of those surveyed said they addressed this risk when obtaining consent from patients for infertility treatment,<sup>623</sup> and 40% of physicians routinely discussed the topic of ovarian cancer with their patients before prescribing fertility drugs.<sup>622</sup> [Evidence level 3]

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.<sup>624</sup>

The association between ovulation induction therapy and breast cancer, thyroid cancer, endometrial cancer, cervical cancer, colorectal cancer and melanoma has not been established.<sup>614</sup> Further studies are needed in this area.

### 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 Creutzfeldt–Jacob disease.<sup>625</sup> 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 Creutzfeldt–Jacob disease. This reflects the position in the UK 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 Creutzfeldt–Jacob disease was reported in Italy. Other urinary products available in the UK are not affected because the urine is sourced from countries with no reported cases of variant Creutzfeldt–Jacob disease.

Recombinant products, where bovine materials are used in their manufacture, are subject to strict controls to ensure freedom from prion agents. These controls, agreed across Europe, cover the source of starting materials and donor animals, the type of tissue involved, manufacturing processes, quality control and audit procedures and how the material is used in the production of the recombinant medicine.

All recombinant and urinary gonadotrophins available in the UK comply with European safety requirements for transmissible spongiform encephalopathies.

### RECOMMENDATION

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

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.

# 8. Tubal and uterine surgery

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Proximal tubal occlusion is a common cause of tubal infertility. However, proximal tubal obstruction is probably overdiagnosed, as intrauterine pregnancies do occur spontaneously in women with proximal tubal blockage diagnosed by HSG and/or laparoscopy and dye.<sup>626</sup> [Evidence level 3]

If tubal surgery is effective it may enable couples to conceive naturally without further intervention.<sup>627</sup>

## 8.1 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 case series study reported that 27%, 47% and 53% of women with proximal tubal blockage who had microsurgical tubocornual anastomosis achieved a live birth within one, two and 3.5 years of surgery, respectively.<sup>628</sup> [Evidence level 3] A review of nine other case series studies reported that about 50% of women with proximal tubal blockage who had microsurgical tubocornual anastomosis achieved a term pregnancy but it did not specify the time period upon which this figure was based.<sup>629</sup> [Evidence level 3]

A cohort study with a follow-up period of three years reported higher pregnancy rates in women who underwent tubal surgery compared with those who did not (29% with surgery versus 12% without surgery;  $p < 0.05$ ).<sup>630</sup> [Evidence level 2b] The surgery was more effective in women with milder pelvic disease (stage I, 67% with surgery versus 24% without surgery,  $p < 0.05$ ; stage II, 41% with surgery versus 10% without surgery,  $p < 0.05$ ; stage III, 12% with surgery versus 3% without surgery, not significant; and stage IV, 0% with surgery, pelvic disease so severe that surgery not offered). Several case series reported that pregnancy rates after tubal surgery were comparable with those resulting from IVF in women with filmy adhesions, mild distal occlusion or proximal tubal blockage.<sup>631–635</sup> [Evidence level 2b–3]

Case series following up women after surgery for distal tubal occlusion reported live birth rates of 20–30%.<sup>631,636,637</sup> [Evidence level 3] The success of tubal microsurgery assessed in case series was reported to range from 5% term pregnancy rate at 36 months<sup>284</sup> to 25% cumulative pregnancy rates at 12 months and 40% at 50 months.<sup>637</sup> [Evidence level 3] This included a heterogeneous group of women with proximal or distal tubal disease. The severity of tubal damage was linked closely to outcome, with better results in those with filmy adhesions and limited damage, compared with those with more extensive pathology. Success rates with tubal surgery are also thought to depend upon the severity of the tubal damage as well as the age of the woman, duration of infertility and other associated infertility factors.<sup>637</sup> [Evidence level 3] It has also been suggested that specialised training, experience and availability of equipment have a major effect on the outcome of tubal surgery.<sup>2,284,637</sup> [Evidence level 4]

A narrative review of ten case series ( $n = 1128$ ) reported a cumulative ectopic pregnancy rate per pregnancy of 23% in women who underwent salpingoneostomy for distal tubal occlusion.<sup>636</sup> [Evidence level 3] Another narrative review of five case series studies ( $n = 118$ ) reported a cumulative ectopic pregnancy rate per pregnancy of 8% in women who underwent tubocornual anastomosis for proximal tubal occlusion.<sup>629</sup> [Evidence level 3]

A number of trials have evaluated different surgical techniques for tubal surgery. One systematic review of eight RCTs and 14 observational studies evaluating various surgical techniques for treating tubal infertility found no difference in pregnancy rates between the different techniques used such as CO<sub>2</sub> laser adhesiolysis versus diathermy adhesiolysis (53% with laser versus 52% with diathermy; OR 1.04; 95% CI 0.65 to 1.67), with laser salpingostomy versus diathermy salpingostomy (35% with laser versus 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 versus

78% with loupes; OR 0.75; 95% CI 0.26 to 2.15).<sup>638</sup> [Evidence level 1a] Women with proximal and distal tubal disease and reversal of sterilisation were included in this review. [Evidence level 1a] The review of the 14 observational studies did not detect a difference between laparoscopic adhesiolysis and microsurgical adhesiolysis in improving outcome. [Evidence level 2b]

A systematic review of five RCTs (n = 588) found no improvement in pregnancy rates with the use of postoperative 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.<sup>639</sup> [Evidence level 1a]

The appropriate therapeutic approach to tubal infertility will depend upon careful patient selection according to the individual's clinical circumstances and involving the couple in the decision-making process.<sup>640–643</sup>

Retrospective case series suggest that most pregnancies occur between 12 and 14 months after tubal surgery, although conception have occurred sooner in those with minimal disease.<sup>627,631,631,637,644–646</sup> [Evidence level 3] It may be reasonable to discuss IVF with women who have not conceived 12 to 18 months after tubal surgery.

### RECOMMENDATION

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

D

### RESEARCH RECOMMENDATION

Further research is needed to evaluate the clinical and cost effectiveness of tubal surgery compared with no treatment and other treatment options, particularly in vitro fertilisation. This research should include consideration of any adverse consequences of treatment, such as ectopic pregnancy.

## 8.2 Tubal catheterisation or cannulation

Tubal catheterisation/cannulation can be performed using either a radiographic approach (selective salpingography combined with tubal cannulation) or a hysteroscopic approach (hysteroscopic tubal cannulation).

Selective salpingography can provide information about proximal and distal tubal obstruction. An RCT (n = 273) reported that selective salpingography was a better diagnostic test for proximal tubal obstruction than laparoscopy and dye.<sup>647</sup> [Evidence level 1b] 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 effects of selective salpingography plus tubal catheterisation or hysteroscopic cannulation with no treatment on pregnancy rates in women with proximal tubal obstruction.

A systematic review of observational studies included ten cohort and 11 other observational studies of selective salpingography and tubal catheterisation (n = 482 women), and four observational studies of hysteroscopic tubal cannulation for proximal tubal blockage (n = 133 women). Hysteroscopic tubal cannulation was associated with a higher pregnancy rate than selective salpingography plus tubal catheterisation (49% with hysteroscopy versus 21% with salpingography).<sup>648</sup> [Evidence level 2b–3] As no untreated group was included in any of the studies reviewed, the likelihood of spontaneous pregnancy without treatment cannot be determined. Intrauterine pregnancy in women with proximal tubal blockage diagnosed by both HSG and laparoscopy/dye does occur without surgical treatment.<sup>626</sup> [Evidence level 3]

Tubal perforation (a complication associated with tubal cannulation) has been reported to occur in 2–5% of women undergoing tubal cannulation,<sup>649,650</sup> although the clinical significance of this was not reported. Ectopic pregnancy occurred in 3–9% of women undergoing selective salpingography plus tubal catheterisation.<sup>648</sup> [Evidence level 2b–3]

### RECOMMENDATION

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

B

## 8.3 Uterine surgery

### Uterine myoma (leiomyoma)

We did not find any RCTs comparing myomectomy versus expectant management for women with leiomyomas. The incidence of myoma in women with infertility without any obvious cause of infertility is estimated to be 1.0–2.4%.<sup>651,652</sup>

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 associated 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).<sup>653</sup> [Evidence level 2b] 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.<sup>401</sup> [Evidence level 2b]

A case–control study found a lower pregnancy rate in women with myoma when compared with women without myoma (11% versus 25%). The pregnancy rate in women following myomectomy was higher than that in women with untreated myoma (42% versus 25%).<sup>654</sup> [Evidence level 3]

An RCT (n = 109) that compared different surgical methods for undertaking myomectomy (abdominal myomectomy versus laparoscopic myomectomy) found no differences in pregnancy rates (55.9% with abdominal myomectomy versus 53.6% with laparoscopic myomectomy) or miscarriage rates (12% versus 20%) in women with large myomas. There was significantly higher incidence of postoperative fever and a drop in haemoglobin and hospital stay in the group following abdominal myomectomy.<sup>655</sup> [Evidence level 1b]

### 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%).<sup>656,657</sup> It is more common in women who have had recurrent pregnancy loss or preterm birth.<sup>658–660</sup> Hysteroscopic metroplasty has not been shown to increase pregnancy rates in women with infertility who have a septate uterus.<sup>661–664</sup> [Evidence level 2b–3]

### Intrauterine adhesions

Intrauterine 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.<sup>665</sup> [Evidence level 3]

### RECOMMENDATION

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

C

### RESEARCH RECOMMENDATIONS

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

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

# 9. Medical and surgical management of endometriosis

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## 9.1 Medical management (ovarian suppression)

A systematic review and meta-analysis of 16 RCTs compared the effectiveness of ovulation suppression agents with no treatment (six RCTs) or danazol (ten RCTs). Treatment with ovulation suppression agents (medroxyprogesterone, gestrinone, combined oral contraceptives and GnRHa) did not improve clinical pregnancy rates in women with endometriosis-associated infertility compared with no treatment (pooled OR 0.74; 95% CI 0.48 to 1.15) or danazol (pooled OR 1.3; 95% CI 0.97 to 1.76).<sup>666</sup> [Evidence level 1a] Similar results were reported in a subsequent RCT comparing medroxyprogesterone acetate to placebo.<sup>667</sup> [Evidence level 1b] Two reviews in 1993 and 1994 which included RCTs and cohort studies also concluded that ovulation suppression was ineffective in the treatment of endometriosis-associated infertility.<sup>668,669</sup> [Evidence level 1b–2b]

Commonly used ovulation suppression agents have been known to cause significant adverse effects such as weight gain, hot flushes and bone loss.<sup>666</sup>

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.<sup>670</sup> [Evidence level 1a]

### RECOMMENDATION

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

A

## 9.2 Surgical ablation

### Minimal and mild endometriosis

A systematic review and meta-analysis of two RCTs (n = 444) showed that laparoscopic ablation or resection of minimal and mild endometriosis plus laparoscopic adhesiolysis increased ongoing pregnancy and live birth rates compared with diagnostic laparoscopy (pooled OR 1.64; 95% CI 1.05 to 2.57).<sup>671</sup> [Evidence level 1a] There was no difference in miscarriage rates between the two treatment groups (pooled OR 1.33; 95% CI 0.60 to 2.94). Surgical complications were reported in one of the trials but these were minor and did not require laparotomy or transfusion.<sup>672</sup> However, it was not clear from either trial whether the study subjects were blinded as to the treatments they received or whether intention-to-treat analysis was performed.

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 versus 84% with laparotomy versus 54% with medical treatment).<sup>673</sup> [Evidence level 2b] The benefits of surgery should be balanced against the risks of general anaesthesia and surgical complications<sup>674</sup> such as postoperative 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% versus 23.5%; OR 2.83, 95% CI 1.01 to 7.50).<sup>675</sup> [Evidence level 1b]

### Moderate and severe endometriosis

Cohort studies of women with moderate and severe endometriosis operative treatment with laparoscopy or laparotomy suggest that pregnancy rates may be the same or increased in those treated by laparoscopy (54–66% with operative laparoscopy versus 36–45% with laparotomy).<sup>676–679</sup> [Evidence level 2b]

### Postoperative medical treatment

Two RCTs compared postoperative GnRH with expectant management and found no significant difference in pregnancy rates between the two regimens (11.6% with goserelin versus 18.4% with expectant management and 33% with leuprolide depot versus 40% with expectant management, respectively).<sup>680,681</sup> [Evidence level 1b] Similar outcomes were shown between postoperative danazol (55% with danazol versus 50% with expectant management)<sup>682</sup> and between postoperative nafarelin and placebo (19% with nafarelin spray versus 18% with placebo),<sup>683</sup> in women with moderate to severe endometriosis. [Evidence level 1b]

## RECOMMENDATIONS

Women with minimal or mild endometriosis who undergo laparoscopy should be offered surgical ablation or resection of endometriosis plus laparoscopic adhesiolysis because this improves the chance of pregnancy.

A

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

A

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

B

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

A

# 10. Intrauterine insemination

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IUI may involve timed insemination of sperm into the uterus in natural (unstimulated) cycles or insemination following stimulation of the ovaries using oral anti-oestrogens or gonadotrophins.

## 10.1 Male factor fertility problems

IUI is used to manage male factor infertility where semen is of sufficient quality for there to be two to five million motile sperm available after sperm preparation. However, the specific semen criteria for the use of IUI vary from clinic to clinic.

We found two systematic reviews comparing IUI to timed intercourse and/or intracervical insemination in couples with male subfertility. The first review included ten RCTs<sup>684</sup> with timed intercourse or intracervical insemination. The second review<sup>685</sup> included a total of 17 RCTs but excluded four RCTs which evaluated intracervical insemination. Only two of the RCTs included in the second review reported total motile sperm counts after semen preparation for study subjects (greater than 100,000 in both cases). When compared with timed intercourse, IUI was associated with increased pregnancy rates per cycle in both natural cycles (pooled OR 2.5, 95% CI 1.6 to 3.9, based on six RCTs) and stimulated cycles (pooled OR 2.2, 95% CI 1.4 to 3.6, based on seven RCTs).<sup>685</sup> [Evidence level 1a] This systematic review found no difference between pregnancy rates in stimulated and unstimulated IUI cycles (OR 1.8, 95%CI 0.98 to 3.3, based on four RCTs). 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.<sup>686</sup> This RCT 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). [Evidence level 1b]

A small crossover RCT found no significant difference in pregnancy rates between hCG/ultrasound timed IUI versus clomifene citrate-stimulated and LH-timed IUI in patients with male factor (12.5% versus 0%), anovulation and unexplained infertility.<sup>687</sup> [Evidence level 1b]

## 10.2 Unexplained fertility problems

We found no RCTs that evaluated the effects of unstimulated or stimulated IUI compared with expectant management (no treatment) of couples with unexplained fertility problems.

An RCT (n = 932 couples, n = 2678 cycles) reported lower pregnancy rates per couple in patients with unexplained fertility problems undergoing unstimulated intracervical insemination compared with unstimulated IUI, stimulated intracervical insemination and stimulated IUI (10% versus 18% versus 19% versus 33%, p < 0.01).<sup>688</sup> [Evidence level 1b] The corresponding pregnancy rates per treatment cycle were 2%, 5%, 4% and 9% (p < 0.01).<sup>688</sup> [Evidence level 1b]

A crossover RCT (n = 67) reported greater fecundity with clomifene-citrate-stimulated IUI as compared to periovulatory intercourse (0.095 versus 0.033).<sup>689</sup> [Evidence level 1b]

The RCTs described above represent the nearest approximations we could find to RCTs that had expectant management groups. It is recognised, however, that unstimulated intracervical insemination (a surrogate for placebo treatment) or timed intercourse cannot be assumed to have exactly the same effects as sexual intercourse in true expectant management.

We found three systematic reviews that compared gonadotrophin-stimulated IUI with gonadotrophins plus timed intercourse.<sup>684,690,691</sup> [Evidence level 1a] The reviews included a total of 24 RCTs. The largest review included 22 RCTs (1117 couples and 5214 cycles); the other

reviews included subsets of these studies plus one additional trial each, but all three reviews reached the same conclusions. The largest review was the best-quality review and was used for this guideline.<sup>691</sup> [Evidence level 1a] 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).<sup>691</sup> [Evidence level 1a]

An RCT conducted in the USA (n = 465 couples, n = 1335 cycles) compared unstimulated with stimulated IUI in couples 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).<sup>688</sup> [Evidence level 1b] 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.<sup>688</sup>

It is possible that the drug doses used in stimulated IUI in the UK are different from those in the USA. However, an unpublished multicentre observational study conducted in the UK reported the outcome of 1580 stimulated IUI cycles.<sup>692</sup> [Evidence level 3] Among the 126 pregnancies reported, there were 11 twins (9%), two triplets (1.6%) and one higher-order (quadruplet) pregnancy (0.8%).

An RCT conducted in the Netherlands (n = 120 couples, n = 486 cycles) compared unstimulated and stimulated IUI in couples with unexplained fertility problems.<sup>686</sup> This 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). [Evidence level 1b]

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).<sup>693</sup> [Evidence level 1a] 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% versus 14.3%; RR 1.02, 95% CI 0.39 to 2.69), miscarriage rates (14.3% versus 14.3%; RR 1.0, 95% CI 0.08 to 13.02) or multiple pregnancy rates (28.6% versus 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% versus 8.3%; RR 3.32, 95% CI 1.16 to 9.46).<sup>694</sup> [Evidence level 1b]

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% versus 81% versus 79%) or pregnancy rates (5.4% versus 0% versus 0%). There was no occurrence of cycle cancellation or OHSS.<sup>695</sup> [Evidence level 1a]

A further RCT (n = 91 couples,<sup>695</sup> 131 cycles) compared two approaches to stimulated IUI (GnRHa plus gonadotrophins versus 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% versus 11.3%; RR 0.87, 95% CI 0.34 to 2.19).<sup>696</sup> [Evidence level 1b]

A systematic review of five RCTs included two small RCTs that compared IUI with IVF in couples with unexplained fertility problems.<sup>697</sup> [Evidence level 1a] 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).<sup>697</sup> However, the results of these RCTs should be interpreted with caution because of their limited sample sizes.

### 10.3 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, some studies have reported on the use of IUI in this specific category. These studies are discussed below.

We found a systematic review of three RCTs comparing IUI with and without ovulation induction in women with minimal–mild endometriosis. The RCTs 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 versus 8% with no treatment; RR 3.3, 95% CI 1.2 to 9.4).<sup>698</sup> [Evidence level 1b] The second RCT (n = 49) showed no difference in birth rates between hMG plus IUI compared with expectant management (29% with hMG plus IUI versus 20% with expectant management; OR 1.46, 95% CI 0.5 to 4.0) but reported five cases of OHSS (20%).<sup>699</sup> [Evidence level 1b] 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 versus expectant management.

The third (crossover) RCT (n = 119, 57 with endometriosis) found that alternate cycles of gonadotrophins plus IUI increased pregnancy rates when compared with IUI alone (19% with gonadotrophins plus IUI versus 0% with IUI).<sup>700</sup> [Evidence level 1b] Multiple pregnancy rates were reported to be between 18% and 33% in these three trials.

### 10.4 Single versus double intrauterine insemination

A systematic review of three RCTs compared double and single IUI with ovarian stimulation (two inseminations per treatment cycle versus one insemination per treatment cycle). 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).<sup>701</sup> [Evidence level 1a]

### 10.5 Fallopian sperm perfusion

Fallopian sperm perfusion is an insemination technique in which sperm are suspended in a large volume of solution (4 ml) to allow the inseminate not only to be deposited in the uterine cavity but also to perfuse the fallopian tubes.<sup>702</sup>

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 women with unexplained infertility who underwent controlled ovarian stimulation with gonadotrophin/insemination protocols (OR 1.9, 95% CI 1.2 to 3).<sup>397</sup> [Evidence level 1a]

Similar results were found in a subsequent RCT (n = 65, pregnancy rate 42.4% with fallopian sperm perfusion versus 15.6% with IUI; RR 2.72, 95% CI 1.11 to 6.66).<sup>703</sup> [Evidence level 1b]

A further RCT (n = 96 couples, 100 cycles) found no difference in clinical pregnancy rates between fallopian sperm perfusion and IUI in a subgroup of patients with unexplained infertility (21% with fallopian sperm perfusion versus 25% with IUI).<sup>704</sup> [Evidence level 1b]

Another RCT compared IUI with 1-ml sperm suspension, fallopian sperm perfusion with 4-ml sperm suspension and fallopian sperm perfusion using a special system to ensure good cervical sealing. This study found no significant differences between fallopian sperm perfusion with 4-ml sperm suspension and fallopian sperm perfusion using the special system in terms of pregnancy outcomes but the combined pregnancy rate of these two interventions was significantly higher than with IUI using 1-ml sperm suspension (40% versus 18%). There were, however, no significant differences between the three interventions in terms of miscarriage, multiple pregnancy or OHSS rates.<sup>705</sup> [Evidence level 1b]

In the eight RCTs referred to above, twin and triplet pregnancy rates ranged from 0% to 26% and 0% to 6% in the fallopian sperm perfusion group compared with 0% to 25% and 0% to 12.5% in the IUI group. Adverse effects of fallopian sperm perfusion were addressed in two trials<sup>703,705</sup> but no complications were reported.

One of the studies described above<sup>703</sup> showed that the total cost of fallopian sperm perfusion was a little higher than that of IUI (approximately US\$3 more per cycle than IUI). This study also suggested that fallopian sperm perfusion was well tolerated by patients and did not require more staff assistance than IUI, although the procedure lasted three to four minutes longer.

### 10.6 Cost effectiveness of stimulated versus unstimulated intrauterine 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 of stimulated IUI in terms of pregnancy or live birth rates. 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 review has evaluated studies that reported the economic consequences of preterm birth and low birth weight, both of which are associated with higher-order (more than twin) multiple births.<sup>706</sup> The evidence suggests that NHS 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.

We found no studies that evaluated the relative cost effectiveness of stimulated and unstimulated IUI in the UK setting. We therefore constructed an economic model that set out the costs and benefits associated with stimulated and unstimulated IUI where data could be identified from published RCTs. The model was based on pregnancy and multiple birth rates using IUI for unexplained fertility problems reported in a US RCT<sup>688</sup> because we could not identify any other RCTs that reported pregnancy and multiple birth rates for known causes of fertility problems. This RCT showed a difference in the number of cycles of IUI between the two treatment groups, with the stimulated group receiving an average of 5.6 cycles of treatment and the unstimulated group receiving an average of 4.3 cycles. Reported cumulative pregnancy rates of 33% for stimulated IUI and 18% for unstimulated IUI were used in the economic model because pregnancy rates per cycle were not reported. The multiple birth rates for twins, triplets and quadruplets were 22%, 4% and 3%, respectively, in the stimulated IUI group and there were no multiple births in the unstimulated group.

The costs of IUI were taken from a UK study published in 1997. This study reported a cost of £1,005 per cycle for stimulated IUI and £449 per cycle for unstimulated IUI.<sup>707</sup> Since the additional cost associated with multiple births was not known, various scenarios were explored. The model assumed that the costs associated with the birth of singletons and twins would be the same, but additional costs associated with the birth of triplets and quadruplets were included in the analysis. These costs were confined to the costs of neonatal intensive care from birth until discharge from hospital. The assumption in the model was that all infants resulting from triplet and quadruplet births would require neonatal intensive care for an average of seven weeks.

The model indicated that, under these assumptions, the cost of achieving at least one live birth per couple with unexplained fertility problems was higher in the stimulated IUI group, even though stimulated IUI led to a greater number of pregnancies. Assuming that the cost of neonatal intensive care was negligible (£1 per day), the cost per pregnancy associated with stimulated IUI was £17,000 per couple compared with £10,700 in the unstimulated group. At a cost of £1 per day for neonatal intensive care, the cumulative pregnancy rate for stimulated IUI would need to be 53% for stimulated and unstimulated IUI to be equally cost effective. In reality, the cost of

neonatal intensive care would be much greater than £1 per day and higher costs would increase the favourability of unstimulated IUI compared to stimulated IUI. Since the model may underestimate the true pregnancy rate for unstimulated IUI, this form of treatment may be even more cost effective compared with stimulated IUI.

If the cost of neonatal intensive care were nearer to £600 per day (this would be a more realistic assumption, based on higher costs immediately after birth and lower costs before discharge from the neonatal intensive care unit), the cost per pregnancy associated with stimulated IUI would be £23,500. Under this scenario, the cost of neonatal intensive care associated with stimulated IUI would exceed the cost of achieving a live birth from unstimulated IUI, implying that stimulated IUI would always be the less cost-effective option, regardless of the pregnancy rate for stimulated IUI.

If the costs associated with stimulated IUI were lower (for example, if the market price of the drugs used for ovarian stimulation was reduced), this would clearly have an impact on the overall cost effectiveness of stimulated IUI. If the cost of neonatal intensive care was £1 per day, the cost of stimulated IUI per cycle of treatment would need to be reduced to 63% of the current cost (that is, a reduction in cost from £1,005 to £633) in order for stimulated IUI to be as cost effective as unstimulated IUI. However, if the cost of neonatal intensive care was £600 per day, then the cost of stimulated IUI per cycle of treatment would need to be reduced to less than 75% of the current cost of £1005. This would equate to a cost per cycle that was less than half the cost of unstimulated IUI, and this is clearly unrealistic.

## 10.7 Cost effectiveness of different drug regimens in stimulated intrauterine insemination

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

A US retrospective cohort study considered the relative cost effectiveness of various forms of treatment for subfertility: 54 couples underwent unstimulated IUI, 91 had clomifene citrate-stimulated IUI and 52 had hMG-stimulated IUI.<sup>708</sup> 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 \$8,674 for unstimulated IUI, \$7,808 for clomifene-stimulated IUI and \$10,282 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.<sup>686</sup> One hundred 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 US study addressed the efficacy and cost effectiveness of treatments for unexplained fertility problems.<sup>710</sup> Clomifene-stimulated IUI and hMG-stimulated IUI were evaluated using

unstimulated IUI as a baseline comparator. 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 \$15,823 for hMG plus IUI. Raising the untreated pregnancy rate to 1.4%, the additional costs per pregnancy were \$11,905 and \$19,230, respectively.

### RECOMMENDATIONS

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

A

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

A

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

A

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

A

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

A

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

A

### RESEARCH RECOMMENDATIONS

Research is needed to define semen quality criteria for assisted reproduction 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 intrauterine insemination in couples with unexplained fertility problems.

# 11. Factors affecting the outcome of in vitro fertilisation treatment

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The main procedures involved in IVF treatment are:

- pituitary downregulation: 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
- luteal support: administration of hormones to aid implantation of the embryos.

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.<sup>711</sup> 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.<sup>711</sup>

## Immediate versus delayed in vitro fertilisation

A recent multicentred RCT (n = 139 couples) reported significantly higher live birth rates per IVF/ICSI cycle when compared with no treatment for three months in women with fallopian tube patency (29% with IVF/ICSI versus 4% with no treatment).<sup>712</sup> [Evidence level 1b]

Another RCT compared the effectiveness of immediate IVF with six-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 live birth rates per couple (12% with immediate IVF versus 5% with delayed IVF; RR 2.36, 95% CI 1.03 to 5.66) and pregnancy rates per couple (17% with immediate IVF versus 8% with delayed IVF; RR 2.43, 95% CI 1.18 to 5.07). No details of the fertility treatment received by the control group were presented.<sup>713</sup> [Evidence level 1b]

A further RCT compared early IVF with late IVF (after six 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 six-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 versus 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 versus 5% with delayed IVF; RR 1.86, 95% CI 0.72 to 4.79).<sup>714</sup> [Evidence level 1b]

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.<sup>715</sup> 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 3]

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.<sup>716</sup> [Evidence level 3]

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

We found no RCTs comparing IVF versus 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.<sup>714</sup> [Evidence level 1b]

### **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 women with endometriosis did not detect a significant difference in pregnancy rates between immediate and delayed IVF (33.3% immediate IVF versus 0% delayed IVF). However, this result should be interpreted with caution because it is a subgroup analysis based on a small sample.<sup>714</sup> [Evidence level 1b]

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).<sup>717</sup> [Evidence level 2b] The overall chance of achieving a pregnancy with IVF in these 22 studies was about 25%. [Evidence level 2b] The effect of endometrioma on the outcome of IVF treatment is unclear.<sup>718-721</sup> [Evidence level 3]

Duration of infertility has been shown to be an important factor in determining the chance of pregnancy, with or without treatment.<sup>722</sup> 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 two years have only a 12% chance of conceiving in the following year (see Section 3.1). [Evidence level 3]

Analysis of the HFEA database showed a significant decrease in the IVF live birth rate with increasing duration of infertility from one to 12 years, which persisted after adjusting for the woman's age.<sup>723</sup> 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.<sup>724</sup> [Evidence level 3]

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.<sup>725,726</sup> [Evidence level 3]

With the exception of ovulatory disorders, the final treatment option for most categories of fertility problem is IVF and its related technologies. (With ovulatory disorders, the options centre on therapies to correct the specific disorders; see Chapter 7). The recognised indications for in vitro fertilisation treatment include:

- male factor fertility problems where medical/surgical management and intrauterine insemination have not resulted in a live birth or are judged to be inappropriate
- tubal disease where tubal surgery has not resulted in a live birth or is judged to be inappropriate
- endometriosis where surgery and IUI have not resulted in a live birth or are judged to be inappropriate
- unexplained fertility problems of three years' duration where medical management and IUI have not resulted in a live birth or are judged to be inappropriate
- failure of spermatogenesis caused by prior treatment for cancer where cryopreserved semen is unsuitable for IUI

- ovarian failure caused by prior treatment for cancer where eggs or embryos have been cryopreserved
- a requirement for egg donation.

In addition, female age should be considered when determining the timescale over which other treatments should be explored before proceeding to in vitro fertilisation treatment.

### Cost effectiveness of in vitro fertilisation versus intrauterine insemination

A US study compared a protocol with clomifene citrate and hMG plus IUI with a protocol of only hMG and IUI.<sup>727</sup> 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 \$1,850). 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 UK study has evaluated the efficacy and cost effectiveness of stimulated IUI (clomifene citrate and FSH) versus stimulated IVF using the same drug regimen.<sup>707</sup> 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 £32,280 in the stimulated IVF group, compared with £15,384 in the stimulated IUI group. The cost of multiple birth was not included in the analysis. The authors calculated a cost per maternity of £4,611 for IVF and £1,923 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 using partners' sperm.<sup>728</sup> 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 £1,670 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 US study considered the cost effectiveness of three different assisted reproduction protocols: ovarian stimulation only (with clomifene citrate), IUI with hMG and IVF.<sup>729</sup> The study was based on a nonsystematic 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.

## 11.1 Surgery for hydrosalpinges before in vitro fertilisation treatment

Hydrosalpinx is dilation of the fallopian tube in the presence of distal tubal obstruction, which may result from a number of causes.<sup>730</sup> In women undergoing IVF, the presence of hydrosalpinx is associated with early pregnancy loss and poor implantation and pregnancy rates,<sup>730,731</sup> probably due to alteration in endometrial receptivity.<sup>732,733</sup> [Evidence level 2b]

A systematic review of three RCTs showed that tubal surgery such as laparoscopic salpingectomy significantly increased live birth rate (OR 2.13; 95% CI 1.24 to 3.65) and pregnancy rate (OR 1.75; 95% CI 1.07 to 2.86) in women with hydrosalpinges before IVF when compared with no treatment.<sup>734</sup> [Evidence level 1a] 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).<sup>734</sup>

### RECOMMENDATIONS

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

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### RESEARCH RECOMMENDATIONS

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

Further research is needed to determine the relative effectiveness of intrauterine 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.

## 11.2 Female age

### Live birth rates

#### *Fresh embryo treatment cycles*

Analysis of HFEA data on all IVF cycles carried out in the UK 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 to 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.<sup>723</sup> [Evidence level 3]

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 11.1, 11.2, 11.3, 11.4 and 11.5 below). 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 are self-reported data which 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 11.1 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 11.1 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. Women of 40 and older have a declining chance, which reduces to 1% at the age of 45 years. [Evidence level 3]

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

Age (years)	Treatment cycles (n)	Live births (n)	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

### Frozen embryo treatment cycles

Embryo cryopreservation allows any supernumerary embryos arising from 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 not resulted in a live birth or because further children are desired. The ability to preserve embryos routinely 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 OHSS by substituting frozen-thawed embryo transfer in unstimulated cycles. Embryo quality has the most significant impact on post-thaw survival.<sup>735</sup> Freezing poor quality embryos will lead to poor cryosurvival and low implantation rates.<sup>736</sup> As with fresh embryos, pregnancy rates are affected by factors such as patient age.<sup>736–739</sup> A beneficial outcome is also more likely if a pregnancy resulted from the original stimulation cycle from which the frozen embryos were derived.<sup>738–740</sup> The number of oocytes retrieved in the initial stimulation cycle and the number of embryos available for cryopreservation also affects outcome.<sup>741</sup> [Evidence level 3] Methods of embryo freezing, protocols for post-thawing embryo selection and culture conditions may affect outcome.

HFEA data from the year 1997–98 reported a live birth rate (per attempted frozen embryo replacement) of 10.4% per treatment cycle in 4533 patients using their own gametes.<sup>742</sup> The corresponding figure for 1999–2000 was 13.8% of 5131 treatment cycles.<sup>743</sup> [Evidence level 3]

The most recent data on live birth rates with frozen IVF cycles obtained from the HFEA are shown in Table 11.2. 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

**Table 11.2** Comparison of live birth rates per cycle started by age of woman based on frozen embryo transfer and excluding donor eggs, 1995 to 1999 (Source: Human Fertilisation and Embryology Authority)

Age (years)	Treatment cycles (n)	Live births (n)	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

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 11.2, 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 3]

Four further studies have shown decreasing live birth rates with increasing female age using fresh embryo transfer.<sup>744–747</sup> [Evidence level 3] Two of these studies showed that live birth rates were positively associated with donor insemination,<sup>746</sup> embryo quality,<sup>746,747</sup> number of embryos transferred,<sup>747</sup> and cause of infertility.<sup>747</sup>

A retrospective review of experience with embryo cryopreservation over an eight-year period (March 1984 to December 1991) reviewed freeze–thaw cycles (4898 frozen embryos, of which 3288 were thawed) excluding those following oocyte donation. Those that survived (n = 2002) were replaced in 897 cycles, resulting in an ongoing clinical pregnancy rate of 10.9%, 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%.<sup>741</sup> [Evidence level 3] This study was conducted in the 1980s and early 1990s when it was usual practice to use all surviving embryos. The current practice of selecting embryos good quality embryos from a larger pool of surviving embryos could be expected to increase cumulative pregnancy rates. However, we found no recent studies that addressed this issue.

A cohort study (n = 485 couples, 1086 cycles) which assessed the efficiency and efficacy of an IVF programme between 1989 to 1991 found that embryo cryopreservation (n = 193) (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 live birth rate for women entering the IVF programme.<sup>748</sup> Another case-series study (n = 364) reported a cumulative viable pregnancy rate of 40.7% following one fresh and two freeze-thaw embryo replacements (using two embryos only) in women requesting IVF.<sup>749</sup> [Evidence level 3]

Available data on the effects of cryopreservation of embryos did not indicate any apparent negative impact on perinatal outcome, early infant development or congenital malformation rate.<sup>750</sup> A retrospective study compared babies (n = 283) from births from cryopreserved embryos with babies (n = 961) after conventional IVF. There was no difference in the incidence of twins, triplets, their mean gestational age, birth weight and perinatal mortality rates between the two groups. The incidence of major congenital malformations was significantly lower in the cryopreserved group (1%) than in the IVF group (3%).<sup>751</sup> One study 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.<sup>752</sup> [Evidence level 3]

### Pregnancy rates

Table 11.3 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

**Table 11.3** Comparison of clinical pregnancy rates per cycle started by age of woman based on fresh (not frozen) embryo transfer and excluding donor eggs, 1995 to 1999 (Source: Human Fertilisation and Embryology Authority)

Age (years)	Treatment cycles (n)	Clinical pregnancies (n)	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

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 11.3, 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 than 14%. [Evidence level 3]

A cohort study has shown that pregnancy rates decline significantly after the age of 40 years, and again after the age of 42 years.<sup>753</sup> [Evidence level 2b]

Several other studies have shown that pregnancy rates following IVF treatment decline after the age of 35 years,<sup>754–757</sup> 37 years<sup>758</sup> and 40 years.<sup>334,724–726,759–763</sup> [Evidence level 3]

The decline in pregnancy rates with age may be related to declining embryo quality.<sup>746</sup> Embryo quality is difficult to assess. For apparently equal embryo quality, maternal age does not significantly reduce pregnancy rates.<sup>764</sup> 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.<sup>588</sup> [Evidence level 3]

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.<sup>765–767</sup> [Evidence level 3]

A retrospective review on IVF outcomes of patients (n = 322) enrolled in a shared oocyte programme from 1997 to 1999 reported a significantly higher clinical pregnancy rate for recipients who had a fresh embryo transfer compared with recipients whose first embryo transfer consisted of frozen-thawed embryos (63.4% versus 43.6%). However, no difference between the clinical pregnancy rates from fresh and frozen first embryo transfers were found (47.7% versus 40.9%).<sup>768</sup> [Evidence level 3]

### Ectopic pregnancy rates

Table 11.4 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 3]

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.<sup>755</sup> [Evidence level 3]

### Miscarriage rates

Table 11.5 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 3] These data were based on numbers of pregnancies shown in Table 11.3 and they give miscarriage 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.

Several other studies have reported increased miscarriage rates following IVF in women aged more than 34 years,<sup>726</sup> 35 years<sup>755,757,769</sup> and 40 years.<sup>758,759,762,770</sup> [Evidence level 3]

### Fertilisation rates

Several studies have reported decreased fertilisation rates following IVF in women aged more than 35 years,<sup>754</sup> 37 years<sup>771</sup> and 40 years.<sup>770</sup> Two other studies found significantly lower fertilisation rates in older women<sup>772,773</sup> and after previous IVF failure.<sup>773</sup> However, no significant decline in fertilisation rates with age was found in a further study.<sup>334</sup> [Evidence level 3]

**Table 11.4** Comparison of ectopic pregnancy rates per cycle started by age of woman based on fresh (not frozen) embryo transfer and excluding donor eggs, 1995 to 1999 (Source: Human Fertilisation and Embryology Authority)

Age (years)	Treatment cycles (n)	Ectopic pregnancies (n)	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

### Implantation rates

Two studies have reported decreased implantation rates following IVF in women aged more than 35 years<sup>755</sup> and 37 years.<sup>774</sup> However, a third study showed no significant difference in implantation rates between women aged over 35 years and younger women.<sup>775</sup> 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.<sup>775</sup> [Evidence level 3]

### 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.<sup>776</sup> 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.<sup>756</sup> [Evidence level 3]

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.<sup>777</sup> [Evidence level 3]

**Table 11.5** Comparison of miscarriage rates per cycle started by age of woman based on fresh (not frozen) embryo transfer and excluding donor eggs, 1995 to 1999 (Source: Human Fertilisation and Embryology Authority)

Age (years)	Treatment cycles (n)	Miscarriages (n)	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

### Treatment discontinuation rates

A high percentage of women discontinue IVF treatment after unsuccessful cycles. An analysis of the French National In Vitro organisation (FIVNAT) database showed that 40–50% of women discontinued IVF treatment after unsuccessful treatment cycles.<sup>778,779</sup> [Evidence level 3] One study found that 17.7% of women aged less than 30 years and 50% of women aged 38 to 40 years discontinued IVF treatment after unsuccessful cycles.<sup>780</sup> [Evidence level 3] Another study found significant increases in discontinuation rates with age (38% for women aged 25 to 39 years, 50% for women aged 40 to 43 years and 70% for women aged 44 to 45 years).<sup>745</sup> [Evidence level 3]

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.

### RECOMMENDATION

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

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

C

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

C

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

Multiple gestations are associated with more complications during pregnancy, increased perinatal, neonatal and infant morbidity and mortality,<sup>592</sup> as well as significant financial<sup>593,594</sup> and psychological<sup>595</sup> consequences for the parents. Surveys have suggested that the prospect of multiple pregnancies may not be viewed as an adverse outcome by prospective patients.<sup>598–602</sup> [Evidence level 3]

Much of the increased risk for multiple births is due to the increased risk of preterm 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.<sup>596,597</sup> [Evidence level 3] 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.<sup>781</sup> [Evidence level 2b]

The increase in triplet deliveries following assisted reproduction has been linked to the increased sale and use of ovulation induction agents.<sup>782</sup> [Evidence level 3] A report by the FIVNAT showed that 7.3% of all IVF conceptions between 1986 and 1993 related to triplets or higher-order multiple gestation.<sup>783</sup> [Evidence level 3]

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 UK 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 August 2001, the HFEA announced its decision to reduce the maximum number of embryos transferred from three to two, except in exceptional circumstances, where three might be transferred.<sup>784</sup> The HFEA 6th Code of Practice, 2004,<sup>218</sup> states that in a single treatment cycle, a maximum of two eggs or embryos can be transferred to a woman of less than 40 years of age, regardless of the procedure used. Women aged 40 years and over may receive a maximum of three eggs or embryos, regardless of the procedure used. [Evidence level 4]

It has been suggested that the concept of an elective single embryo transfer may warrant serious consideration in future to reduce the overall incidence of multiple pregnancy.<sup>785</sup> [Evidence level 4]

An RCT (n = 932) comparing superovulation versus no superovulation and intracervical insemination versus intrauterine insemination found that 23.6% of superovulation live births were twins, 5.6% were triplets and 4.2% were quadruplets.<sup>688</sup> [Evidence level 1b] There were no multiple pregnancies in the no superovulation group. In the UK, analysis of data from the HFEA (1991 to 1995) showed that among 29,262 transfers of three embryos, 1755 of 6091 deliveries (28.9%) were twins and 5.8% were triplets or more.<sup>786</sup> [Evidence level 3]

Analysis of data from 7170 IVF and 530 ICSI cycles reaching fresh embryo transfer at one fertility centre in the UK between 1984 and 1997 showed that 1889 cycles (25%) resulted in pregnancy. A total of 1256 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 births has remained unchanged, despite HFEA legislation limiting the number of embryos transferred to three in 1991.<sup>787</sup> [Evidence level 3]

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%, respectively, in 1999 to 2000, as compared with 6.2% and 0.43% in 2000 to 2001.<sup>743</sup> [Evidence level 3] The corresponding birth rates for twins and triplets per live birth were 30% and 2.5% in 1999 to 2000 and 28.6% and 1.9%, in 2000 to 2001, respectively.<sup>743</sup> [Evidence level 3]

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 versus two embryos.<sup>788-790</sup> [Evidence level 1b] 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 with 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. However, the multiple pregnancy rate associated with single embryo transfer was significantly lower (combined OR 0.17, 95% CI 0.07 to 0.40). [Evidence level 1a]

Cumulative pregnancy rates were reported in two of the RCTs.<sup>789,790</sup> [Evidence level 1b] 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.<sup>790</sup> 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.<sup>789</sup>

These data suggest that in selected groups of women, while single embryo transfer significantly reduces the risk of multiple pregnancies, 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 that compared transfers of two versus three embryos could be identified. A single controlled observational study<sup>791</sup> compared two embryo transfers (n = 80) in 'good prognosis' women with three embryo transfers (n = 130) in a similar nonrandomised 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 2b]

A single randomised trial that compared transfers of two versus four embryos was identified.<sup>792</sup> The RCT did not detect a difference in either clinical pregnancy rates (OR 1.34 95% CI 0.46 to 3.87), live birth rates (OR 2.88, 95% CI 0.95 to 8.72) or multiple pregnancy rates per cycle (OR 2.27, 95% CI 0.51 to 10.18). The wide confidence levels reflect the imprecision of the results due to the small sample size. [Evidence level 1b]

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.<sup>786</sup> [Evidence level 3] 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.<sup>786</sup> [Evidence level 3]

### Economic consequences

An American study based on a single retrospective cohort study in one IVF centre followed 413 treatment cycles.<sup>793</sup> This study reported cost differences of about \$39,000 for single and twin pregnancies, and \$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).<sup>794</sup> 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.<sup>795</sup> 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. The cost effectiveness of alternative embryo transfer policies in assisted reproduction is the subject of a study being undertaken at the National Perinatal Epidemiology Unit in Oxford. The results of the study are not yet available, but are due to be disseminated in 2004.

### RECOMMENDATION

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

C

### RESEARCH RECOMMENDATION

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

## 11.4 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 UK between 1991 and 1994 (n = 33,701 cycles).<sup>723</sup> [Evidence level 3] This study reported that the probability of success decreased with each IVF treatment cycle from 14.0% (95% CI 13.5 to 14.5) at the first attempt, to 13.0% (95% CI 12.2 to 13.7) at the second attempt, 11.4% (95% CI 10.4 to 12.5) at the third attempt, 11.5% (95% CI 10.1 to 13.2) at the fourth attempt, 8.9% (95% CI 7.2 to 11.2) at the fifth attempt, 9.3% (95% CI 6.7 to 12.9) at the fifth attempt and 10.2% (95% CI 7.7 to 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 2247 of these cycles (see Table 11.6). The data show that the live birth rate per treatment cycle is largely unchanged over the

**Table 11.6** 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 to 1999 data (Source: Human Fertilisation and Embryology Authority)

Previous treatment cycles (n)	Treatment cycles (n)	Live births (n)	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

**Table 11.7** 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 to 2001 (Source: Oxford Fertility Unit)

a) Women aged less than 39 years

Previous treatment cycles (n)	Treatment cycles (n)	Live births (n)	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

Previous treatment cycles (n)	Treatment cycles (n)	Live births (n)	Live birth rate per treatment cycle (%)
0	334	34	10.2
1	228	22	9.7
2	159	26	16.4 <sup>a</sup>

<sup>a</sup> 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.

first four attempts, but the sample sizes for the fifth, sixth and seventh attempts are too small to make valid conclusions. [Evidence level 3]

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 11.7). This analysis was based on 5028 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 3]

Data from 8362 patients who underwent a first cycle of IVF treatment between 1988 and 1989 have been analysed using the FIVNAT database.<sup>778</sup> 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.<sup>779</sup> 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.<sup>779</sup> [Evidence level 3]

Another study reported data from 4225 women (8207 IVF cycles) who underwent IVF treatment in Australia between 1993 and 1997.<sup>796</sup> [Evidence level 3] 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.<sup>796</sup> [Evidence level 3]

A multicentre retrospective study conducted in the USA reported pregnancy rates per cycle for cycles 1, 2, 3, 4 and over 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.<sup>797</sup> [Evidence level 3] 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.<sup>726</sup> [Evidence level 3] Another small study found that implantation rate was significantly associated with rank of attempt.<sup>774</sup> [Evidence level 3] Another study reported similar clinical pregnancy rates for up to seven treatment cycles (25%, 29%, 28%, 33%, 35%, 30%, and 40%, respectively).<sup>758</sup> [Evidence level 3]

#### RECOMMENDATION

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

C

## 11.5 Pregnancy history

Analysis of the HFEA database showed that previous pregnancy and live birth were associated with increased treatment success.<sup>723</sup> [Evidence level 3] However, rates of secondary infertility are higher in the general population than in IVF clinic referrals.<sup>798</sup> Another study based on the FIVNAT register 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.<sup>799</sup> [Evidence level 3] A further study that examined the relationship between the first cycle of IVF and subsequent cycles found that a previous pregnancy significantly improved a couple's probability of conception in a later IVF cycle.<sup>763</sup> [Evidence level 3]

#### RECOMMENDATION

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

C

## 11.6 Alcohol, smoking and caffeine consumption

Maternal and paternal alcohol consumption in excess of 12 g (one unit) per day up to one year before assisted reproduction have been associated with a significant decrease in the success rates of IVF and GIFT.<sup>800</sup> [Evidence level 3]

Maternal and paternal smoking before assisted reproduction have been associated with significant decreases in the success rates of IVF and GIFT.<sup>801–804</sup> Smoking by males is also associated with a decrease in the success rates of IVF and ICSI (OR 2.95; 95% CI 1.32 to 6.59).<sup>805</sup> [Evidence level 3]

In an observational study, caffeine consumption (over 2–50 mg/day versus 0–2 mg/day; 100 mg caffeine in one cup of coffee) during a lifetime (i.e., usual intake) and during the week of initial visit for infertility were strong risk factors for not achieving a live birth in women undergoing IVF or GIFT, after adjusting for smoking, alcohol, age, race, education, parity, types of infertility, types of procedure, number of assisted reproduction attempts and number of embryos transferred.<sup>806</sup> [Evidence level 3] This study also reported an association between maternal coffee consumption and decreased infant gestational age.<sup>806</sup> [Evidence level 3]

#### RECOMMENDATIONS

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

C

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

C

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

C

## 11.7 Body weight

It has 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 (see Sections 3.6 and 7.1).<sup>497,498</sup> [Evidence level 2b]

Obesity (BMI 25.8 to 30.8 kg/m<sup>2</sup>) has been shown to be a risk factor for spontaneous abortion in women after IVF or ICSI.<sup>807</sup> [Evidence level 2b] Obesity is also associated with lower pregnancy rates after IVF when compared with women with a BMI of 25 kg/m<sup>2</sup> or under.<sup>808</sup> [Evidence level 2b]

Extremes of BMI (over 25–28 kg/m<sup>2</sup> or under 20 kg/m<sup>2</sup>) have been associated with negative effects on IVF parameters leading to decreased chances of pregnancy.<sup>809,810</sup> [Evidence level 2b]

### RECOMMENDATION

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

**B**

### RESEARCH RECOMMENDATION

Further randomised controlled trials are needed to evaluate the effectiveness of assisted reproduction procedures in relation to female body mass index.

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

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

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 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 11.6. 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 B.

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 11.7. 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 11.7) 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.

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

**Table 11.8** Cost of in vitro fertilisation per delivery (1994)<sup>811</sup>

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

review of this evidence shows far higher cost-effectiveness ratios (cost of IVF per delivery) in the USA (as might be expected) but similar results in Scandinavian countries.<sup>811</sup> The data reported in Table 11.8 are for the year 1994.

### RECOMMENDATIONS

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

GPP

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

GPP

## 11.9 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 now widely used because of the need for a laparoscopy. It has been most commonly used in the management of people with unexplained male factor fertility problems, and where transcervical embryo transfer is impossible.

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 (OR 0.12, 95% CI 0.02 to 0.20 with GIFT versus OR 0.018, 95% CI 0 to 0.05 with IUI plus OS; versus OR 0.018, 95% CI 0 to 0.05 with IUI in spontaneous cycle).<sup>812</sup> [Evidence level 1b]

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 versus 36.8% with conventional treatments).<sup>813</sup> [Evidence level 1b]

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 versus 13% with ovarian stimulation; RR 0.63, 95% CI 0.10 to 3.98).<sup>814</sup> [Evidence level 1b]

A small RCT (n = 13) found no significant difference between GIFT and IVF in terms of pregnancy rates (33% with GIFT versus 28.5% with IVF) in couples with male factor fertility problems.<sup>815</sup> [Evidence level 1b]

### Zygote intrafallopian transfer

ZIFT is a technique that is not widely practised; it has been developed alongside IVF using much of the same technology. When transcervical embryo transfer is impossible, laparoscopic transfer of embryos to the fallopian tube after fertilisation in vitro offers an alternative route.

A meta-analysis of six RCTs (458 women, 548 cycles) found no significant difference in pregnancy rates between women undergoing ZIFT and IVF and embryo transfer for all causes of infertility excluding tubal factors (OR 0.99; 95% CI 0.62 to 1.57). There was a trend towards a two-fold greater chance of having an ectopic pregnancy in ZIFT than in IVF (OR 2.05; 95% CI 0.21 to 20.22)<sup>816</sup> [Evidence level 1a]

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.<sup>817,818</sup> [Evidence level 3]

### RECOMMENDATION

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

A

# 12. Procedures used during in vitro fertilisation treatment

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The Human Fertilisation and Embryology Act 1990 (HFE Act) requires that any fertility clinic in the UK offering licensed treatment services, such as IVF or use of donated gametes, must take account of the welfare of the potential child (including the determination of who will have parental responsibility for the child) and of any other existing children who may be affected by the birth, before treatment. Details on the issues of assessment of people seeking treatment, confidentiality, information, consent and counselling are referred to the HFEA Code of Practice.<sup>218</sup>

## 12.1 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 and genetic diseases. The welfare of 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 seropositive for the hepatitis B virus and 0.54% were seropositive for the hepatitis C virus.<sup>819</sup> A cross-sectional study with 409 patients (248 women and 161 men) attending an infertility clinic reported a prevalence of anti-hepatitis C virus positivity of 3.2 % among women and 3.7% among men.<sup>820</sup> Hepatitis C virus was detected in 5% of semen samples from men (n = 39) entering an IVF programme. Consideration needs to be given to the risk of hepatitis C virus transmission not only to the mother and child, but also through laboratory contamination of other non-infected couples' gametes and of technicians, and even through storage and manipulation of cryopreserved semen.<sup>821</sup> [Evidence level 3]

Screening for *C. trachomatis* infection before uterine instrumentation is discussed in Chapter 5, Section 5.3.

### RECOMMENDATION

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

**B**

## 12.2 Management of couples with viral infections

Where patients have chronic infections such as hepatitis B, hepatitis C and/or HIV, this should be taken into account when considering them for fertility treatment. If the treatment proposed is within the remit of the HFEA, then a 'welfare of the child' assessment is mandatory. Patients should be counselled thoroughly and given information about the potential risks and implications for themselves and their children in a manner that is sensitive to and specific for their own situation.

Where a positive case of these infectious agents is detected, fertility diagnosis and treatment must be carried out in facilities and using procedures which are appropriate for the handling of known positive specimens of the appropriate classification. Not all centres currently have such facilities available. Particular considerations apply to the use of cryopreservation, where there may be some risk of cross-contamination between samples.<sup>822–824</sup> Such risks cannot be quantified and relate to the specific methodology used and the viral load of the specimen.

Whether fertility treatment is appropriate and the options available will vary depending upon the viral status of the male partner and/or the female partner, the particular infectious agent, the stage of their disease, their compliance with medication, and their fertility status. A strategy for the management of patients seeking fertility treatment and who are infected with HIV, hepatitis B and hepatitis C has been suggested.<sup>825</sup> [Evidence level 3–4]

### **HIV infection**

Current debates have focused on the welfare of the child perspective relating to vertical transmission or loss of a parent at a young age, and the improved treatment outcomes of antiretroviral drugs.<sup>826,827</sup>

Serodiscordant couples in which the man is HIV-1 positive and the woman is negative have limited options if they wish to have children safely because of the risk of transmitting HIV virus in semen to the female partner and offspring. One option is insemination with sperm from seronegative donors.

Sperm washing<sup>828,829</sup> has been used as a risk-reduction option in which infected sperm are washed to reduce the titre of virus<sup>830,831</sup> before insemination into the female partner at the time of ovulation, resulting in healthy live births and no reported seroconversions in either partners or children.<sup>828,832,833</sup> [Evidence level 3] However, the risk of transmission still exists, as shown by the persistence of virus in washed sperm.<sup>834,835</sup>

In serodiscordant couples where the female partner is HIV positive and has no overt fertility problems, timed self-insemination with the man's sperm can be considered. When assisted reproduction treatment is indicated (ovulation induction, IUI, IVF or ICSI), steps should be taken to minimise any risk of multiple pregnancy because of the increased risk to mother and fetus, perinatal morbidity and burden of caring for two or three babies at the same time when women infected with HIV are prone to ill health. Antiretroviral medication should be discussed with the treating physician. Little is known of the effect of invasive procedures involved in IVF treatment and ICSI (such as oocyte retrieval) on vertical transmission, or the long-term effects of antiretroviral treatments upon offspring.

### **Hepatitis B infection**

Partners of individuals with hepatitis B should be vaccinated before fertility treatments begin and sperm washing will not be necessary. The normal course of pregnancy is not affected by hepatitis B infection and vertical transmission to neonates can be minimised with hepatitis B vaccination within 24 hours of birth and at six months.

### **Hepatitis C infection**

As there is no vaccine for hepatitis C infection, risk-reduction measures such as sperm washing in assisted reproduction may be considered if the male partner is infected.<sup>830</sup> [Evidence level 3] The normal course of pregnancy is not affected by hepatitis C infection. Both vertical transmission and nosocomial transmission (transmission within a health care setting) can be minimised by medical treatment to reduce viral load before fertility treatment or assisted reproduction. No specific vaccine is available to protect neonates.

The decision whether to provide fertility treatment in these patients should include an assessment of the welfare of the child. The patients' own health, any associated high-risk behaviour, existence of a (homo- or heterosexual) couple etc. are all relevant to the decision-making process. Couples carrying HIV, hepatitis B and hepatitis C infections and who have fertility problems should be referred to centres having the appropriate expertise and facilities to provide safe risk-reduction treatment.

**RECOMMENDATION**

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

D

## 12.3 Ovulation induction during in vitro fertilisation treatment

IVF ovulation induction techniques are based on the use of the same drugs that are used in ovulation induction for ovulatory disorders. However, there are specific aspects of the use of these drugs that 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 7, 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.<sup>836</sup> [Evidence level 2b–3] Natural cycle IVF was associated with no risk of OHSS or multiple pregnancy rate when a single embryo was transferred.<sup>836</sup> [Evidence level 2b–3]

### Natural cycle versus 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 versus 0% in natural cycle) but cycle cancellation rate was significantly higher in natural cycle IVF (10 cycles versus none).<sup>837</sup> [Evidence level 1b]

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 versus 4% with natural cycle; RR 5.14, 95% CI 1.81 to 14.55).<sup>838</sup> [Evidence level 1b] Modest side effects were reported following clomifene.

### Natural cycle versus gonadotrophins

A crossover RCT found a significant improved clinical pregnancy rate per cycle with hMG cycle IVF versus natural cycle IVF (23% with hMG cycle versus 0% with natural cycle). There were no data on side effects or multiple pregnancy rate.<sup>839</sup>

### Natural versus stimulated cycles with frozen embryos

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.<sup>840,841</sup>

A partly randomised controlled trial (n = 162) 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.<sup>840</sup> [Evidence level 2a]

In replacing frozen-thawed embryos, pregnancy rates were reported to be similar between natural cycle and programmed cycles;<sup>737</sup> between natural cycle and GnRHa/hormone replacement therapy cycles in women undergoing replacement after elective embryo cryopreservation to minimise the risk of developing OHSS (RR 0.65, 95% CI 0.29, 1.42),<sup>842</sup> between natural cycles and cycles controlled with exogenous oestradiol and progesterone administration,<sup>843</sup> between natural cycle and GnRHa administration followed by oestradiol valerate supplementation,<sup>844</sup> between spontaneous cycles, artificial preparation and ovarian stimulation cycles<sup>845</sup> and between spontaneous cycles, an ovarian stimulation and oestrogen/progesterone replacement therapy.<sup>846</sup> [Evidence level 3]

An RCT (n = 106) 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 and found comparable pregnancy rate per embryo transfer in both groups (26.4% with GnRHa versus 21.1% with no GnRHa).<sup>847</sup> [Evidence level 1b]

### 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 (cetorelix 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 7.

### 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 number of oocytes retrieved, likely to be associated with diminished ovarian reserve.<sup>848,849</sup> [Evidence level 3I]

A systematic review of available studies including RCTs found limited data that assessed the effectiveness of different management strategies in women with poor ovarian response.<sup>849</sup> 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.<sup>849</sup> [Evidence level 1b–2b]

### Adjuvant growth hormone therapy

A systematic review of six RCTs found no significant difference between growth hormone augmented ovulation induction versus 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, 95% CI 0.64 to 10.12).<sup>850</sup> [Evidence level 1a]

Three additional RCTs were found. One small RCT showed no significant difference between adjuvant growth hormone GH 4 IU versus growth hormone GH 12 IU versus no growth hormone in downregulated ovulation induction in pregnancy rate per embryo transfer (0% versus 29% versus 0%).<sup>851</sup> [Evidence level 1b] Another RCT showed no significant difference

between growth hormone-releasing factor versus placebo in clinical pregnancy rate (8.3% versus 8%) and live birth rate (5.2% versus 4%) in poor responders.<sup>852</sup> [Evidence level 1b] One quasirandomised trial showed no significant difference between growth hormone versus no growth hormone in downregulated ovulation induction in pregnancy rate (0% versus 7.7%) in poor responders.<sup>853</sup> [Evidence level 2a]

### RECOMMENDATIONS

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

A

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

B

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

A

## 12.4 Oocyte maturation – human chorionic gonadotrophin

Human chorionic gonadotrophin 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 versus 24.7% with uhCG) and live birth rate (27% with rhCG versus 23% with uhCG) and OHSS incidence (7.2% with rhCG versus 6.4% with uhCG).<sup>854</sup> [Evidence level 1b]

Another RCT showed no significant differences between 250 micrograms and 500 micrograms of rhCG and uhCG in clinical pregnancy rate (35.1% versus 36% versus 35.9%), live births (87.9% versus 84.4% versus 84.8%) or OHSS incidence (3.25% versus 9% versus 3.1%).<sup>855</sup> [Evidence level 1b]

### 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. Consideration should be given to minimising cost when prescribing.

A

## 12.5 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 seven to nine and to determine timing of hCG administration at days 11 to 14. The extent of monitoring is reduced in GnRH antagonist controlled cycles.<sup>856</sup> [Evidence level 3]

One RCT (n = 114) found no significant differences between ultrasonic ovulation control with hormone determination versus ultrasound alone in pregnancy rate per embryo transfer (27.2% versus 29.5%) and OHSS rate (5.3% versus 7%) in women undergoing GnRH<sub>a</sub>-hMG during IVF-embryo-transfer for the first time.<sup>857</sup> [Evidence level 1b]

One RCT (n = 279) found no significant differences between cycle monitoring using both serum oestradiol and ultrasound versus ultrasound alone in clinical pregnancy rate (34.3% versus 31.4%) and OHSS rates (4.9% versus 4.1%) in normal responders undergoing GnRH<sub>a</sub>-rFSH during IVF-embryo-transfer.<sup>858</sup> [Evidence level 1b]

A non-RCT (n = 206) found no significant differences between ultrasound with hormonal determination versus ultrasound alone in clinical pregnancy rate (22.9% versus 23.4%), live birth rate (14.3% versus 14.8%) and OHSS rate (1.04% versus 0.9%) in women undergoing GnRHa-hMG/hCG during IVF-embryo-transfer.<sup>859</sup> [Evidence level 2a]

### RECOMMENDATIONS

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

C

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

A

## 12.6 Ovarian hyperstimulation syndrome

OHSS is an iatrogenic and potentially life-threatening complication of superovulation. The incidence of OHSS varies between 0.6% and 10% in IVF cycles. The severe form of the condition occurs in 0.5–2% of IVF cycles<sup>860</sup> (see also Section 7.11).

Several risk factors have been associated with the development of OHSS:<sup>861</sup>

- Young age (less than 30 years)
- Lean physique
- Polycystic ovary syndrome
- High serum oestradiol (greater than 2500 pg/ml or 9000 pmol/l)
- Rapidly increasing oestradiol levels (greater than 75% from previous day)
- Size and number of follicles and ultrasonographic ovarian 'necklace sign' of multiple small follicles
- hCG administration
- Number of oocytes retrieved (greater than or equal to 20)
- Multiple pregnancy.

Criteria for classifying the severity of OHSS are:

- Mild:
  - abdominal bloating, mild pain
  - ovarian size usually less than 8 cm\*
- 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.<sup>861</sup>

### Prevention

There is no evidence to support the superiority of either hMG or rFSH<sup>517</sup> (OR 1.60, 95% CI 0.60 to 4.3) or urinary preparations<sup>518</sup> (OR 1.36, 95% CI 0.79 to 2.33) in preventing OHSS. [Evidence level 1a]

### Cycle cancellation

Cancellation of a treatment cycle is a strategy that has been considered if ovarian ultrasound reveals a large number of developing follicles and/or serum oestradiol levels are excessively high. The principle behind this decision is to withhold the ovulatory trigger (hCG). In cycles where GnRH agonists have not been used, this may not completely prevent early-onset OHSS as a natural LH surge may still occur.<sup>862</sup>

### Coasting

Coasting involves discontinuation of gonadotrophins in cycles with an excessive response and delaying hCG administration, while continuing GnRH agonist administration in the presence of ultrasound and endocrine monitoring.<sup>863</sup> It is an alternative to cycle cancellation in situations where there is a substantial risk of OHSS associated with high serum oestradiol levels above 2500 pg/ml (9000 pmol/l). The aim is to allow FSH levels to drop, thus inhibiting granulosa-cell proliferation and subsequent availability for luteinisation. The patient is monitored until the oestradiol level falls below a safe limit (< 2500 pg/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 systematic review on the role of coasting for the prevention of OHSS identified only one RCT. Compared with elective unilateral follicular aspiration (elective aspiration of excess ovarian follicles), there was no convincing benefit associated with the use of coasting (OR 0.76, 95% CI 0.18 to 3.24).<sup>864</sup> [Evidence level 1a]

### 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 (for example, more than 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 systematic review has found that there is insufficient evidence to support routine cryopreservation in cases with a high risk of OHSS (OR 5.33, 95% CI 0.51 to 56.24 for elective cryopreservation versus intravenous albumin; OR 0.12, 95% CI 0.01 to 2.29 for elective cryopreservation versus fresh embryo transfer).<sup>865</sup> [Evidence level 1a]

### Luteal-phase support

A systematic review has confirmed the effectiveness of routine luteal phase support after embryo transfer in IVF cycles involving the use of gonadotrophin-releasing hormone agonists.<sup>866</sup> [Evidence level 1a] The use of hCG in this situation can aggravate OHSS and progesterone should be the preparation of choice in high-risk women.<sup>867</sup>

### 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 woman. 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.<sup>861</sup> A systematic review<sup>868</sup> reported that the use of intravenous albumin at the time of oocyte retrieval significantly reduced the incidence of severe OHSS in high-risk women undergoing IVF (OR 0.28, 95% CI 0.11 to 0.73). [Evidence level 1a] 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.<sup>869</sup> The systematic review,<sup>868</sup> suggested that 18 women at risk would need 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.<sup>870</sup>

### *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.<sup>871</sup> 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.<sup>861</sup>

### *Other methods of prevention*

A number of other methods of preventing OHSS have been advocated. These include the use of recombinant LH<sup>872</sup> and GnRH antagonists such as ganirelix or cetrorelix.<sup>873,874</sup> A meta-analysis of five RCTs<sup>561</sup> suggested that treatment with GnRH antagonists did not significantly reduce the incidence of severe OHSS in comparison with those treated with agonists (OR 0.51, 95% CI 0.22 to 1.18). [Evidence level 1a]

In a prospective randomised trial,<sup>875</sup> 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. [Evidence level 1b]

## **Treatment**

Treatment of OHSS is mainly supportive.<sup>862</sup> 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 seven days in nonpregnant 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**

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

**A**

## **RESEARCH RECOMMENDATION**

Further research is needed to determine whether prophylactic albumin treatment administered at the time of egg collection is effective. This research should include issues related to timing and dose.

## **12.7 Oocyte retrieval**

### **Conscious sedation and anaesthesia or analgesia**

It is accepted that transvaginal oocyte retrieval is unpleasant and painful. It is therefore important to provide effective anaesthesia or analgesia to minimise adverse effects and to minimise toxic effects on embryo cleavage rates and pregnancy rates. No technique of anaesthesia, analgesia or sedation is free from adverse effects. Whatever technique is used, it is essential that it should conform to the recognised standards of practice and guidance on the safe use of sedative drugs for patients undergoing health procedures as published by the Academy of Royal Medical Colleges.<sup>876</sup> [Evidence level 4]

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 adverse effects of general anaesthesia 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, although there is a theoretical risk of agents contaminating the follicular fluid.<sup>877</sup> [Evidence level 2b–3]

### *Conscious sedation versus placebo*

An RCT showed significantly higher median vaginal pain and abdominal pain levels in women given paracervical block and placebo as compared with paracervical block and conscious sedation. However, there was no significant difference in pregnancy rates per cycle.<sup>878</sup> [Evidence level 1b]

Another RCT found significantly higher anxiety levels and vaginal and abdominal pain levels in women given placebo when compared with women given premedication with anxiolytic during oocyte retrieval.<sup>879</sup> [Evidence level 1b]

### *Patient-controlled analgesia*

An RCT showed no significant difference in mean pain score and patient satisfaction rate between fentanyl administration via a patient-controlled analgesia delivery system versus administration by a physician. However, significantly more fentanyl was used in the patient-controlled analgesia group.<sup>880</sup> [Evidence level 1b] Another RCT reported no difference in patient satisfaction with conventional intravenous analgesia compared with patient-controlled inhalational isodesox during oocyte recovery, although the mean pain score was higher in the group receiving isodesox. There was no difference in fertility outcomes between the two groups.<sup>881</sup> [Evidence level 1b] Patient-controlled sedation using propofol or alfentanil was also reported to provide less pain relief for patients than physician-administered sedation using diazepam and pethidine during transvaginal ultrasound-guided oocyte retrieval. Fertility outcomes were similar in the two groups.<sup>882</sup> [Evidence level 1b]

### *Conscious sedation versus general anaesthesia*

An RCT found significantly higher mean pain score with conscious sedation using midazolam and ketamine when compared with general anaesthesia using fentanyl and propofol, although the higher pain score with sedation was not sufficiently high to render it unacceptable to women. There was no difference between the two groups in pregnancy rate per embryo transfer (22.7% with sedation versus 23.8% with general anaesthesia). The mean number of embryos transferred was significantly higher in the sedation group (2.8 versus 1.9). Patient satisfaction did not differ between the two groups.<sup>883</sup> [Evidence level 1b]

Intravenous midazolam and remifentanyl and intravenous propofol and fentanyl were reported to be similar in providing effective sedation during oocyte retrieval for IVF procedures. However, a significant proportion of women (13%) given intravenous midazolam and remifentanyl found the experience unpleasant due to awareness during the surgical procedure and said they would not accept conscious sedation for the same procedure in the future. All of the women given propofol and fentanyl were satisfied and said they would accept conscious sedation again.<sup>884</sup> [Evidence level 1b]

Exposure to the intravenous anaesthetic drug propofol was not reported to have a detrimental effect on oocyte quality.<sup>885</sup> [Evidence level 3]

A cohort study (n = 202) compared the effects of general anaesthesia with conscious 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 versus 31.3% with conscious sedation).<sup>886</sup> [Evidence level 2b] Epidural anaesthesia was reported to be effective in pain control when compared with intravenous sedation in an IVF programme. The pregnancy rates were similar in the two groups.<sup>887</sup> [Evidence level 2b] Clinical pregnancy rates and delivery rates were lower following oocyte retrieval performed under general anaesthesia using nitrous oxide compared to epidural and local anaesthesia.<sup>888</sup> [Evidence level 2b] A meta-analysis of three RCTs and one case-control study reported no difference in

pregnancy rates (pooled OR 0.71, 95% CI 0.47 to 1.08) between general anaesthesia and locoregional anaesthesia in patients undergoing laparoscopic oocyte retrieval.<sup>889</sup> Meta-analysis of the three RCTs showed similar results (OR 0.84, 95% CI 0.28 to 2.56) [Evidence level 1a]

A 1997 survey of UK fertility centres found that many different techniques were used for anaesthesia in IVF programmes.<sup>890</sup> [Evidence level 3] A recent survey reported that 84% and 16% of IVF clinics used intravenous sedation and general anaesthesia, respectively, for transvaginal oocyte retrieval.<sup>891</sup> [Evidence level 3] There was wide variation in personnel present during the procedure, the use of drugs, the degree of monitoring and the availability of emergency drugs. This wide variation in current practice within the UK highlighted the need for adoption of national guidelines for safe use of sedation in women undergoing IVF treatment. A set of guidelines with recommendations for good practice for sedation in assisted reproduction procedures has since been developed.<sup>892</sup> [Evidence level 4]

### *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 that would otherwise be missed if aspiration alone were used.

An RCT (n = 36) reported similar oocyte recovery rate using a single-lumen needle without flushing or a double-lumen needle with flushing at ovum pick up. Administration of hCG occurred when the dominant follicle reached 18 mm in diameter in the presence of an appropriate oestradiol level. The number of follicles at the time of hCG administration was not reported. Operating time may be longer with follicle flushing.<sup>893</sup> [Evidence level 1b]

Another RCT (n = 34) showed no significant differences between follicular aspiration with flushing and follicular aspiration only in mean number of oocytes retrieved (7.0 versus 8.5), fertilisation rate (64% versus 60%) and ongoing pregnancy rate (17% versus 19%). This trial included women who had developed at least three follicles that had attained a diameter of 18 mm with corresponding oestradiol levels at the time of hCG administration. Significantly longer time was required for the procedure of flushing.<sup>894</sup> [Evidence level 1b]

A further RCT found no significant differences between follicular aspiration with flushing and follicular aspiration only in mean number of oocytes retrieved (9 versus 11), fertilisation rate (60% versus 55.6%) and clinical pregnancy rate per woman (26% versus 24%; RR 0.92, 95% CI 0.47 to 1.82). This trial excluded women who had developed less than four or more than 25 follicles that were wider than 14 mm on the day of hCG administration. Significantly longer time and higher doses of pethidine were required for the procedure of flushing.<sup>895</sup> [Evidence level 1b]

The use of follicle flushing in women with less than three follicles has not been evaluated but it may be useful for ensuring that oocyte yield is maximised.

### 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.

D

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

A

### RESEARCH RECOMMENDATION

Further research is needed to evaluate the effect of general anaesthesia on oocyte retrieval and outcome of in vitro fertilisation treatment, taking into account patient preference.

## 12.8 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 or nonobstructive azoospermia. Sperm recovery is also used in ejaculatory failure and where only non-motile spermatozoa are present in the ejaculate (see Section 6.3) Ejaculatory failure is not uncommon on the day of egg collection and is usually caused by anxiety.

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. Sperm recovery for ICSI has made it possible for infertile men to father children who are genetically their own.

Surgical techniques 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
- 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 men, sperm can be recovered from naturally occurring spermatoceles by percutaneous puncture.

In nonobstructive 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.<sup>896,897</sup> PESA does not jeopardise future epididymal sperm retrieval.<sup>898</sup>

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 azoospermia 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 dropout or loss to follow-up reported.<sup>899</sup> [Evidence level 1a]

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.<sup>900</sup> Facilities for genetic screening with a view to referral to preimplantation genetic diagnosis should be available in any sperm retrieval programme.<sup>901</sup>

The best method of extracting spermatozoa from the testicular tissue in nonobstructive azoospermia is uncertain. The relative merits of TESA and TESE using small (5-mm), multiple or large (10–15-mm) diameter biopsies is unknown.<sup>902–906</sup> Compared with TESE, TESA has a reduced rate of sperm recovery but is less invasive.<sup>907–910</sup> [Evidence level 3]

### Failure rates of retrieval

Reported failure rates of sperm retrieval vary with study and with technique (see Table 12.1). A further complication is added by the inconsistent method of reporting (for example, per attempt, per patient, or per couple).

In nonobstructive 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.<sup>901,903,911–919</sup> 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.<sup>920</sup>

**Table 12.1** Failure rates of sperm retrieval

Azoospermia	Procedure	Quoted failure rate
Obstructive	MESA	1.7% of men (1/59) <sup>921</sup> 22% of men (2/9) <sup>922</sup>
	PESA <sup>a</sup>	17% of initiated cycles (30/181) <sup>898</sup> 15.8% of initiated cycles (43/234) <sup>896</sup> 11% in men with CBAVD (7/62) and 5% in men with failed reversed vasectomy (3/60) <sup>923</sup>
Non-obstructive	TESA	0% of men (1/197) <sup>924</sup>
	TESE	13% of men (2/15) <sup>925</sup> 19.7% of men (39/159) <sup>921</sup> 38% of men (6/16) <sup>911</sup> 8% of men (10/124) <sup>926</sup> 57% of men (21/37) <sup>903</sup>
		66% of men (34/51) <sup>924</sup>
	TESA	

<sup>a</sup> These studies may include some of the same men

### 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<sup>927,928</sup> and are both successful for establishing pregnancies.<sup>915,922</sup> Some authors report these success rates as being lower than those achieved by spermatozoa from the ejaculate. One study<sup>929</sup> 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 women. However, another study<sup>898</sup> showed that the outcome of PESA–ICSI treatment compares favourably with that of ICSI using ejaculated spermatozoa. One study<sup>896</sup> also found that the results of PESA–TESA were similar to ejaculate sperm. [Evidence level 3]

Another study<sup>930</sup> 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. [Evidence level 3] Spermatozoa can be retrieved from the testis in couples in whom epididymal aspiration failed.<sup>901,928,931</sup> When spermatozoa cannot be recovered by one technique another one can be employed, for example, TESE after MESA.<sup>922</sup> Testicular spermatozoa can be successful in achieving fertilisation and pregnancies for couples in whom epididymal aspiration failed.<sup>901,916</sup> However, some studies report fertilisation or pregnancy rates lower than those achieved with epididymal spermatozoa. For example, one study<sup>901</sup> 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 men with CBAVD and in those with failed reversal of vasectomy.<sup>923,928,932</sup> [Evidence level 3]

Variation in outcome using testicular sperm in nonobstructive azoospermia compared with obstructive azoospermia has been demonstrated by various studies.<sup>933–935</sup> Results in nonobstructive azoospermia are generally inferior.

### Testicular sperm cryostorage

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.<sup>901,927,936</sup> In one study,<sup>901</sup> the only significant factor appeared to be the age of the woman. [Evidence level 3] Using cryopreserved testicular sperm (cryo-TESE) for ICSI is an effective and successful approach for the treatment of severe testicular insufficiency.<sup>921</sup> 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.<sup>921,927</sup> 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.<sup>937</sup>

A retrospective consecutive case series<sup>938</sup> 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% versus 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. [Evidence level 3] In men suspected of having obstructive azoospermia with no work-up or an incomplete one, MESA was preferred 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<sup>939</sup> 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% versus 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% versus 25%), and the live birth rate per transferred embryo was higher in the group in which fresh testicular spermatozoa were used (19% versus 8%). [Evidence level 3]

A retrospective analysis of consecutive ICSI cycles<sup>940</sup> 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 men 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. [Evidence level 3]

## 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 available.

C

## 12.9 Assisted hatching

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 four RCTs and three non-randomised controlled trials 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-three serum FSH and repeated IVF failures. Data from this review did not support generalised assisted hatching for all patients.<sup>941</sup> [Evidence level 1b–2a]

The four RCTs from the previous review<sup>941</sup> were included in a systematic review of 23 RCTs (2572 women) assessing the impact of assisted hatching on live birth, clinical pregnancy and implantation rates.<sup>942</sup> [Evidence level 1a] This review showed that assisted hatching had no significant effect on live birth rate (OR 1.21, 95% CI 0.82 to 1.78; based on six RCTs, n = 523 women). However, there was an increase in clinical pregnancy rate with assisted hatching (OR 1.63, 95% CI 1.27 to 2.09, based on 19 RCTs, n = 2 175 women). This effect may be increased in a subgroup of women who had previously had one or more cycles of IVF or ICSI that did not result in a live birth (OR 2.33, 95% CI 1.63 to 3.34, based on four RCTs, n = 666 women). However, these results should be interpreted with caution because of the poor methodological quality of the included trials, with unclear methods of randomisation in 13 trials and inadequate concealment of allocation in 23 trials.

### Multiple gestation

Monoamniotic multiple gestation may be increased in zona-manipulated cycles. The potential obstetric risks and complications of zona manipulation should be discussed with couples. In an anonymous survey of 42 IVF centres in the USA,<sup>943</sup> 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.<sup>944</sup> [Evidence level 3]

### RECOMMENDATION

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

A

### RESEARCH RECOMMENDATION

Further research is needed to evaluate the effects of assisted hatching on live birth rates and long-term consequences for children born as a result of assisted hatching.

## 12.10 Embryo transfer techniques

### Use of ultrasound

Ultrasound-guided embryo transfer is a complex intervention. Four RCTs<sup>945-948</sup> and four quasi-RCTs<sup>949-952</sup> comparing ultrasound-guided embryo transfer versus clinical touch embryo transfer were identified. [Evidence level 1b-2a]

We performed a meta-analysis using data from all eight studies. This showed a significant increase in pregnancy rates with routine ultrasound-guided embryo transfer (pooled OR 1.46, 95% CI 1.25 to 1.70, n = 3358 embryo transfers). When the quasi-RCTs were excluded, there was still a significant increase in pregnancy rates with routine ultrasound-guided embryo transfer (pooled OR 1.42, 95% CI 1.17 to 1.73, n = 2051 embryo transfers). Overall, the meta-analyses suggest that use of ultrasound at the time of embryo transfer increases pregnancy rates. However, there was clinical heterogeneity among different groups of women and in the specific role of ultrasound in each trial. [Evidence level 1a]

### Day two to three versus day five to six transfers

This has been the subject of a systematic review.<sup>953</sup> 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 to 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 to 1.29). It is not possible to perform an intention-to-treat analysis for blastocyst transfer and so the results of these studies may be biased. [Evidence level 1a]

Four new RCTs were identified.<sup>954-957</sup> Results from these trials were combined with those from the earlier studies. A new meta-analysis showed the following results. [Evidence level 1a]

- Pregnancy and live birth rates per ovum pick up (that is, intention to treat analysis) (OR 1.08, 95% CI 0.94 to 1.25) and embryo transfer (OR 0.92, 95% CI 0.64 to 1.32) are similar in the two groups, suggesting no difference between the groups.
- Pregnancy rate per embryo transfer (combined OR 1.20, 95% CI 1.04 to 1.38, based on 14 RCTs) and live birth rate per embryo transfer (combined OR 1.41, 95% CI 1.0 to 1.98, based on five RCTs) 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 women 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.

### Type of catheter

Seven RCTs have been identified comparing a number of different catheters.<sup>958-964</sup> The results of these trials suggest that the choice of embryo transfer catheter can affect pregnancy rates. In particular, data from large trials suggest that certain types of soft catheter are more effective than other types of catheter. [Evidence level 1b] Data from the various studies could not be aggregated due to significant clinical heterogeneity and differences between individual catheters.

### Endometrial thickness

Endometrial thickness and endometrial pattern are the two anatomical parameters suggested to evaluate the endometrium by ultrasound. The role of endometrial thickness as a single factor in predicting pregnancy following IVF is controversial. A narrative review of 27 cohort and observational studies found insufficient data for an association between endometrial thickness and the probability of conception during IVF cycles. The mean endometrial thickness for conception and non-conception cycles were similar, ranging from 8.6 mm to 12.0 mm. There was also no case in which the endometrial thickness was less than 5 mm which resulted in pregnancy (based on 1605 cycles in 13 studies).<sup>965</sup> [Evidence level 2b-3] 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. Implantation and pregnancy rates were reported to be significantly reduced in women with an endometrial thickness of greater than 14 mm on the day of hCG administration in an IVF programme.<sup>966</sup> [Evidence level 2b] One study reported that reduced endometrial thickness had only a marginal effect on the probability of achieving a pregnancy rates with assisted reproduction.<sup>967</sup> [Evidence level 2b]. However, no significant correlation was found between endometrial volume and thickness and occurrence of pregnancy during IVF treatment in two studies.<sup>968</sup> [Evidence level 3] <sup>969</sup> [Evidence level 2b]

### Bed rest versus no bed rest

One RCT (n = 182) found no significant difference in pregnancy rate per embryo transfer between 20 minutes of bed rest versus 24-hours of bed rest following embryo transfer (24% versus 23.6%), spontaneous miscarriage rate (19% versus 18%) and multiple pregnancy rate (14% versus 13.6%).<sup>970</sup> [Evidence level 1b] 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 that was assigned to bed rest.<sup>971</sup> [Evidence level 3]

## RECOMMENDATIONS

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

A

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

B

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

B

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

A

### RESEARCH RECOMMENDATIONS

Further research is needed to evaluate the effect of cleavage (day 2 or 3) and blastocyst (day 4 or 5) stage methods of embryo transfer on live birth rates.

Further research is needed to evaluate the effects of different types of embryo transfer catheters on pregnancy rates.

## 12.11 Luteal support

### Progesterone versus no support in non-downregulated cycles

A 1988 meta-analysis of five RCTs found no significant difference between luteal-phase progesterone support in non-downregulated IVF cycles and no such support in pregnancy rate (OR 1.25, 95% CI 0.93 to 1.66) in women undergoing IVF or GIFT after ovarian stimulation with clomifene and hMG.<sup>972</sup> [Evidence level 1a]

### Human chorionic gonadotrophin versus no treatment/human chorionic gonadotrophin versus progesterone in downregulated cycles

A meta-analysis of 18 RCTs showed significantly higher pregnancy rate per cycle in women 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.<sup>866</sup> [Evidence level 1a] 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 women treated with hCG compared with progesterone (OR 2.0, 95% CI 1.1 to 3.9). However, this effect was due to a difference in the effectiveness of hCG and oral (rather than intramuscular) progesterone. There was no significant difference in spontaneous abortion rate between women 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) versus 0% (n = 193) with progesterone or no treatment.<sup>866</sup> [Evidence level 1a]

Another meta-analysis<sup>973</sup> 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.<sup>973</sup> [Evidence level 1a]

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. Given the increased risk of OHSS associated with hCG use, progesterone was favoured for luteal-phase supplementation with addition of oestrogen.<sup>973</sup> [Evidence level 1a]

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 USA.<sup>974</sup> [Evidence level 3] 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

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

A

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

A

### RESEARCH RECOMMENDATION

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

# 13. Intracytoplasmic sperm injection

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ICSI is a technique used within the IVF treatment process where it is necessary to use micromanipulation to achieve fertilisation. ICSI is usually required when the numbers of sperm are 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 poor semen quality or where spermatozoa have to be retrieved surgically because the man has azoospermia (see Section 12.10).

## 13.1 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.<sup>975</sup> Approximately 90% of couples had an embryo transfer and 19–22% of them achieved a viable pregnancy, irrespective of the origin of the spermatozoon. [Evidence level 3]

### Use in oligozoospermia and other causes of poor semen quality

A systematic review<sup>976</sup> of ten 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 was no difference in pregnancy rate or fertilisation rates per retrieved oocyte or 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 to 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 to 4.85 per oocyte retrieved, combined OR 3.90, 95%CI 2.96 to 5.15 per oocyte inseminated). Couples with very poor semen (concentration less than 10 million/ml, motility less than 30%, morphology less than 4% normal forms) will have better fertilisation outcomes with ICSI than with subzonal sperm injection or additional IVF; however, there were only two RCTs that considered couples with very poor semen quality. [Evidence level 1a]

An RCT reported lower ongoing pregnancy rates with ICSI compared to conventional IVF (10.8% with ICSI versus 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.<sup>977</sup> [Evidence level 1b]

An 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 a significant difference between standard IVF and ICSI in overall fertilisation rate per oocytes injected (37.4% with IVF versus 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 versus 67.6% with ICSI; RR 1.13, 95% CI 0.99 to 1.29). Pregnancy outcomes were not measured.<sup>978</sup> [Evidence 1b] A meta-analysis of this trial and eight other RCTs, including three RCTs from the previous systematic review,<sup>976</sup> 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; however, 3.1 ICSI cycles may

be needed to avoid one complete fertilisation failure after conventional IVF (95% CI 1.7 to 12.4).<sup>978</sup> [Evidence 1a]

It has been reported in case series studies that despite severe semen impairment such as cryptozoospermia, total astheno- or teratozoospermia, fertilisation failure after ICSI was mainly caused by immotile sperm,<sup>979</sup> poor sperm morphology<sup>980</sup> and poor quality oocytes.<sup>981</sup> [Evidence level 3]

### Use 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%.<sup>982</sup> [Evidence level 3] 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.<sup>931</sup> [Evidence level 3]

#### *Nonobstructive azoospermia*

A case series study (n = 15) reported a two-pronuclear fertilisation rate of 48% and an ongoing pregnancy rate of 25% (3 of 12 embryo replacements) in men with azoospermia due to testicular failure.<sup>925</sup> [Evidence level 3]

Inferior outcome in nonobstructive azoospermia relative to obstructive azoospermia has been demonstrated in three case series studies.<sup>915,933,935</sup> [Evidence level 3]

ICSI clinical pregnancy rates with epididymal spermatozoa in obstructive azoospermia were not significantly different from those achieved using testicular spermatozoa in men with nonobstructive azoospermia, although fertilisation rates with epididymal spermatozoa were higher (57% versus 81%).<sup>983</sup> [Evidence level 3] A case series reported that although fertilisation rate after ICSI with testicular spermatozoa in non-obstructive azoospermia is significantly lower than in obstructive azoospermia, pregnancy and embryo implantation rates are similar.<sup>939</sup> [Evidence level 3] Another case series reported significantly lower fertilisation and pregnancy rates from ICSI with testicular sperm from men with nonobstructive azoospermia, compared with men with obstructive azoospermia.<sup>984</sup> [Evidence level 3] Both case series reported significantly higher fertilisation rates with testicular spermatozoa in obstructive azoospermia than those with nonobstructive azoospermia.<sup>939,984</sup> [Evidence level 3]

### Use in couples with failed fertilisation

ICSI is offered to couples with previously failed fertilisation in IVF cycles, with good results.<sup>985</sup> 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.<sup>986-989</sup> [Evidence level 3] Others found that none of the sperm parameters of the original semen analysis were associated with the outcome of ICSI cycles<sup>990</sup> and that pregnancy and fertilisation rates did not differ between men who had previously failed fertilisation in conventional IVF, men with moderately poor semen quality, men with semen parameters of 1–10 million/ml, and men with less than 1 million/ml.<sup>980</sup> Another case series<sup>991</sup> 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 men who produced a pregnancy and those who did not, although the fertilisation rate was higher in men with more adequate sperm parameters. [Evidence level 3]

Poor ICSI results may be due to the coexistence of oocyte defects not bypassed by ICSI.<sup>986,989</sup> A number of studies have found a significant negative correlation between female age and pregnancy results,<sup>773,990,991</sup> especially after the age of 35 years.<sup>992</sup> 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 of factors influencing ICSI outcomes reported a significant correlation between the occurrence of pregnancy with female age (90th quantile: 38 years), number of oocytes retrieved (tenth quantile: five oocytes) and number of oocytes injected (tenth 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.<sup>993</sup> [Evidence level 3]

One study<sup>994</sup> 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. [Evidence level 3]

### Use in couples with non-male subfertility

A systematic review of one RCT (n = 415) reported no difference in pregnancy rates (OR 1.40, 95% CI 0.95 to 2.20) between ICSI and IVF in couples with non-male subfertility.<sup>995</sup> [Evidence level 1a] The RCT did not report live birth rates or miscarriage rates.<sup>996</sup>

### RECOMMENDATION

The recognised indications for treatment by ICSI include:

- severe deficits in semen quality
- obstructive azoospermia
- nonobstructive 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**

## 13.2 Genetic issues and counselling

The likelihood of genetic abnormalities (such as chromosomal abnormalities) is greater in men with nonobstructive azoospermia than in men with obstructive azoospermia. The clinical features of obstructive and nonobstructive azoospermia and CBAVD are important to elicit. For example, in nonobstructive 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<sup>997</sup> 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 to 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 nonseminoma and were not influenced by adjustment for potential confounding factors. [Evidence level 3] 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 (see Chapter 16). Recovery of spermatogenesis after treatment may take longer than five years in some patients.<sup>998</sup> 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.<sup>998</sup> Effective counselling depends upon understanding the illness itself, the context of men's lives, the assault upon the sense of self, the impact on intimate relationships and treatment options and psychosexual effects.<sup>999</sup> Infertility after testicular cancer can be treated effectively with IVF or ICSI.<sup>1000</sup> For example, one study<sup>1001</sup> obtained an ongoing pregnancy rate of 57% per cycle. [Evidence level 3]

Male infertility due to severe oligozoospermia and azoospermia has been associated with a number of genetic factors, including numerical and structural chromosomal abnormalities,<sup>1002</sup> microdeletions of the Y chromosomes<sup>1003,1004</sup> and mutations in the cystic fibrosis transmembrane conductance regulator gene, commonly associated with congenital vas deferens abnormalities.<sup>1005,1006</sup> [Evidence level 3]

Chromosomal abnormalities have been detected in 2.1–8.9% of men attending infertility clinics,<sup>1007</sup> compared with 1% of the general male population.<sup>1008</sup> 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.<sup>1009,1010</sup> [Evidence level 3] Higher prevalence of chromosomal abnormalities in the male rather than the female partner of couples referred for ICSI has also been reported.<sup>1008,1011,1012</sup> [Evidence level 3] Genetic abnormality was identified in 24% of men with extreme oligozoospermia and azoospermia in couples requesting ICSI.<sup>1013</sup> [Evidence level 3] Sperm of azoospermic men, when compared with ejaculated spermatozoa of healthy men, has been reported to have a higher incidence of chromosomal abnormalities, of which sex chromosome aneuploidy was the most prominent.<sup>1014,1015</sup> [Evidence level 3] 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 that 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 97–98% of males with cystic fibrosis are infertile.<sup>1016</sup> CBAVD leads to obstructive azoospermia in otherwise normal men and is responsible for approximately 2% of male infertility.<sup>1</sup>

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<sup>1017</sup> 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. Among oligozoospermic men, sex and autosomal abnormalities are found in 0.9 to 3.6% and 0.9 to 4.9%, respectively. [Evidence level 3] 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 nonobstructive 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 oligozoospermic and azoospermic men.<sup>1018</sup> The prevalence is higher in azoospermic than oligospermic men.<sup>1019</sup> [Evidence level 3] 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% versus 71%, 95% CI 67 to 74%;  $p < 0.01$ ), but no significant differences in pregnancy, implantation or live birth rates were found.<sup>1018</sup> [Evidence level 3] The presence of Y deletions was reported to have no impact on fertilisation and pregnancy rates in one case-series study.<sup>1020</sup> [Evidence level 3]

Several screening programmes have confirmed the common occurrence of microdeletions in the Yq part of the chromosome among men with otherwise unexplained oligo- or azoospermia.<sup>1021,1022</sup> [Evidence level 3] 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.<sup>1016</sup> [Evidence level 3] 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.<sup>1023,1024</sup>

Testing for Y chromosome microdeletions should not be regarded as a routine investigation before ICSI. A recent survey among staff working in UK fertility 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 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.<sup>1025</sup> [Evidence level 3]

## 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.



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

B

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

B

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

B

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

GPP

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

### 13.3 Intracytoplasmic sperm injection versus 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 ten RCTs compared ICSI versus IVF, ICSI versus additional IVF and ICSI versus subzonal sperm injection in couples with mild–moderate male factor infertility, unexplained infertility and tubal subfertility.<sup>976</sup> [Evidence level 1a] 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<sup>1026</sup> 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 versus subzonal sperm injection significantly increased fertilisation rate per oocyte injected (33% with ICSI versus 16% with subzonal sperm injection, OR 2.59, 95% CI 1.11 to 6.04) and ICSI versus additional IVF significantly increased fertilisation rate per oocyte injected (63% with ICSI versus 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 quality.<sup>976</sup> [Evidence level 1a]

#### RECOMMENDATION

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

A

#### RESEARCH RECOMMENDATION

Further research is needed to evaluate the effect of intracytoplasmic sperm injection on live birth or pregnancy rates in couples where the male partner has poor semen quality.

### 13.4 Cost effectiveness of intracytoplasmic sperm injection

The cost effectiveness models for ICSI treatment are described in detail in Appendix B. We found no live birth rates for ICSI and so the cost effectiveness models were based upon 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, including drugs) and an OHSS incidence rate of 0.2% was £14,029. At a lower cost per ICSI treatment (£1,936, excluding drugs) the cost per live birth was £9,056.

# 14. Donor insemination

## 14.1 Indications for donor insemination

Male infertility affects about 25% of all infertile couples.<sup>1</sup> 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)<sup>1027</sup> by donor insemination has led to the mandatory quarantine of donor sperm for six months by cryopreservation prior to its use in the UK,<sup>1028</sup> [Evidence level 3–4] despite the fact that pregnancy rates are significantly higher when fresh sperm is used compared with cryopreserved sperm.<sup>1029</sup> [Evidence level 1b] 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

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

- obstructive azoospermia
- nonobstructive azoospermia
- infectious disease in the male partner (such as HIV)
- severe rhesus isoimmunisation
- severe deficits in semen quality in couples who do not wish to undergo intracytoplasmic sperm injection.

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

B

## 14.2 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.<sup>1030</sup> [Evidence level 3] 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 them 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.<sup>1030</sup> [Evidence level 3]

Implication counselling is particularly important when donor gametes are considered, both for the donor and the recipient couple.<sup>218,1031</sup> [Evidence level 4]

### RECOMMENDATION

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

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

C

C

### 14.3 Screening of sperm donors

The HFEA Code of Practice requires clinics to take all reasonable steps to avoid transmission of serious genetic disorders stating a mandatory upper age limit of 45 years for sperm donors. It is also 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.<sup>218,1031</sup> [Evidence level 4]

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 recipient women from infection. The British Andrology Society guidelines suggest an upper age limit of 40 years for sperm donors.<sup>1028</sup> [Evidence level 3–4] However, the guidance issued by the British Andrology Society is optional, whereas the HFEA upper age limit is mandatory. The British Andrology Society guidelines recommend that sperm donors are screened for karyotyping of chromosomal abnormalities, autosomal recessive conditions (such as cystic fibrosis, beta-thalassaemia, sickle-cell disease and Tay–Sachs disease) and rhesus antigens.<sup>1028</sup> [Evidence level 3–4] These guidelines also recommend the exclusion of sperm donors who are seropositive for HIV, hepatitis B virus, hepatitis C virus, syphilis, *C. trachomatis* and cytomegalovirus.

Serological testing for HIV will not detect early infection in the first 6–12 weeks, when the individual has not yet seroconverted. Potential recipients of donated sperm should therefore be informed that an HIV test in the donor does not absolutely exclude the transmission of HIV. With hepatitis B, hepatitis C, syphilis and cytomegalovirus, positive serology does not necessarily indicate an ongoing risk of infection. The suitability as sperm donors of people who are seropositive for hepatitis B, hepatitis C, syphilis or cytomegalovirus should, therefore, be considered in relation to their history of treatment, subsequent follow-up and change in serological titre level.

The prevalence of sexually transmitted diseases in potential semen donors in an urban area of Canada was found to be 34.5% (n = 29).<sup>1032</sup> [Evidence level 3] 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.<sup>1033</sup> [Evidence level 3]

#### 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 counselling from someone who is independent of the treatment unit regarding the implications for themselves and their genetic children, including any potential children resulting from donated semen.

GPP

### 14.4 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 (0.0% in the azoospermic group and 7.6% in the nonazoospermia group) in a group of infertile couples requiring donor insemination.<sup>1034</sup> [Evidence level 3] Before the use of frozen-thawed semen, donor insemination with fresh semen resulted in cycle fecundity rates that approached natural conception.<sup>1035–1037</sup> [Evidence level 3]

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.<sup>1038</sup> [Evidence level 3]

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 upon the population studied, and more cycles are needed to achieve conception.<sup>22,1039–1043</sup> [Evidence level 2b–3] Previous success with donor insemination is associated with quicker conception with subsequent donor insemination attempts.<sup>1035,1040</sup> [Evidence level 3]

Before treatment with donor insemination begins, a history should have been taken from the female partner confirming regular menstrual cycles and a mid-luteal phase progesterone assessment should be made 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. Recognition of such a condition 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.<sup>1036,1045,1046</sup> [Evidence level 3]

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.<sup>1036,1046</sup> However, a low incidence of abnormal HSG findings (2.8%) has been reported in asymptomatic ovulatory women with no history of pelvic disease.<sup>1047</sup> This significantly decreased fecundity in the first six cycles of treatment. No corresponding study using laparoscopy has been reported. [Evidence level 3]

#### 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 factors in their history should be offered tubal assessment after three cycles if treatment has been unsuccessful.

GPP

## 14.5 Intrauterine insemination versus intracervical insemination

A systematic review<sup>1048</sup> of 12 RCTs compared IUI with intracervical insemination using fresh and frozen donor sperm. The overall pregnancy rate per cycle was 18% in the IUI group versus 5% in the intracervical 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 woman (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 intracervical insemination when fresh semen was used (OR 0.90, 95% CI 0.36 to 2.24).<sup>1048</sup> [Evidence level 1a] The cost of using IUI has been estimated to be 1.5–2.0 times greater than intracervical insemination,<sup>1049</sup> mostly because of the additional sperm preparation required.

A meta-analysis of seven RCTs (included in the previous systematic review<sup>1048</sup>) found significant higher fecundability rate with IUI compared with intracervical insemination using frozen sperm (OR 2.4; 95% CI 1.5 to 3.8).<sup>1050</sup> [Evidence level 1a]

#### RECOMMENDATION

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

A

## 14.6 Unstimulated versus 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.<sup>743</sup> [Evidence level 3]

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,<sup>1041,1045,1046,1051,1052</sup> [Evidence level 3] 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

## 14.7 Timing of donor insemination

Traditional methods for timing insemination have used basal body temperature charts or cervical mucus assessment. Newer methods involve kits to detect LH in urine. There are four RCTs comparing these two methods of timing insemination.<sup>1053–1056</sup> Two of these trials used intracervical insemination while the other two were presumed to use insemination but did not clearly say so. Meta-analysis of these trials<sup>1057</sup> showed no benefit of using the LH kits in terms of pregnancy rates per cycle (OR 0.98 95%CI 0.64 to 1.48), although one study<sup>1056</sup> found a significant reduction in number of patient visits per insemination cycle. [Evidence level 1a] Another study<sup>1054</sup> 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 1b] These findings could represent cost and organisational benefits from using LH detection in some circumstances. For stimulated IUI, insemination between cycle day 13 and day 16 was shown to be significantly associated with a higher clinical pregnancy rate when compared with insemination after cycle day 13 (27.3% versus 14.5%).<sup>1038</sup> [Evidence level 3]

### RECOMMENDATIONS

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

C

## 14.8 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.<sup>1058</sup> Data from Sheffield covering 980 treatment cycles over four years from 1992 to 1996 gave a live birth rate per cycle of 11.6% for the 768 unstimulated cycles.<sup>1059</sup> 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.<sup>1038</sup> [Evidence level 3]

A retrospective study compared perinatal and obstetric outcomes of donor insemination pregnancies using cryopreserved semen (n = 1552) with normally conceived pregnancies (n = 7717) and found no significant differences in the incidence of preterm birth, low birthweight, multiple birth, perinatal death and birth defects or in the sex ratio between the two groups. However, pregnancies conceived by donor insemination were significantly more likely than controls to have an induced labour (OR 1.6, 95% CI 1.4 to 1.8), a forceps delivery (OR 1.5; 95% CI 1.3 to 1.8), and/or a caesarean section (OR 1.6; 95%CI 1.4 to 1.9), and to develop pre-eclampsia (OR 1.4; 95%CI 1.2 to 1.8) after adjusting for maternal age, multiple birth, parity and presentation.<sup>1060</sup> [Evidence level 3]

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.<sup>1089</sup> 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 unsuccessful cycles of donor insemination.

**GPP**

# 15. Oocyte donation

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## 15.1 Indications

### Premature ovarian failure

The major indication for use of donor oocytes is premature ovarian failure, either primary or secondary. Causes of premature ovarian failure that 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.

Donor oocyte IVF success rates were reported to be similar in women with or without primary ovarian failure, despite recognisable differences in recipient age and degree of male factor infertility.<sup>1061</sup> [Evidence level 2b]

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.<sup>1062</sup> [Evidence level 4] Egg donation is the most successful technique for producing pregnancy in perimenopausal women.<sup>1063</sup> [Evidence level 4] Early menopause due to the exhaustion of the ovarian follicles occurs in approximately 1% of women before the age of 40 years and, when there is little remaining follicular capacity, ovum donation may represent the best chance of a successful pregnancy.<sup>1064</sup> [Evidence level 3] While oocyte donation for women with premature menopause has become widely accepted within the UK, 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

Spontaneous pregnancies among women with Turner syndrome are associated with a high risk of miscarriage and an increased risk of trisomy 21 in the offspring.<sup>1149,1065,1066</sup> [Evidence level 3] Oocyte donation offers women with ovarian failure due to Turner syndrome the chance of pregnancy and live birth. Pretreatment screening is essential to exclude phenotypic manifestations of the syndrome that might jeopardise successful pregnancy, including aortic dilation and cardiac lesions.<sup>1067</sup> An observational study (n = 29) assessing the factors influencing outcomes of oocyte donation in women with Turner syndrome reported a pregnancy rate of 41.2% per treatment cycle (n = 68 cycles; 50 fresh cycles and 18 frozen cycles) of embryo or zygote transfer (27 embryo transfer and 41 GIFT) The implantation rate was 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% versus 9.99%; 51.3% versus 27.6%). An endometrial thickness of  $\geq 6.5$  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% versus 8.2%; 48% versus 22.2%) but the route of transfer was of no statistical importance.<sup>1068</sup> [Evidence level 3]. Pregnancy rates in women with Turner syndrome following oocyte donation were similar to those in women with other causes of primary ovarian failure.<sup>1069</sup> [Evidence level 3]. Another observational study (n = 18) reported a clinical pregnancy rate of 46% for fresh embryo transfer and implantation rate of 30% among women with Turner syndrome treated in an oocyte donation programme. This was similar to the corresponding rates among oocyte recipients with primary ovarian failure in general. However, the miscarriage rate

was high, at 40%, and so was the risk of cardiovascular and other complications such as hypertension and pre-eclampsia. This suggested that a careful assessment before and during follow-up of pregnancy and transfer of one embryo at a time to avoid additional complications caused by multiple pregnancy are important considerations.<sup>1070</sup> [Evidence level 3]

One cohort study (n = 53) reported that women with Turner syndrome had a significantly higher rate of biochemical pregnancies (22.7% versus 4.3%), a lower clinical pregnancy rate (22.7% versus 33.3%), a significantly higher rate of early abortions (60% versus 8.7%) and a significantly lower rate of deliveries per pregnancy (20.0% versus 73.1%) compared women without Turner syndrome following oocyte donation, suggesting that those with Turner syndrome may have an inherent endometrial abnormality affecting receptivity in oocyte donation.<sup>1071</sup> [Evidence level 2b]

### 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.<sup>1072</sup> Success following oocyte donation has been reported in women who had previously received chemotherapy or radiotherapy. Two cases of normal live births with embryos from donated oocytes have been reported in women (aged 36 years and 33 years) who have been treated with bone marrow transplantation following total body irradiation and cyclophosphamide for leukaemia.<sup>1073,1074</sup> [Evidence level 3] A successful live birth was achieved with oocyte donation in one woman following radical surgery (with uterine conservation) and chemotherapy for ovarian cancer.<sup>1075</sup> [Evidence level 3]

### 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.

An observational study (n = 32 couples, 119 cycles) reported a pregnancy rate of 24.5% per cycle following oocyte donation in women with previously failed IVF treatment. 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.<sup>1076</sup> [Evidence level 3] Pregnancy rates of 33.3% per started cycle and 38.4% per embryo transfer were reported in another study (n = 15 couples, 15 cycles) in women following oocyte donation by ICSI in women with previous failed IVF.<sup>1077</sup> [Evidence level 3]

### Genetic disorders

Heritable genetic diseases can be avoided with the use of donor oocytes. A case series study 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.<sup>1078</sup> [Evidence level 3]

## 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 in vitro fertilisation treatment failure.

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

C

## 15.2 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%.<sup>1079</sup> [Evidence level 3]

Younger donors were reported to provide a significant higher pregnancy success rates for recipients (59.1%, 45.9%, 30.5%, 30.9% and 27.3% for the age groups 20–22 years, 26–28 years, 32–34 years and over 38 years, respectively), suggesting that age should be a major factor in selecting prospective donors.<sup>1080</sup> [Evidence level 3]. Limiting oocyte donors to women under 35 years of age<sup>218,1031,1081,1082</sup> and under 34 years old<sup>1083</sup> to decrease the risk of aneuploid offspring has been suggested. [Evidence level 3–4]

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<sup>1084</sup> 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.

Given the high prevalence of cystic fibrosis, which is the most common autosomal recessive disorder in northern Europeans, the HFEA<sup>218</sup> recommends screening both egg and sperm donors for carrier status in cystic fibrosis and Tay–Sachs, and also screening for cytomegalovirus and HIV (see Section 14.3). All licensed clinics are now required to inform couples 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. Regarding screening for other infectious diseases, the HFEA recommends that the guidelines of the British Fertility Society for egg and embryo donors should be followed.<sup>1082</sup> [Evidence level 4]

### 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

## 15.3 Oocyte donation and egg sharing

### Oocyte donation

Shared oocyte donation can be an efficient use of precious resource of human oocytes. In a retrospective analysis of a programme using shared anonymous oocyte donation (n = 249 donor cycles, 241 retrievals), the efficacy of shared oocyte donation between two phenotypically matched recipients has been shown to provide a high delivery rates per donor retrieval (95.4%).<sup>1086</sup> [Evidence level 3] However, the number of treatment cycles undertaken in the UK 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 downregulation, 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,<sup>1087</sup> only 50% of women wishing to

participate in oocyte donation were considered suitable candidates; 50% 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. [Evidence level 3]

Concerns about complications and logistic factors such as travel and time commitment involved were major reasons for non-donation in a survey of women on anonymous oocyte donation.<sup>1088</sup> [Evidence level 3] A survey of UK licensed centres reported that nearly all have experienced difficulty in obtaining a sufficient supply of donated oocytes. Seventy-five percent of potential donors changed their mind about donating after receiving information on the procedures involved. There is also a shortage of both oocyte and semen donors from specific ethnic groups.<sup>1089</sup> [Evidence level 3]

For many volunteer donors, guaranteeing anonymous oocyte donation plays a crucial role in their decision to donate.<sup>1090</sup> In the UK, nonidentifying 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 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.<sup>1091</sup> [Evidence level 3]

A survey of a sample of couples in Canada 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.<sup>1092</sup> [Evidence level 3]

In a follow-up study of the first 30 Finnish volunteer oocyte donors, most donors were very satisfied with the experience at 12–18 months after donation. The adverse 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 whether pregnancy had been achieved in the recipient (67%). A majority thought the offspring should be told about their 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 50% of the others would agree to the release of nonidentifying information. All donations had been carried out anonymously and without payment and no one regretted their donation.<sup>1093</sup> [Evidence level 3]

The attitudes of anonymous couples undergoing IVF toward sperm and oocyte donation were explored in a UK survey (n = 234). 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, 25% of the couples would prefer a relative or friend as the recipient. Provision of nonidentifying information about the donor to the recipient couple was acceptable to almost 70%, whereas 40% found giving the same information to the child acceptable.<sup>1094</sup> Another UK survey (n = 399) compared the attitudes towards egg and sperm donation in four groups of subjects: women receiving egg donation, women 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.<sup>1095</sup> [Evidence level 3]

A follow-up study (n = 23) of donor satisfaction in the USA found a high satisfaction rate with the experience (91%) 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.<sup>1096</sup> [Evidence level 3] A survey in the USA (n = 25) assessed the psychological characteristics and post-donation satisfaction of anonymous oocyte donors. Following oocyte donation, 80% of women stated that they would be willing to donate again. Post-donation satisfaction was high. Although monetary compensation for donation was

provided, altruism was reported as the most salient motivating factor. A significant negative correlation was found between pre-donation financial motivation and post-donation satisfaction and between pre-donation ambivalence and post-donation satisfaction, suggesting that careful screening and counselling of donors with high levels of pre-donation financial motivation or ambivalence might be prudent.<sup>1097</sup> The increasing demand for young and healthy donors and the recent escalation of payment to oocyte donors in the USA have raised concerns in the attitudes of young donors who may not be able to adequately weigh the risks of ovarian hyperstimulation and oocyte retrieval against the benefit of large monetary reward.<sup>1098</sup> [Evidence level 3]

A review of the methodological adequacy of the psychosocial literature on information access when donated gametes and embryos are used identified ten major flaws which may preclude any conclusion either way about the wisdom of promoting information disclosure and access to all parties concerned.<sup>1099</sup> [Evidence level 3]

Generally, oocyte donation is acceptable with oocyte donors having a high satisfaction rate. Counselling from someone who is independent of the treatment unit could contribute to this, as well as to the understanding of the potential risks and complications associated with this process.

Some 2000 children are born each year in the UK as a result of the use of donated gametes. Recent debates have focused on the issues surrounding privacy and disclosure among donor gamete recipients.<sup>1100</sup> In 2002, the Department of Health held a public consultation on the amount of information that should be given to donor offspring and parents of those who donated gametes. The HFEA recommended that there should be a move toward the removal of donor anonymity and that stronger guidelines should be developed on the counselling needs of those considering treatment with donor gametes and donor offspring seeking information on donors. A two-track system that allows some donors to be identified and others to preserve their anonymity should be rejected.<sup>743</sup> [Evidence level 4]

### Egg sharing

A 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 (n = 55, 25 donors and 30 recipients, 73 fresh and frozen cycles) 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. Although the recipients were older than the donors (41.4 ± 0.9 years versus 31.6 ± 0.5 years), there were no differences in the number of eggs allocated, fertilisation rates or the mean number of embryos transferred. There were more births per woman among recipients than among donors (30% versus 20%), although the groups were too small to determine if this was statistically significant or not. This suggested that providing the donors are selected carefully, the egg-sharing scheme whereby a subfertile donor helps a subfertile recipient is a constructive way of solving the problem of shortage of eggs for donation.<sup>1101</sup> A cohort study which compared 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.<sup>1102</sup> Careful patient selection and counselling from someone who is independent of the treatment unit for both the donors and recipients and their partners is clearly essential. [Evidence level 3]

A survey of attitudes of egg donors and recipients in the UK (n = 217) found that: donating or sharing eggs is a social issue, with 94% of respondents having discussed it with partners, family or 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.<sup>1103</sup> [Evidence level 3]

Egg sharing is a new area of practice that has developed in response to a shortage of donor gametes. As yet, there has been little research to evaluate the effectiveness of counselling in relation to oocyte donation and egg sharing, and research to evaluate the effectiveness of counselling in terms of long-term psychological and social implications of these practices is needed.

**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 counselling from someone who is independent of the treatment unit regarding the physical and psychological implications of treatment for themselves and their genetic children, including any potential children resulting from donated oocytes.

**GPP**

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

**GPP****RESEARCH RECOMMENDATION**

Research is needed to evaluate the effectiveness of counselling in relation to oocyte donation and egg sharing in terms of the long-term psychological and social implications of these practices.

# 16. Applications of cryopreservation in cancer treatment

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Oncologists should be aware of conditions for which treatment is available and facilities for cryopreservation of gametes and/or embryos. A working party of the Royal College of Physicians and the Royal College of Radiologists<sup>1104</sup> has recommended procedures to be followed before commencing chemotherapy or radiotherapy likely to affect fertility and the management of post-treatment infertility. A strategy for developing policy and practice in fertility preservation for survivors of cancer has recently been proposed by the British Fertility Society.<sup>1105</sup> [Evidence level 4]

## 16.1 Semen cryostorage

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 those 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 people has become a realistic option to preserve fertility, regardless of diagnosis and treatment.<sup>1105</sup>

Semen quality is adversely affected by the presence of cancer<sup>1106</sup> 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.<sup>1107,1108</sup> For men, elective sperm cryopreservation and banking at cancer diagnosis before the initiation of specific medical treatment and regardless of semen quality should be encouraged<sup>1109-1112</sup> and offered<sup>1105</sup> as an essential part of any comprehensive cancer care programme.<sup>1113,1114</sup> Some people may later decide that the specimens are not needed.<sup>1112</sup> Successful outcomes with IUI and IVF following successful treatment for malignancy have been reported in one retrospective review.<sup>1115</sup> Cryopreserved semen from cancer patients before chemotherapy, although generally of poor quality, are sufficient for success with IVF or ICSI, irrespective of the duration of storage.<sup>1110,1115-1118</sup> [Evidence level 3] An abstinence period of 24 to 48 hours can be recommended for sperm banking in cancer patients,<sup>1119</sup> although in practice any samples available in the short period before cancer treatment begins are acceptable.

The possibilities for successful reproductive outcomes by means of sperm cryopreservation are encouraging for cancer patients whose complete loss of fertility could otherwise occur. As recommended by the report of a Working Party of the Joint Council for Clinical Oncology, 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 or radiotherapy, of the procedures likely to affect fertility and of the management of post-treatment infertility.<sup>1104</sup> [Evidence level 4]

The particular issues facing adolescent boys who may also be capable of producing mature sperm and therefore benefiting from semen storage should be known to those treating their

cancer and specialist advice and counselling should be available. A strategy for fertility services for survivors of childhood cancer has recently been developed, which highlights the concerns relating to consent to treatment and the need to consider the extent to which children are able and/or wish to participate in decision making.<sup>1120</sup> [Evidence level 3–4]

## 16.2 Cryostorage of embryos, oocytes and ovarian tissue

Cryopreservation of embryos formed before anticancer treatment is undertaken is possible. A retrospective record review (n = 69) found that chemotherapy diminished the response to ovulation induction in assisted reproductive technologies. IVF with cryopreservation of embryos allows embryo banking before chemotherapy for women newly diagnosed with cancer. Delivery rates after the women had undergone chemotherapy tended to be lower among the systemic treatment group than it was for the local cancer treatment group (13% versus 40%).<sup>1150</sup> [Evidence level 3]

Another possible treatment, available after anticancer treatment has been concluded, is IVF using donated oocytes (see Section 15.3).

Anticancer treatment can cause ovarian failure; however, cryopreservation of oocytes has had very limited success.<sup>1105,1121,1151</sup> [Evidence level 3–4] Live births following ICSI for fertilisation of in vitro cryopreserved oocytes has been reported in women with<sup>1121</sup> and without cancer.<sup>1122,1123</sup> [Evidence level 3]

Cryopreservation of ovarian cortex before cancer treatment may be a valuable fertility conservation option<sup>1124</sup> but its clinical practicality followed by ovarian transplantation needs further development and evaluation, as there has been no pregnancy in humans with this technique.<sup>1105,1121,1125</sup> [Evidence level 3–4]

The handling and storage of tissues containing immature gametes (that is, ovarian cortex and immature testicular tissue) is outside the remit of the HFEA and is regulated by the Department of Health.<sup>218</sup>

### Counselling

Counselling from someone who is independent of the treatment unit and information giving are an integral part of the management which will require a multidisciplinary input.<sup>1105</sup> Local protocols between all health professionals involved are essential. However, many technical, legal and ethical considerations remain. For example, where cryopreservation is offered to young people who are preparing for medical treatment that is likely to make them infertile, secure long-term storage facilities may be needed.

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

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 sensitively and effectively.

C

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

C

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

D

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

GPP

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

GPP

# 17. Follow-up of children born as a result of assisted reproduction

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## 17.1 Genetic risks and congenital malformations

The ability of assisted reproduction to circumvent natural barriers to conception has led to concerns about the safety of IVF and ICSI, including their potential to transmit genetic aberrations to the next generation and the long-term consequences on later development of children born as a result of these procedures. Overall, more than one million children in the world have been conceived through IVF since 1978.<sup>603</sup> In England and Wales, about 23,000 women were treated and about 8000 babies were born as a result of IVF and/or ICSI in 2000–2001 (about 2500 of these babies were born as a result of ICSI).<sup>743</sup> This accounts for about 1.3% of all live births.<sup>1126</sup> [Evidence level 3]

To date, there have been no adequate prospective RCTs of sufficient power to assess the efficacy and safety of the various forms of assisted reproduction. Long-term follow-up studies are needed to investigate the safety implications for children born as a result of assisted reproduction.<sup>1127</sup> Thus far, follow-up studies have been hampered by the type of surveillance protocol, attrition rate, sample size and lack of standardisation in defining major anomalies. It is also important to recognise that any increased risk may be due to parental factors associated with infertility, which may have led to the use of IVF or ICSI in the first place.<sup>1128</sup> [Evidence level 3]

A systematic review<sup>1133</sup> 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 subfertility to male offspring).<sup>1133</sup> Of the 30 studies included in the review, 13 were rated as acceptable quality cohort studies with well-defined control groups and 17 were cohort or case studies of weaker design. The outcome most reported was congenital malformations. Overall, no increased risk of major birth defects, including chromosomal abnormalities, was found in offspring resulting from treatment of severe male infertility with ICSI compared with offspring conceived by standard IVF treatment or naturally (OR 1.13, 95% CI 1.00 to 1.29,  $p = 0.06$ ; test for heterogeneity  $p = 0.35$ , based on seven cohort studies and two reports). The available data did not indicate an increased risk of any particular malformation, as separate meta-analyses on specific categories of malformations did not show any increased risk after ICSI.<sup>1133</sup> [Evidence level 2b–3]

In contrast, a prospective multicentred cohort study carried out in Germany (not included in the systematic review) compared ICSI infants ( $n = 3372$ ) with normally conceived infants ( $n = 30,940$ ) and found major malformation in 8.6% of ICSI children versus 6.9% of normally conceived children (crude RR 1.25, 95% CI 1.11 to 1.40).<sup>1128</sup> [Evidence level 3]

Whether ICSI treatment of infertile couples with normal karyotypes increases the occurrence of chromosomal abnormalities in offspring is unclear. Sons of infertile males with Y chromosome microdeletions will probably inherit the same abnormality and are therefore likely to be infertile. Males with no known genetic cause for severely compromised sperm quality may also father sons with Y chromosome microdeletions.

A review of seven studies reporting fetal karyotypes analysis (n = 2139) showed that, in comparison with a general neonatal population, there was a slight but significant increase in de novo sex chromosomal aneuploidy (0.6% versus 0.2%) and structural autosomal abnormalities (0.4% versus 0.07%); there was also an increase in the number of inherited structural aberrations (most of which were inherited from infertile fathers).<sup>1129</sup> [Evidence level 2b–3]

Attention has focused on reports of imprinting disorders. Several observational studies have reported the occurrence of imprinting defects such as Beckwith–Wiedemann syndrome<sup>1130,1131</sup> and Angelman syndrome,<sup>1132</sup> in children born after assisted reproduction. The reports on Beckwith–Wiedemann syndrome suggest a six-fold increase in risk against a background prevalence of around 1.3 per 100,000 newborn infants.<sup>1130,1131</sup> [Evidence level 3] Further studies are needed to understand the disorders and evaluate their association with assisted reproduction.

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, increases the risk of birth and other developmental defects.<sup>1133</sup> [Evidence level 2b–3] There is a need for further research on the clinical outcomes of ICSI IVF pregnancies.

## 17.2 Cancer

A cohort study found that cancer incidence at the age of five 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 UK (2.0 cases observed versus 3.5 cases expected, standardised incidence ratio 57, 95% CI 7 to 206). The mean follow-up time was 8.6 years.<sup>1134</sup> [Evidence level 2b] 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.

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 (4.0 cases observed versus 3.6 cases expected). However, this study had limited power to compare cancer incidence.<sup>1135</sup> [Evidence level 3]

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 (6.0 cases observed versus 4.33 cases expected, standardised incidence ratio 1.39, 95% CI 0.62 to 3.09). The medium follow-up time was three years and nine months.<sup>1136</sup> [Evidence level 3]

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 (16.0 cases observed versus 15.5 cases expected, 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 six years.<sup>1137</sup> [Evidence level 2b]

A report on childhood cancer from the Netherlands suggested an increased risk of childhood retinoblastoma.<sup>1138</sup> [Evidence level 3] This study reported a relative risk in the range 4.9 to 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 one to four years.

## 17.3 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. Infants conceived by IVF were within the normal ranges of these indices and did not differ from their matched controls.<sup>1139</sup> [Evidence level 3]

A cohort study found no significant differences at three years in psychomotor development of children conceived by IVF compared with children born after ovarian stimulation without IVF and children conceived naturally.<sup>1140</sup> [Evidence level 2b]

Another cohort study compared families with children conceived through assisted reproduction (including IVF treatment and donor insemination) with families with naturally conceived children.<sup>1141</sup> [Evidence level 2b] This study found that the quality of parenting in families with children conceived through assisted reproduction 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 children conceived by IVF over the age of four 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 children conceived by IVF or compared with the control group.<sup>1142</sup> [Evidence level 3]

### RECOMMENDATION

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

A light blue square box containing the letter 'C' in a dark blue font, indicating the evidence level for the recommendation.

### RESEARCH RECOMMENDATION

Long-term longitudinal follow-up of children resulting from assisted reproduction is needed. This research should focus on physical, genetic, psychological and social development, and it should be co-ordinated on a national basis.

# 18. Auditable standards

## 18.1 Measures that could be used as a basis for an audit

One or more audits could be carried out on the investigation and management of fertility problems. In vitro fertilisation treatment is one of several assisted reproduction techniques regulated by the HFEA and all cycles of in vitro fertilisation treatment are registered with the HFEA. Thus, HFEA records would form one potential source of data for monitoring compliance with recommendations relating to in vitro fertilisation treatment (see Table 18.1).

Outcomes of treatment (for example, the proportion of cycles of in vitro fertilisation treatment that result in a live birth) as well as offers of treatment could also be used for audit purposes.

**Table 18.1** Suggested audit criteria

Criterion	Exception	Definition of terms
Percentage of women with documented offer of screening for <i>Chlamydia trachomatis</i> before undergoing uterine instrumentation	Women currently being treated for <i>C. trachomatis</i>	Screening for <i>C. trachomatis</i> using an appropriately sensitive technique
Percentage of women with pelvic inflammatory disease, previous ectopic pregnancy or endometriosis with documented offer of hysterosalpingography (HSG)	Women without pelvic inflammatory disease, previous ectopic pregnancy or endometriosis	
Percentage of couples with mild male factor fertility problems, unexplained fertility problems or minimal to mild endometriosis with documented offer of up to six cycles of intrauterine insemination	Couples with severe male factor fertility problems or moderate to severe endometriosis	
Number of couples in which the woman is aged 23–39 years at the time of treatment who have an identified cause for their fertility problems or who have infertility of at least three years' duration and who have a documented offer of up to three cycles of in vitro fertilisation treatment	Women aged younger than 23 years or older than 39 years at the time of treatment	Identified causes for fertility problems include azoospermia and bilateral tubal occlusion
Number of embryos transferred during any one treatment cycle in women undergoing in vitro fertilisation treatment registered by the Human Fertilisation and Embryology Authority	Women not undergoing in vitro fertilisation treatment	

# Appendix A

## Assessment and treatment for people with fertility problems. Understanding NICE guidance: information for people with fertility problems, their partner and the public

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### About this information

This information describes the guidance that the National Institute for Clinical Excellence (called NICE for short) has issued to the NHS on assessing and treating people with fertility problems. It is based on *Fertility: assessment and treatment for people with fertility problems*, which is a clinical guideline produced by NICE for doctors, nurses, counsellors and others working in the NHS in England and Wales. Although the information in this booklet has been written chiefly for people with fertility problems, it may also be useful for their partners and anyone with an interest in fertility or in healthcare in general.

An 'Explanation of medical terms' appears at the back of this booklet. Terms that appear are highlighted in **bold**.

### Clinical guidelines

Clinical guidelines are recommendations for good practice. The recommendations in NICE guidelines are prepared by groups of health professionals, lay representatives with personal experience or knowledge of the condition being discussed, and scientists. The groups look at the evidence available on the best way of treating or managing a condition and make recommendations based on this evidence.

There is more information about NICE and the way that the NICE guidelines are developed on the NICE website ([www.nice.org.uk](http://www.nice.org.uk)). You can download the booklet *The Guideline Development Process – Information for the Public and the NHS* from the website, or you can order a copy by phoning 0870 1555 455 and quoting reference number N0038.

### What the recommendations cover

NICE clinical guidelines can look at different areas of diagnosis, treatment, care, self-help or a combination of these. The areas that a guideline covers depend on the topic. They are laid out at the start of the development of the guideline in a document called the scope.

The recommendations in *Fertility: assessment and treatment for people with fertility problems*, which are also described here, cover:

- the best forms of treatment for people who have problems getting pregnant
- ways of treating people who have a known condition or reason for their fertility problems
- ways of treating people when no reason for their fertility problems can be found.

The recommendations here do not tell you about:

- how fertility problems can be prevented in the first place
- how a pregnancy is managed following fertility treatment
- investigation and treatment of underlying conditions which may reduce fertility, such as endometriosis or sexual dysfunction, other than in relation to treatment for fertility problems
- the use of pre-implantation genetic diagnosis, in which cells from an embryo are tested for inherited disorders before being transferred to the woman's womb.

The information that follows tells you about the NICE guideline on fertility. It doesn't attempt to explain fertility or describe the treatments for it in detail. If you want to find out more about fertility, NHS Direct may be a good starting point (phone: 0845 46 47 if you are in England or Wales). Website: [www.nhsdirect.nhs.uk](http://www.nhsdirect.nhs.uk).

### How guidelines are used in the NHS

In general, health professionals working in the NHS are expected to follow NICE's clinical guidelines. But there will be times when the recommendations won't be suitable for someone because of a specific medical condition, their general health, their wishes or a combination of these. If you think that the treatment or care you receive does not match the treatment or care described in the pages that follow, you should discuss your concerns with your doctor or nurse.

### If you want to read the other versions of this guideline

There are three versions of this guideline:

- this one
- the NICE guideline *Fertility: assessment and treatment for people with fertility problems*, which has been issued to people working in the NHS
- the full guideline, which contains all the details of the guideline recommendations, how they were developed and information about the evidence on which they are based.

All versions of the guideline are available from the NICE website ([www.nice.org.uk](http://www.nice.org.uk)). This version and the NICE guideline are also available from the NHS Response Line – phone 0870 1555 455 and quote reference N0466 for this version, and N0465 for the NICE guideline.

## About fertility problems

**Fertility problems** affect one in seven couples in the UK. Most couples (about 84 out of every 100) who have regular sexual intercourse (that is, every 2 to 3 days) and who do not use contraception will get pregnant within a year. About 92 out of 100 couples who are trying to get pregnant do so within 2 years.

Women become less fertile as they get older. For women aged 35, about 94 out of every 100 who have regular unprotected sexual intercourse will get pregnant after 3 years of trying. For women aged 38, however, only 77 out of every 100 will do so. The effect of age upon men's fertility is less clear.

If you have not been able to get pregnant after 2 years of regular unprotected sexual intercourse either one, or both, of you may have a fertility problem.

In men, a fertility problem is usually because of low numbers or poor quality of **sperm**. A woman may have fertility problems because she does not produce **eggs** regularly or because her **fallopian tubes** are damaged or blocked and the sperm cannot reach her eggs.

For nearly one third of people, no reason can be found for their problem. This is known by healthcare professionals as having **unexplained fertility problems**.

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## Guideline recommendations

The following information is written for people looking for advice and treatment for possible fertility problems. It tells you what you can expect as a couple at each stage of assessment, investigation and treatment for fertility problems and about the tests and treatments you may be offered.

The use of the word 'you' in the following information may refer to men or women or a man and a woman together as a couple, as appropriate.

### Trying for a baby

There may be some things you can do to improve your chances of getting pregnant. Your doctor should tell you more about the following points.

#### *How often to have sexual intercourse*

To give yourselves the best chance of success, you need to have sexual intercourse every 2 to 3 days throughout the month. You do not need to time it to coincide with the days when the woman is **ovulating** (that is, when her **ovaries** are producing **eggs**).

If you are under psychological stress, it can affect your relationship and is likely to reduce your sex drive. So if, as a result, you do not make love as often as usual, this may also affect your chances of getting pregnant.

#### *Alcohol*

If you are a woman trying to get pregnant you can cut down the risk of harming a developing baby by not drinking to excess and drinking no more than 1 or 2 units of alcohol once or twice a week. A unit of alcohol is about the same as a small glass (125 ml) of wine or a half-pint of beer or lager.

If you are a man, your fertility is unlikely to be affected if you drink no more than 3 or 4 units of alcohol a day. Drinking excessive amounts of alcohol can affect the quality of a man's sperm.

#### *Smoking*

Smoking may reduce fertility in women. Breathing in someone else's cigarette smoke (known as passive smoking) may also affect a woman's chances of getting pregnant.

For men, there is a link between smoking and poorer quality of sperm, although the effect that this has on a man's fertility is not certain. Stopping smoking will improve your general health.

If you smoke, your doctor should offer you help to stop if you wish. The NHS Smoking Helpline can also provide advice and support – the phone number is 0800 169 0 169 or the website is [www.givingupsmoking.co.uk](http://www.givingupsmoking.co.uk).

#### *Caffeine*

Caffeine is a stimulant that is found in drinks such as tea, coffee and cola. There has been little research into the effect of caffeine on fertility and there is no clear evidence of a link between caffeine and fertility problems.

#### *Body weight*

The range of healthy weight is defined by a measurement known as the **body mass index** (BMI). Your BMI is calculated by dividing your weight in kilograms by your height in metres squared (that is, your height in metres multiplied by itself). A healthy weight is one that gives a BMI of between 20 and 25.

Women who have a BMI of more than 29 can take longer to conceive than women whose weight is in the normal range.

If you are overweight (you have a BMI of more than 29) and you have irregular periods, or no periods at all, losing weight may increase your chances of getting pregnant. If your weight gets down to the normal range, your ovaries may start working again.

Evidence shows that women who take part in group exercise and diet programmes have a better chance of getting pregnant than those who try to lose weight on their own.

If you are underweight (you have a BMI under 19) and you have irregular periods, or no periods at all, you may find that if your weight gets back up to the normal range your ovaries will start working again and so improve your chances of getting pregnant.

If you are a man and you are overweight (you have a BMI of more than 29), your fertility is likely to be lower than normal.

### *Tight underwear for men*

Some studies have suggested that wearing tight-fitting underwear could reduce the quality of a man's sperm, because it raises the temperature in the testicles. On balance, however, it is not clear whether wearing loose-fitting underwear improves a man's fertility.

### *Your work*

Certain types of work conditions expose people to things (such as X-rays and pesticides) that can affect their fertility. Your doctor should ask you about the work that you do, and should advise you about any possible risks to your fertility.

### *Medicines and drugs*

A number of prescribed and over-the-counter medicines can interfere with your fertility. Your doctor should therefore ask you both about any medicines you are taking so that they can offer you appropriate advice. They should ask you about medicines that have been prescribed for you and about medicines that you have bought over the counter. They should also ask you about drugs you may have obtained yourself (including recreational drugs, such as cannabis and cocaine, and anabolic steroids).

### *Complementary therapies*

There have not been enough studies looking at complementary therapy treatments for fertility. Further research is therefore needed before any of these treatments can be recommended.

### *Folic acid*

Women who are trying to get pregnant should usually take folic acid tablets (0.4 mg a day). Your doctor should give you more information about this. Taking folic acid when you are trying for a baby and for the first 12 weeks of pregnancy reduces the risk of having a baby with conditions such as spina bifida or anencephaly (these are known as neural tube defects, where parts of the brain or spinal cord do not form properly). If you have previously had a child with a neural tube defect, or you are taking medication for epilepsy, your doctor should recommend that you take a larger dose of 5 mg a day.

### *German measles (rubella)*

Your doctor should offer women a test to find out whether they are immune to German measles (also known as rubella). If you are not immune you should be offered a rubella vaccination before you try to become pregnant, because infection with rubella can harm unborn babies. You should be advised to avoid pregnancy for 1 month following your rubella vaccination.

### *Cervical smear tests*

Your doctor will want to know when you last had a cervical smear test and what the result was. If a cervical smear test is due, you should be offered the test before you try to get pregnant. This is because if any abnormalities in cervical cells are missed early on, it could delay treatment of any fertility problem. It is also more complicated to treat abnormalities of cervical cells if you are pregnant.

### What happens if you have fertility problems?

If you are concerned that you may have a fertility problem, your doctor should first ask you about aspects of your lifestyle, your general health and your medical history that could be affecting your chances of having a baby. This is known as an 'initial assessment'.

If you have been trying to get pregnant for more than 1 year your doctor should offer you tests to check the man's sperm and to check if the woman is ovulating or if her fallopian tubes are blocked (although you should not be offered tests to check whether your fallopian tubes are blocked until the results of semen tests and tests to find out if you are ovulating are known). If either one or both of you has an existing condition or problem that is known to affect fertility (such as a woman has irregular or infrequent periods, previous **pelvic inflammatory disease** or is aged over 35, or a man has had undescended testicles), these tests may be undertaken sooner.

If there is already a known reason for your fertility problems (such as having had treatment for cancer that could have affected your fertility), you should be referred for specialist treatment.

If you are known to have a long term-viral infection (such as hepatitis B, hepatitis C or HIV) and you are concerned about your fertility, you and your doctors will need to think about the implications for any children you might have, before you decide on any fertility treatment. If you do go on to have treatment, you should be referred to a centre that has the facilities and expertise to investigate and treat your problems as safely as possible.

### What you can expect from your care

Any decisions you make on investigation and treatment will affect both you and your partner. You should therefore be seen together as a couple whenever possible.

You have a right to be involved in and make decisions on your care and treatment. To be able to do this, you need to understand what is involved and what your choices are. Your healthcare team should therefore tell you about this and give you information in writing, or in some other form that you can easily access and understand (if you do not speak or read English, for example, or if you have a disability). They should encourage you to ask questions if there is anything you do not understand.

Any investigation of your fertility problems should take place in an environment that enables you to discuss sensitive issues, such as sexual problems, if you wish.

If you are diagnosed with a fertility problem, you should be treated by a specialist team. They should tell you about your diagnosis in a sensitive and tactful manner, and give you information about appropriate support groups which you can contact if you wish.

Having fertility problems and going through tests and treatment can in itself be a stressful process. It may put a strain on you individually and as a couple.

### *Counselling*

You should have the opportunity to see a qualified counsellor before, during, and after any treatment you have, regardless of whether the treatment is successful. The counsellor should be someone who is not directly involved in managing your treatment. They should talk over and help you think about what your fertility problems and treatment will mean for you.

### Investigating your fertility problems

The rest of this information tells you more about what you can expect at each stage of having fertility treatment.

When you first talk to your doctor about a suspected fertility problem, they should ask you about how long you have been trying to get pregnant, your current health, previous illness, operations or treatments you have had and aspects of your sexual health and history.

If they think that you may have a fertility problem they should offer you tests to check the quality of the man's sperm and to check if the woman is producing eggs regularly and that her fallopian tubes are not blocked (although you should not be offered tests to check whether your fallopian tubes are blocked until the results of semen tests and tests to find out if you are ovulating are known). Depending on the results, you may need treatment to help you get pregnant.

### *Investigating fertility problems in men*

You should be offered a **semen** test to measure the quantity and quality of your sperm. Men produce about 40 million sperm each time they ejaculate. Sperm need to be capable of moving (known as being **motile**) to reach the **egg** and **fertilise** it. About one in 10 men will have an abnormal result on the first semen test but this does not always mean they have a 'true' abnormality. So if the results of the first semen test are abnormal, the test should be repeated.

Ideally this repeat test should be done 3 months after the first, but if it looks as though your sperm count is very low or you have no sperm at all it should be repeated as soon as possible. Only two men out of 100 will have a second abnormal test. If you have two abnormal tests you should be offered further investigations.

The semen test should not include a test for substances in your sperm known as 'antisperm antibodies'. It is not clear how important these are in affecting fertility and there is no effective treatment available to improve fertility if you have them.

### *Investigating fertility problems in women*

Your doctor should ask you how often and how regular your periods are. If you have regular monthly periods (every 26 to 36 days), you are likely to be **ovulating**. The use of charts of a woman's body temperature taken first thing in the morning (known as basal body temperature) should not be used to check whether you are ovulating normally as they are not a reliable test for this.

### *Checking your hormone levels*

If you have been trying to get pregnant for more than 1 year or if you do not have periods or your periods do not occur often, you should be offered blood tests. These are to measure your hormone levels and find out if you are ovulating, and should include:

- a test to measure a hormone called **progesterone**, which is produced by the **ovaries** after the **egg** is released. (If you have regular monthly periods this test is taken about 21 days, or 3 weeks, after the first day of your last period).
- a test to measure hormones called **gonadotrophins**, which stimulate the ovaries to produce eggs (there are two types: **follicle-stimulating hormone** [FSH] and **luteinising hormone** [LH]).

If tests show you have high levels of gonadotrophins this may mean your fertility is lower than normal.

The value of other tests of **ovarian reserve** (how many eggs you have left, which predicts how close to the menopause you are), such as measuring a substance called inhibin B, is uncertain and should therefore not be offered to you.

You should not routinely be offered blood tests to measure other hormones. You should only be offered a thyroid test if you show symptoms of thyroid disease, as you are no more likely than any other woman to have thyroid problems. You should only be offered a blood test to measure **prolactin** if you are not ovulating regularly or you have **galactorrhoea** (a condition where the woman produces breast milk not related to a recent pregnancy) or have a tumour in the **pituitary gland** (a gland at the base of the skull).

### *Checking your fallopian tubes*

If you have been trying to get pregnant for more than 1 year or you have had **pelvic inflammatory disease** or **endometriosis** (a condition where cells like those in the lining of the womb are found in other areas of the pelvis, usually causing pain and damage), you should be offered tests to check whether your **fallopian tubes** are blocked. You should not be offered these until the results of semen tests and tests to find out if you are ovulating are known.

Before you have any procedure to check whether your fallopian tubes are blocked, you should also be offered testing (known as screening) for an infection called **Chlamydia trachomatis** (known as chlamydia). Chlamydia can damage your fallopian tubes if it is not diagnosed and treated with antibiotics. If you are infected, you and your partner (or partners) should be referred for treatment and follow up.

If you have not been screened for chlamydia but you are having a procedure to check whether your fallopian tubes are blocked, you should be offered antibiotics beforehand. This is a precaution to deal with the infection in case you do have it.

If you have had no problems in the past, you may be offered an examination of your fallopian tubes by:

- an X-ray (known as a **hysterosalpingogram** or HSG), using fluid injected through the neck of the womb. An HSG can be done in an outpatient clinic, or
- a special ultrasound scan (known as **hysterosalpingo-contrast-sonography**).

Both procedures work well. Which one you are offered will depend on the centre where you are being treated.

You should be offered an operation called a **laparoscopy** and dye test to check your pelvic area and your fallopian tubes if you have, or have had, any of the following:

- pelvic inflammatory disease
- endometriosis
- an ectopic pregnancy (where the embryo develops outside the womb, usually in the fallopian tubes).

The laparoscopy is an operation and should be done under a general anaesthetic. The doctor looks at the womb and fallopian tubes through a very small telescopic instrument (called a **laparoscope**). Dye is injected through the neck of the womb (called the cervix). Through the laparoscope, the doctor can see whether the dye can get into the fallopian tubes or if there are any blockages.

### *Checking your womb*

Your doctor should only offer you a special examination of your womb (known as a **hysteroscopy**) if there is a good reason. Hysteroscopy is done by putting a small microscope (a hysteroscope) through the cervix and into the womb. Treating problems in this way has not been shown to improve the chances of getting pregnant.

You should not be offered:

- routine tests on your cervical mucus after sexual intercourse (known as a post-coital test) because they do not help to predict your chances of getting pregnant, so are not necessary
- a **biopsy** (a procedure to take a small sample of tissue) of the lining of your womb.

### **Men: treatment for underlying conditions**

Your fertility problems may be caused by a hormone disorder, a blockage in your testicles, a low sperm count (known as **oligozoospermia**), poor sperm quality or because you are unable to ejaculate.

- If you have low levels of gonadotrophin hormones (which stimulate the production of sperm) you should be offered treatment with gonadotrophin drugs to improve your fertility.
- If the flow of sperm from your testicles is blocked you may be offered surgery to remove the blockage, as an alternative to using other methods such as surgical **sperm recovery** (see page 151) or **in vitro fertilisation** (IVF; see page 149).

You should not be offered the following treatments because they are not known to improve fertility:

- surgery for varicose veins in the scrotum (known as varicoceles)
- antibiotic treatment for white cells in your semen
- steroids for antisperm antibodies
- treatment with certain hormones (anti-oestrogens, gonadotrophins, androgens, bromocriptine) or kinin-enhancing drugs, if you have an abnormal sperm count for which no cause has been found.

### *If you are unable to ejaculate*

If you are unable to ejaculate, there may be treatments which will restore your ability to do so and improve your fertility. Alternatively, you may be offered surgical **sperm recovery** (see page 151) or **assisted reproduction** procedures (see page 148).

If your sperm count is found to be abnormal you should be offered appropriate treatment. If your sperm count is:

- mildly abnormal – you and your partner should be offered up to six cycles of **intrauterine insemination** (IUI) (see page 148 for more information).
- moderately abnormal – you may be offered IVF (see page [40] for more information).
- severely abnormal – you may be offered **intracytoplasmic sperm injection** (ICSI) to inject your sperm directly into your partner's eggs. This may improve your chances of having a baby. (See page 152 for more information.)

### **Women: treatment for underlying conditions**

Your fertility problems may be because you are not **ovulating** normally or because there is a blockage in your **fallopian tubes**.

### *If you are not ovulating normally*

In a natural cycle a woman should produce one **egg**. If you are not producing eggs normally you should be offered treatment to stimulate your **ovaries** to produce eggs (this is known as **ovulation induction**). The type of treatment you receive will depend on what is causing the problem.

### *Polycystic ovary syndrome (PCOS)*

**Polycystic ovary syndrome** (PCOS) is a condition where your ovaries produce more small **follicles** (the sacs in which eggs develop) than normal but you do not ovulate regularly. If you have PCOS the first treatment you should be offered is drug treatment with either **clomifene citrate** or **tamoxifen**. If you ovulate in response to this treatment, you can take this for up to a maximum of 12 months. There is an increased risk of having twins, triplets and quadruplets with this treatment (known as **multiple pregnancy**). Therefore, if you are treated with clomifene citrate or tamoxifen, your healthcare team should offer you an **ultrasound** scan to monitor your response in at least your first cycle of treatment. This cuts down the risk of having more than one baby at a time.

If you ovulate with clomifene citrate but you have not become pregnant after 6 months of treatment you should be offered continued treatment with clomifene citrate but also have **intra-uterine insemination** (IUI, see page 148).

Clomifene citrate and tamoxifen do not work for everyone. If you have PCOS, and you have not ovulated on clomifene citrate or tamoxifen alone and you are overweight (that is, you have a **body mass index** [BMI] of more than 25), you may be offered treatment with clomifene citrate and another drug called metformin. Treatment with both of these drugs together increases the chance of ovulation and pregnancy. By following these recommendations, doctors would be using metformin in a way that is not covered by its licence. NICE has reminded doctors that they should explain this to you and seek your consent to taking the drug. You should also be made aware that metformin can have side effects (such as nausea and vomiting).

Alternatively, if you have not ovulated on clomifene citrate, you should be offered an operation called '**laparoscopic ovarian drilling**'.

Laparoscopic ovarian drilling works just as well as some other treatments such as gonadotrophin hormone treatment, but it does not increase the risk of having more than one baby at a time. It does, however, involve a **laparoscopy**, which is a surgical procedure that requires a general anaesthetic. The doctor makes small cuts just below your navel and above your bikini line and looks at your ovaries through a tiny microscope (called a laparoscope). Heat is then applied (a process known as diathermy) to destroy some of the extra follicles.

If you have not ovulated on clomifene or tamoxifen and you have PCOS, you may be offered gonadotrophin hormone treatment. **Gonadotrophins** (follicle-stimulating hormone [FSH] and

luteinising hormone [LH]) occur naturally in our bodies. Gonadotrophin treatments can be made either from human sources or produced artificially from yeast cells in a laboratory. They may contain either FSH alone or both FSH and LH. All the preparations work equally well in increasing your chance of having a baby. Your doctor should therefore prescribe the least expensive preparation. Your response to treatment should be monitored using ultrasound.

Your doctors should tell you more about the risks and side effects of these treatments before you start any of them.

- Clomifene citrate and tamoxifen increase the risk of becoming pregnant with more than one baby. You may also get hot flushes and menopausal symptoms.
- Metformin has side effects, which can include nausea, vomiting and other digestive symptoms.
- Laparoscopic ovarian drilling involves having surgery and a general anaesthetic.
- Gonadotrophins increase the risk of becoming pregnant with more than one baby. Your ovaries may get over-stimulated (**ovarian hyperstimulation syndrome** [OHSS], see page [47]). You will also get symptoms of the menopause, such as hot flushes. Gonadotrophins need to be given by injection.
- There are concerns about a possible link between ovulation induction and ovarian cancer, but the link remains uncertain. Your doctor should use the lowest effective dose and duration for ovulation induction.

#### *Other ovulation disorders*

If you have an ovulation disorder caused by low levels of gonadotrophin hormones and you have low oestrogen, you should be offered **pulsatile gonadotrophin-releasing hormone** or gonadotrophins, as they will help you to ovulate.

If you have a disorder called **hyperprolactinaemia** (a disorder of the **pituitary gland** which can cause irregular periods, production of breast milk and fertility problems) you should be offered treatment with drugs such as bromocriptine. You should be involved in the decision about taking these drugs – this will include discussing with your doctors the safety of bromocriptine (and similar drugs known as dopamine agonists) for women who are intending to get pregnant and the costs of the drugs.

#### *If your fallopian tubes are blocked*

If you have blocked fallopian tubes:

- you should be offered in vitro fertilisation, or
- if you have a mild abnormality and are being treated in a centre with appropriate expertise, you may be offered surgery to correct this. Surgery is more effective than having no treatment at all but more research is needed to assess it in comparison to assisted reproduction procedures such as in vitro fertilisation.

If the blockage in your fallopian tubes is close to your womb you may be offered a procedure called ‘selective salpingography with tubal catheterisation or cannulation’ to clear it and improve your chances of getting pregnant. The doctor should use a tiny microscope called a hysteroscope, and then insert a small tube into the fallopian tubes to clear the blockage.

#### *Endometriosis*

**Endometriosis** is a condition where cells like those in the lining of the womb are found in other areas of the pelvis. Endometriosis can cause pain and damage and it can be mild, moderate or severe.

If you have a laparoscopy that shows you have mild, moderate or severe endometriosis you may be offered an operation (known as surgical ablation or resection) to remove or destroy the endometriosis and improve your chances of getting pregnant.

Following surgical removal of your endometriosis you do not need to have drug treatment because this prevents you ovulating and does not help your fertility.

If you have mild endometriosis you should be offered up to six cycles of intrauterine insemination (IUI, see page 148) to help you get pregnant.

You should not be offered medicine for treatment of mild endometriosis because it does not improve fertility.

### *If your periods have stopped and you have adhesions in your womb*

If you have no periods and tests have shown that tissues in your womb have joined together (known as having adhesions), you may be offered a procedure that involves having a tiny microscope (hysteroscope) inserted into your womb. This enables the surgeon to see and clear the adhesions. It may help your periods to start again, and so improve your chances of getting pregnant.

### **Treatment for unexplained fertility problems**

If your doctors can find no reason for your fertility problems you may be offered one of the following treatments:

- clomifene citrate to stimulate the woman's ovaries to produce eggs
- assisted reproduction through:
  - intrauterine insemination using fallopian sperm perfusion (see below)
  - in vitro fertilisation (IVF, see page 149).

Other methods of assisted reproduction called **gamete intrafallopian transfer** (GIFT) or **zygote intrafallopian transfer** (ZIFT) are not recommended.

### **Assisted reproduction**

**Assisted reproduction** is the name given to treatments that can help you get pregnant without you having sexual intercourse. There are a variety of procedures available and what is suitable for you will depend on your own circumstances. They include:

- intrauterine insemination (IUI)
- in vitro fertilisation (IVF)
- IVF with **intracytoplasmic sperm injection** (ICSI)
- the use of donor sperm (**donor insemination**) or eggs (**egg donation**).

Certain forms of assisted reproduction (IVF, ICSI, donor insemination and egg donation) are regulated by law and their use is controlled by the Human Fertilisation and Embryology Authority (HFEA).

If you are considering any method of assisted reproduction, your healthcare team should give you up-to-date information about the health and welfare of any children you have as a result. Current research is broadly reassuring about the health and welfare of children born as a result of assisted reproduction.

### **Intrauterine insemination (IUI)**

Intrauterine insemination (IUI) is a procedure in which a man's sperm is placed (**inseminated**) in a woman's womb.

You and your partner should be offered up to six cycles of IUI if:

- you have unexplained fertility problems
- the man's sperm count is slightly abnormal.

In these instances, the woman should not be offered drugs for **ovulation induction** (this is known as an unstimulated cycle). Ovulation induction increases your chances of getting pregnant but also increases the risk of having more than one baby at a time and so it is not recommended in these circumstances.

If you have unexplained fertility problems, you should be offered IUI with **fallopian sperm perfusion**. Fallopian sperm perfusion is a technique where the sperm is mixed with a larger volume of fluid. This gives you a better chance of getting pregnant.

You may also be offered up to six cycles of IUI if the woman has minimal to mild endometriosis. In this case, however, it has been proved that using drugs for ovulation induction with IUI will

increase your chances of getting pregnant. When drugs are used with IUI, this is known as a **stimulated cycle**. It is not clear how effective IUI is without ovulation induction for women with minimal to mild endometriosis.

If you have PCOS and ovulate with clomifene citrate but you have not become pregnant after 6 months of treatment, you should be offered continued treatment with IUI and clomifene citrate for a further 6 months.

In all cases, you should only be offered a single **insemination** of sperm per cycle of IUI because double insemination does not improve pregnancy rates.

### **In vitro fertilisation (IVF)**

**In vitro fertilisation** (IVF) is one of the main methods of assisted reproduction. It involves:

- step 1: 'switching off' the woman's natural cycle of egg production in the ovaries (**downregulation**)
- step 2: stimulating the ovaries to produce more than one egg (**ovulation induction**)
- step 3: collecting the mature eggs from a woman's ovaries
- step 4: collecting sperm from the man
- step 5: mixing the eggs and sperm in the laboratory
- step 6: incubating the fertilised eggs for a few days (fertilised eggs that have started to develop are called **embryos**)
- step 7: putting one or two embryos into the woman's womb after a few days. If an embryo successfully attaches to the inside of the womb and continues to grow, the result is a pregnancy.

You should be offered up to three cycles of IVF if

- the woman is between 23 and 39 years old at the time of treatment **and**
- one or both of you has been diagnosed with a fertility problem (such as having no sperm or both fallopian tubes being blocked) **or**
- you have had infertility for at least 3 years.

### *Factors affecting your chance of a pregnancy*

Your chances of having a baby through IVF are the same for the first three cycles of treatment, but they vary depending on your age. The older a woman is, the less likely she is to get pregnant:

- for every 100 women who are 23 to 35 years old, more than 20 will get pregnant after one cycle of IVF treatment
- for every 100 women who are 36 to 38, around 15 will get pregnant
- for every 100 women aged 39, around 10 will get pregnant
- for every 100 women aged 40, or over around 6 will get pregnant.

You therefore have the best chance of success with IVF if you are between 23 and 39 years old. Very few women under 23 have IVF, so it is uncertain what their chances of being successful are.

IVF is more effective for women who have been pregnant or had a baby before. Women also have a better chance of success if they have a normal body weight (**body mass index** [BMI] between 19 and 30).

If you drink more than one unit of alcohol a day (see page [10]) or you consume caffeine (which is found in drinks such as coffee, tea and colas), it will lessen your chances of success with assisted reproduction procedures, including IVF. This may also be the case if either of you smoke.

### *Before the treatment*

Before you start IVF you should both be offered tests for HIV, hepatitis B and hepatitis C. This is to avoid passing these infections on to any resulting children or to other people. If you test positive for any of them, you should be offered appropriate treatment and counselling. You and your doctors will need to think about the implications for any children you might have, in deciding on whether to go ahead with IVF.

If you are having IVF because your fallopian tubes are blocked and swollen (a condition known as hydrosalpinx), you should be offered the choice of having your tubes removed through **laparoscopy** before IVF. This increases your chances of a successful pregnancy, but it means you will be unable to conceive naturally in future.

The cycle of treatment begins with stimulation of the ovaries (ovulation induction) and includes collecting eggs and sperm, and the transfer of one or two resulting embryos back into the womb. A **stimulated cycle** of IVF is one in which embryos produced from eggs collected after ovulation induction are used without previously being frozen (see page [59] for more information on freezing embryos). If you have two or more frozen embryos these should be used before starting another stimulated cycle of IVF.

### Ovulation induction and IVF

Ovulation induction therapy involves taking hormones to help your ovaries to produce more than one egg at a time (unlike your natural cycle). If you are having IVF, you should usually be offered a combination of drugs to make your ovaries temporarily inactive (known as **down-regulation**) and then others to make them active again (known as **ovulation induction**). This usually gives better results than using drugs for stimulation alone as it allows your healthcare team to time your egg collection more precisely.

#### *Downregulation of the ovaries (step 1)*

You should be offered drugs (known as **gonadotrophin-releasing hormone agonists**) to ‘switch off’ egg production in the ovaries. They make the ovaries more receptive to the gonadotrophin hormones which are used later on to stimulate the ovaries into producing eggs. They are taken in the form of nasal spray or an injection.

Some other drugs for down-regulation, called **gonadotrophin-releasing hormone antagonists**, reduce the chance of pregnancy, so they should not be offered to you unless you are taking part in a research study.

If you are having down-regulation with gonadotrophin-releasing hormone agonists for IVF, you should also be offered either **progesterone** or **human chorionic gonadotrophin** (HCG, see page [47]) to help any resulting embryo attach to the womb. This will improve your chances of a pregnancy.

#### *Ovulation induction (step 2)*

Using fertility drugs to stimulate your ovaries helps to produce more than one egg at a time. You should be offered IVF with ovulation induction, as this increases your chances of getting pregnant. IVF using your natural cycle can be offered if you are unable to take the necessary hormones, but this is rare.

The **gonadotrophins** (FSH and LH) are used to stimulate the ovaries to produce eggs in IVF. These are the same drugs used to help produce eggs if you do not ovulate normally (see page [31]). These can come from human sources or can be made artificially in a laboratory. All the preparations work equally well in terms of successful birth rates when they are used with down-regulation for IVF treatment. Your doctor should prescribe the least expensive preparation.

If you have ovulation induction with gonadotrophins, you should not be offered growth hormone treatment in addition to ovulation induction treatments because it does not improve your chances of a pregnancy.

#### *Side effects and risks of fertility drugs*

Fertility drugs such as gonadotrophins have certain side effects and risks.

- You will get symptoms of the menopause such as hot flushes. Gonadotrophins need to be given by injection.
- You may become pregnant with more than one baby. Multiple pregnancies carry a higher risk of complications for both mothers and babies. You should be offered **ultrasound** scans to monitor the state of your ovaries while you are having ovulation induction, in order cut down

the risk of having more than one baby. However, it is not necessary for your doctors to monitor your **oestrogen** levels as well, as this will not give them any extra information.

- Your ovaries may get over-stimulated (**ovarian hyperstimulation syndrome** [OHSS]) which can cause very serious problems. Some women are more at risk of OHSS than others. If you are having ovulation induction with gonadotrophins, your clinic should have procedures in place for preventing, diagnosing and managing OHSS. You should not be offered the hormone **human chorionic gonadotrophin** (HCG) for ovulation induction if you have any condition which means you have a significant risk of OHSS.
- There are concerns about a possible link between ovulation induction therapy and ovarian cancer, but the link remains uncertain. Your doctor should use the lowest effective dose and duration for ovulation induction.

Your healthcare team should tell you more about these risks before you start treatment. Your doctors should assess what your risks are as an individual before they decide which drugs to offer you.

Human chorionic gonadotrophin (HCG) is a hormone which helps the eggs mature. It can also be used to help an embryo attach to the womb. HCG increases the risk of developing OHSS, and so it should not be offered for maturing eggs in women who have a high risk of developing OHSS, and it should not be offered as a matter of routine to help embryos attach to the womb. HCG can come from human sources or can be made artificially in a laboratory. All the preparations work equally well in terms of pregnancy rates when they are used to mature eggs. Your doctor should prescribe the least expensive preparation.

### *Egg collection (step 3)*

Your eggs should be collected through a needle, guided through your vagina by ultrasound (known as **ultrasound-guided aspiration**). You will be awake during the procedure but you should be offered an injection to relieve any pain and to make you sleepy. Your healthcare team should follow procedures for sedative drugs published by the Academy of Medical Royal Colleges.

During the egg collection, it has previously been common practice that each **follicle** (the sac containing the egg) is flushed out to ensure the egg is removed. However, if you have developed at least three follicles you should not be offered this procedure, as there is no advantage in it. It also takes longer and may cause more pain.

### *Obtaining sperm (step 4)*

The man should usually be asked to produce a sperm sample on the same day as the woman's eggs are collected.

Some men are not able to ejaculate at this time. The most common reason for this is anxiety. Sometimes an existing condition (such as a spinal cord injury, diabetes or multiple sclerosis) prevents men from ejaculating. If you are unable to ejaculate, your doctors should investigate the reason for it and offer you treatment if necessary.

One option is to obtain sperm through a small surgical procedure (known as **sperm recovery**). If you need to have this done, you should be offered a procedure that is appropriate for your medical circumstances and is in line with your wishes.

You should be offered the chance to freeze some of your sperm after it is retrieved, for possible use later on (see page 154).

If your sperm count is low, or the quality of your sperm is poor, there are further procedures which may be appropriate, depending on your circumstances, and which can be used as well as IVF. They are **intracytoplasmic sperm injection** (see page 152) and **donor insemination** (see page 153).

### *Fertilisation of the eggs (step 5)*

Once your eggs and sperm have been collected, they should be put together in a dish or tube and placed in an incubator. The sperm may then fertilise some of the eggs. Any resulting

**embryos** should be kept in the incubator for up to 6 days before they are put back into the woman's womb.

If for some reason the eggs are not fertilised, you may in the future be offered intracytoplasmic sperm injection (ICSI) or treatment using donor sperm or eggs (see pages [52] and [54]).

Your doctors should explain what these treatments involve. Any discussion they have with you as a couple should allow you equal access to both kinds of treatment.

### *Transfer of the embryos (steps 6 and 7)*

With IVF, the risk of getting pregnant with more than one baby increases with the number of embryos that are transferred into the womb. To balance the chances of a successful birth against the risk of having more than one baby, you should have no more than two embryos transferred in any cycle.

One or two embryos should be transferred into your womb when they are between 2 and 6 days old. The doctor should use ultrasound to guide the placement of embryos into your womb as it can help to improve your chances of getting pregnant.

Women do not need to stay in bed for a prolonged length of time after the embryo transfer. Staying in bed for more than 20 minutes has not been shown to make any difference to the chance of pregnancy.

If you have taken gonadotrophins for downregulation (see page 150), you also have a better chance of a pregnancy if you take **progesterone** to help the embryo to attach inside the womb.

When the embryo is due to be transferred, the woman is unlikely to be able to get pregnant if the lining of her womb is less than 5 mm thick, so transfer of embryos is not recommended at this time.

**Assisted hatching** is a method used to thin or open the shell of an embryo in the early stages of development, with the aim of increasing the chances of implanting it successfully into the womb. Research has shown that it does not make any difference to the pregnancy rate, however, so you should not be offered this option.

### **Intracytoplasmic sperm injection (ICSI)**

For some men their sperm are not capable of fertilising eggs in the usual way. If this is the case, you may be offered a procedure called **intracytoplasmic sperm injection (ICSI)** to inject a single sperm directly into an egg.

ICSI increases the chances of fertilising eggs more than if IVF is used on its own. However, once the eggs are fertilised it makes no difference to the chances of a successful pregnancy.

You should be offered ICSI if:

- you have few sperm in your semen (known as **oligozoospermia**) or your sperm are of poor quality, or
- you have no sperm in your semen (known as **azoospermia**) either because of a blockage or because of some other cause, but you do have sperm in your testes.

You may also be offered ICSI if you have already tried IVF and produced eggs but your eggs did not fertilise.

If you are not able to ejaculate there are a number of ways of obtaining your sperm, such as by using a small surgical procedure (known as **sperm recovery**). If you need to have this done you should be offered a method that is appropriate to your medical circumstances and is in line with your wishes. You should be offered the chance to freeze some of your sperm after it is retrieved for possible use later on (see page [59]).

Before you consider ICSI, your healthcare team should offer both of you appropriate tests and discuss the results and their implications with you. They should also consider whether a genetic problem is involved in your fertility problems. Some men have a fertility problem as a result of a gene abnormality on their Y chromosome (the male sex chromosome). However, unless this is suspected, you do not normally need tests for this before having ICSI.

If your healthcare team know or suspect that you have a specific gene defect they should offer you appropriate genetic counselling and tests.

If your sperm quality is very poor or you don't have sperm in your semen but this is not caused by a blockage, you should be offered a test known as karyotyping. This checks for abnormalities in your **chromosomes**.

### Donor insemination

This form of treatment involves using sperm donated anonymously by another man. As a couple, you may wish to consider using donor insemination as an alternative to **intracytoplasmic sperm injection** (ICSI). Your doctors should give you access to both options.

You should be offered donor insemination if:

- the man's sperm count or quality is very low and you have decided against having ICSI, or
- he has no sperm in his semen, or
- he has an infectious disease which could be passed on to any children, or
- his blood group is not compatible with the woman's.

Donor insemination may also be considered if the man has a genetic disorder which could be passed on to any children.

Donor insemination can be used for IVF if necessary. The clinic where you are treated should follow the guidelines laid down by the British Andrology Society on selecting and screening sperm donors.

If you are considering donor insemination you should be offered independent counselling as a couple about the implications for you and any potential children. All potential sperm donors should also be offered the chance to see an independent counsellor, to help them to look at what donation will mean for them, any children they have, and any children they might have as a result of donation.

Before you start treatment by donor insemination your doctors should confirm that the woman is **ovulating**. You should be offered tests to check your **fallopian tubes** if there is anything about your medical history that suggests they may be damaged. If you have no history of damage to your fallopian tubes, you should be offered tests to check your fallopian tubes after three cycles of unsuccessful treatment.

If you are ovulating regularly, you should be offered at least six cycles of donor insemination. To cut down the risks of having more than one baby you should not be offered fertility drugs to stimulate your ovaries.

There are two methods used for timing donor insemination. One is based on measuring the woman's body temperature during her menstrual cycle. The other uses a kit to measure the levels of **luteinising hormone** (LH) in her urine. Both methods are equally effective. Measuring LH levels, however, cuts down the number of visits you need to make to the clinic in each cycle.

You should be offered **intrauterine insemination** (IUI, see page 148) rather than insemination into the neck of the womb (the cervix) because IUI gives you a better chance of getting pregnant.

If you have not managed to get pregnant after six cycles of donor insemination, your doctors should offer you continued treatment with donor insemination as well as other forms of treatment.

### Egg donation

Some women cannot produce eggs, usually because their ovaries are not functioning or have been removed.

If you are a couple in this situation, you may wish to consider egg donation – that is, using another woman's eggs – in order to get pregnant.

Couples should be offered the option of egg donation if:

- the woman's ovaries have stopped working early, or after chemotherapy or radiotherapy

- she has a chromosome abnormality, such as Turner syndrome
- her ovaries have been removed.

As a couple you may also be offered the option of egg donation if:

- depending on the reasons for failure, you have not had success with IVF treatment
- there is a high risk of passing on a genetic disorder to any children.

If you are considering egg donation, you should be offered the chance to see an independent counsellor to talk over what the treatment will mean for you, any children you have, and any children you might have as a result of treatment.

Women who donate or share their eggs should be screened beforehand for infectious and genetic diseases, in line with guidance issued by the Human Fertilisation and Embryology Authority (HFEA).

If you are considering donating your eggs your doctor should offer you information on the risks associated with **ovulation induction** and **egg collection**.

### Egg sharing

An alternative to egg donation is **egg sharing**. This is where a woman undergoing IVF donates half of her eggs to be given to another woman or a number of women.

Egg sharing is done anonymously. Anyone who is considering taking part in an egg-sharing scheme should be offered the chance to see an independent counsellor, to talk over what it will mean for them.

### Freezing sperm, eggs or embryos

Sperm, eggs or embryos can be frozen and stored for possible use in the future. This is known as **cryopreservation** (freezing) and **cryostorage** (storage).

If you are having medical treatment that is likely to make you infertile (such as treatment for cancer), you should be offered the opportunity to have some of your sperm, eggs or embryos frozen and stored before you start your treatment. You should be offered the chance to see an independent counsellor to help you cope with the stress involved. They should discuss the potential physical and psychological implications for you, your partner and any potential children resulting from a freezing and storage procedure.

### Sperm

Some medical treatments, such as chemotherapy or radiotherapy for other conditions and illnesses, can affect your fertility. If you are a man or adolescent boy about to have surgery on your testes or medical treatment that is likely to make you infertile, your healthcare team should offer you the option of freezing your sperm for later use. The clinic or centre where you are treated should have procedures in place to make sure that healthcare staff understand the value of doing this, so that they can respond quickly and effectively to the situation. Your healthcare team should follow procedures recommended by the Royal College of Physicians and the Royal College of Radiologists.

### Eggs and embryos

If you are about to have medical treatment that is likely to make you infertile and you are well enough to have **ovulation induction** and have your eggs collected, you should be offered egg or embryo storage as appropriate. You need to be aware that the success of storing frozen eggs is very limited. Freezing parts of the ovaries is still in the early stage of development.

If you produce more embryos than you need in the course of an IVF cycle, you should be offered the chance to freeze them, provided they are suitable for freezing. Not all the embryos survive the freezing process so some will not be suitable for transfer after thawing.

If any embryos are suitable for freezing, they should be transferred to your womb before you can start another stimulated cycle of IVF involving **downregulation**, ovulation induction and **egg collection**. This cuts down the number of times you need to have drugs for ovulation induction

and the procedure to recover eggs from your ovaries, both of which carry some risks. It also improves the chances of a successful birth.

An embryo that has previously been frozen can be thawed and transferred into your womb either as part of your natural cycle (**unstimulated cycle**) or as part of a cycle controlled by hormone treatment (**stimulated cycle**). If you ovulate regularly, your chances of a successful birth are the same whether your cycle is natural or stimulated.

Your healthcare team should tell you more about what is involved in using previously frozen embryos and discuss it with you before you start IVF treatment.

### Where you can find more information

If you need further information about any aspects of fertility or the care that you are receiving, please ask your doctor, nurse or other relevant member of your healthcare team. You can discuss this guideline with them if you wish, especially if you are not sure about anything in this booklet. They will be able to explain things to you.

For further information about the National Institute for Clinical Excellence (NICE), the Clinical Guidelines Programme or other versions of this guideline (including the sources of evidence used to inform the recommendations for care), you can visit the NICE website at [www.nice.org.uk](http://www.nice.org.uk). At the NICE website you can also find information for the public about other maternity-related guidance on:

- antenatal care: routine antenatal care for healthy pregnant women (guideline 6)
- pregnancy and childbirth: electronic fetal monitoring (guideline C)
- pregnancy and childbirth: induction of labour (guideline D)
- pregnancy – routine anti-D prophylaxis for rhesus negative women (technology appraisal no. 41)

You can get information on common problems during pregnancy from NHS Direct (telephone 0845 46 47; website [www.nhsdirect.nhs.uk](http://www.nhsdirect.nhs.uk)).

### Explanation of medical terms

Assisted hatching	A technique used in <b>IVF</b> to thin or open the shell of an embryo in the early stages of development, with the aim of increasing the chances of implanting it successfully into the womb.
Assisted reproduction	The name for treatments that enable people to conceive by means other than sexual intercourse. Assisted reproduction techniques include <b>intrauterine insemination (IUI)</b> , <b>in vitro fertilisation (IVF)</b> , <b>intracytoplasmic sperm injection (ICSI)</b> , <b>donor insemination</b> and <b>egg donation</b> .
Azoospermia	When a man has no sperm in his semen.
Biopsy	A procedure to take a small sample of tissue.
Body mass index (BMI)	The measurement used to define the range of healthy weight. Your BMI is calculated by dividing your weight in kilograms by your height in metres squared (that is, your height in metres multiplied by itself).
Chlamydia trachomatis (Chlamydia)	A sexually transmitted infection which can damage a man's or woman's reproductive system if it is not diagnosed and treated. It can go unnoticed for a long time but can be found through screening tests.
Chromosome	A structure found in cells that contains a person's genetic information in the form of genes.
Clomifene citrate	A fertility drug which stimulates a woman's ovaries to produce one or more <b>follicles</b> .

Cryopreservation	The freezing of <b>eggs, sperm</b> and/or <b>embryos</b> that may be thawed for use in future IVF treatment cycles.
Cryostorage	The storage of frozen <b>eggs, sperm</b> and/or <b>embryos</b> that may be thawed for use in future IVF treatment cycles.
Donor insemination	The placing of donor <b>sperm</b> into a woman's womb.
Down-regulation	Drug treatment used as part of <b>ovulation induction</b> to turn off the natural cycle of <b>ovulation</b> before a <b>stimulated cycle</b> .
Egg	The female reproductive cell. A woman usually produces one egg in a normal monthly cycle.
Egg collection	A procedure by which a woman's <b>eggs</b> are collected from her <b>ovaries</b> , usually using a needle guided by <b>ultrasound</b> . Also known as egg retrieval.
Egg donation	The process by which a fertile woman donates her <b>eggs</b> for use in the treatment of other women or for use in research.
Egg sharing	When a woman having <b>IVF</b> donates half of her <b>eggs</b> for use by another woman or a number of women.
Embryo	A fertilised <b>egg</b> .
Embryo transfer	Transfer of one or two <b>embryos</b> into the womb as part of <b>IVF</b> .
Endometriosis	A condition where cells like those in the lining of the womb are found in other areas of a woman's pelvis, usually causing pain and damage.
Fallopian sperm perfusion	A technique where the sperm is mixed with a larger volume of fluid than in standard <b>IUI</b> .
Fallopian tube(s)	The pair of tubes leading from a woman's <b>ovaries</b> to the womb. Each month the ovary releases an <b>egg</b> into the fallopian tube, and the egg travels through the tube to the womb. The fallopian tube is where <b>fertilisation</b> of the egg by a <b>sperm</b> takes place in the natural conception process.
Fertilisation	When a sperm penetrates an <b>egg</b> and forms an <b>embryo</b> . Natural fertilisation takes place in a woman's fallopian tubes, but fertilisation can also be done in the laboratory for <b>IVF</b> .
Fertility problem	Where no pregnancy results for a couple after 2 years of regular (at least every 2 to 3 days) unprotected sexual intercourse.
Follicle	A small sac in the ovary in which the <b>egg</b> develops.
Follicle-stimulating hormone (FSH)	A hormone produced by the <b>pituitary gland</b> which stimulates the <b>ovaries</b> to produce <b>follicles</b> . It can be used as part of ovulation induction therapy.
Galactorrhoea	A condition where a woman produces breast milk not related to a recent pregnancy.
Gamete	A reproductive cell (a male <b>sperm</b> or female <b>egg</b> ). The male and female gamete fuse together in fertilisation.
Gamete intrafallopian transfer (GIFT)	A technique by which a woman's <b>eggs</b> are collected, mixed with <b>sperm</b> and immediately replaced in one or

	other of her <b>fallopian tubes</b> , so that they can fertilise there.
Gonadotrophin-releasing hormone agonist	A drug that temporarily switches off the release of <b>gonadotrophins</b> . Used for downregulation.
Gonadotrophin-releasing hormone antagonist	A drug that temporarily switches off the release of gonadotrophins but which is not recommended for use outside research studies.
Gonadotrophins:	<b>Follicle-stimulating hormone</b> (FSH) and <b>luteinising hormone</b> (LH) are two kinds of gonadotrophin hormones made by the <b>pituitary gland</b> . In women they stimulate the <b>ovaries</b> to produce <b>eggs</b> . They can be given during <b>ovulation induction</b> . Their side effects are hot flushes, multiple pregnancy and <b>OHSS</b> . In men, they stimulate sperm production. They can be given to men who have low levels of gonadotrophins to stimulate sperm production.
Human chorionic gonadotrophin (HCG)	A gonadotrophin hormone made by the placenta. The presence of HCG in a woman's blood or urine indicates that she is pregnant. HCG may be used to mature eggs in <b>IVF</b> downregulated cycles and to help embryos attach to the womb in IVF.
Hyperprolactinaemia	A disorder of the <b>pituitary gland</b> which can cause irregular periods, production of breast milk and fertility problems.
Hysteroscopy	A procedure to examine the womb with a small microscope called a hysteroscope.
Hysterosalpingogram (HSG)	An X-ray of the <b>fallopian tubes</b> , using fluid injected through the neck of the womb, to check for any blockages.
Hysterosalpingo-contrast-sonography	An ultrasound test of the <b>fallopian tubes</b> , using fluid injected through the neck of the womb, to check for any blockages.
Implantation	The process by which an <b>embryo</b> attaches to the lining of the womb.
In vitro fertilisation (IVF)	A technique by which <b>eggs</b> are collected from a woman and fertilised with a man's <b>sperm</b> outside the body. Usually one or two resulting <b>embryos</b> are then transferred to the womb. If one of them attaches successfully, it results in a pregnancy.
Insemination	A technique to place <b>sperm</b> into a woman's vagina or womb.
Intracytoplasmic sperm injection (ICSI)	A variation of <b>IVF</b> in which a single sperm is injected into an <b>egg</b> .
Intra-uterine insemination (IUI)	A technique to place <b>sperm</b> into a woman's womb through the cervix.
Laparoscopic ovarian drilling	Uses a laparoscope to operate on a woman's <b>ovaries</b> , and apply heat (a process known as diathermy) to destroy extra <b>follicles</b> in the ovaries.
Laparoscopy	A 'keyhole' operation in which the surgeon uses a very small telescopic microscope, called a laparoscope, to examine or operate on an area in a woman's pelvis. Done under general anaesthetic.

Luteinising hormone	One of the <b>gonadotrophin</b> hormones made by the <b>pituitary gland</b> . It can be used as part of <b>ovulation</b> induction therapy.
Motile sperm	<b>Sperm</b> that are capable of moving.
Multiple pregnancy	When a woman is pregnant with more than one baby at a time.
Oestrogen	A female sex hormone produced by developing eggs in the <b>ovaries</b> .
Ovarian hyperstimulation syndrome (OHSS)	A complication following stimulation of the <b>ovaries</b> with <b>gonadotrophin</b> drugs.
Ovarian reserve	How many eggs a woman has left. Predicts how close a woman is to the menopause.
Oligozoospermia	Low sperm count.
Ovaries	A pair of organs in women which produce <b>follicles</b> and <b>eggs</b> .
Ovulation	The process by which the <b>ovaries</b> produce <b>eggs</b> . If you have periods every 28 days you should be ovulating around day 14 or 2 weeks after the first day of your period.
Ovulation induction	A course of fertility drugs used to control and/or stimulate a woman's <b>ovulation</b> .
Pelvic inflammatory disease	An infection of the womb, fallopian tubes and/or pelvis which can be caused by infections such as chlamydia. Can cause scarring or blockage of the fallopian tubes.
Pituitary gland	A gland in the brain which produces hormones.
Polycystic ovary syndrome (PCOS)	A condition where the <b>ovaries</b> often produce more small <b>follicles</b> than normal but the woman does not ovulate.
Progesterone	A hormone produced by the ovary after the egg is released. Low levels might mean the woman is not ovulating. Used in IVF to help embryos attach to the womb.
Prolactin	A hormone produced by the pituitary gland that can make a woman produce breast milk.
Pulsatile gonadotrophin-releasing hormone	A drug given to a woman through a pump every 90 minutes to mimic the natural delivery of <b>gonadotrophins</b> .
Semen	The fluid containing sperm and secretions that is expelled in an ejaculation.
Sperm	The male reproductive cell produced by men, usually through ejaculation, which fertilises a woman's <b>eggs</b> . Men usually have millions of sperm in their <b>semen</b> .
Sperm recovery	A surgical procedure to obtain <b>sperm</b> from the testicles in men who cannot ejaculate or have a blockage in the flow of sperm from their testicles.
Stimulated cycle	A round of treatment in which drugs are used to make the woman's <b>ovaries</b> produce more <b>eggs</b> than usual in a monthly cycle.
Tamoxifen	A fertility drug which stimulates the ovaries to produce one or more <b>follicles</b> .

Ultrasound	High frequency sound waves used to provide images of the body, tissues and internal organs.
Ultrasound-guided aspiration	A procedure to collect <b>eggs</b> using ultrasound images to guide the path of a needle through which the eggs are retrieved.
Unexplained fertility problems	Problems for which no reason can be found.
Unstimulated cycle	A woman's natural cycle. A cycle where no drugs are used to stimulate <b>egg</b> production.
Zygote intrafallopian transfer	A process in which eggs are fertilised outside the body and then transferred into the <b>fallopian tubes</b> .

# Appendix B

## Economic models

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### B.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 published evidence reported a range of estimates for several important parameters.

### B.2 Structure of the economic models

#### **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 upon 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 Chapter 11, Tables 11.1 to 11.5). The lowest age used in the economic mode was 24 years because below this age there were fewer than 100 treatment cycles (see Table 11.1). 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 B.1, which, for the purposes of illustration, shows only one of the six potential fresh cycles of IVF treatment. The outcomes of each IVF cycle with fresh or frozen embryo transfer are:

- a live birth (in which case treatment ceases)
- an ectopic pregnancy
- a miscarriage
- no pregnancy.

The options for couples without a live birth are:

- to discontinue treatment
- to attempt a frozen embryo transfer
- 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 purpose of estimating costs per live birth from up to to six fresh cycles of IVF treatment was to explore the impact of offering treatment beyond the three fresh cycles that have been shown to be of similar clinical effectiveness (see Chapter 11).



**Table B.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	Age-specific rates used	HFEA data 1995–99 (see Table 11.1)
	All frozen	Age-specific rates used	HFEA data 1995–99 (see Table 11.2)
Ectopic pregnancy	All	Age-specific rates used	HFEA data 1995–99 (see Table 11.4)
Miscarriage	All	Age-specific rates used	HFEA data 1995–99 (see Table 11.5)
Discontinuation	All fresh	40–50 (including pregnancy) 20 (without pregnancy)	FIVNAT 1998 <sup>779</sup>
	All fresh, under 30 years	17.7	Mardesic et al. 1984 <sup>780</sup>
	All fresh, 38–40 years	50.0	
OHSS	All cycles	0.2–1.0	Various <sup>586–588</sup>

### Cycle-specific models

The models based on the number of cycles were structured so that couples were offered three or four fresh cycles of IVF treatment and no frozen embryo transfers. Two models were used because two data sets with different structures were available.

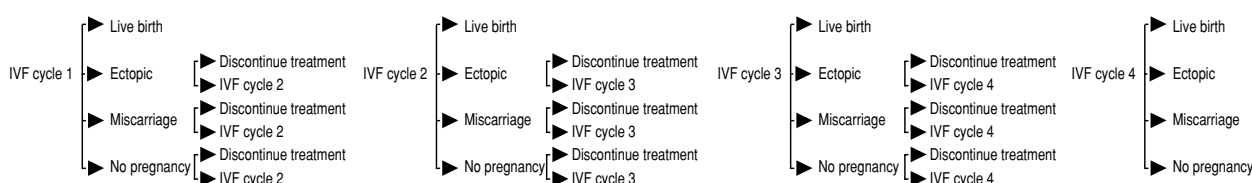
The first cycle-specific model was based on live birth rates by number of previous unsuccessful cycles obtained from the HFEA (see Table 11.6) This dataset included estimates for up to four fresh (not frozen) cycles of treatment (see Section 11.4). The dataset did not include miscarriage or ectopic pregnancy 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 11.4 and 11.5, respectively). The structure of the model is presented in Figure B.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
- no pregnancy.

The options for couples without a live birth are:

- to discontinue treatment
- 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 B.2.



**Figure B.2** Structure of the in vitro fertilisation treatment model for deriving cycle-specific cost per live birth; the figure shows all four potential fresh cycles of IVF treatment for the model, and uses different live birth rates for different cycles

**Table B.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	1	18.2	HFEA data 1995–99 (see Table 11.6)
	2	17.2	
	3	18.8	
	4	19.4	
Ectopic pregnancy	All	Overall rate (0.5) used	HFEA data 1995–99 (see Table 11.4)
Miscarriage	All	Overall rate (2.7) used	HFEA data 1995–99 (see Table 11.5)
Discontinuation	All	40.0–50.0	FIVNAT 1998 <sup>779</sup>
		(including pregnancy) 20 (without pregnancy)	
		All fresh, under 30 years All fresh, 38–40 years	

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 11.7). This dataset included estimates for up to three fresh (not frozen) cycles of treatment for two different age groups (under 39 years versus 39 years and over; see Chapter 11, Section 11.2). 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 B.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 B.3.

**Table B.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	1: under 39 years	24.0	Oxford Fertility Unit, 1995–2001 (see Table 11.7)
	1: 39 years and over	10.2	
	2: under 39 years	24.2	
	2: 39 years and over	9.7	
	3: under 39 years	1.9	
	3: 39 years and over	6.4 <sup>a</sup>	
Miscarriage	1: under 39 years	10.2	Oxford Fertility 1995–2001
	1: 39 years and over	19.4	
	2: under 39 years	9.9	
	2: 39 years and over	5.3	
	3: under 39 years	9.8	
	3: 39 years and over	16.1	
Discontinuation	All	40.0–50.0	FIVNAT 1998 <sup>779</sup>
		(including pregnancy) 20.0 (without pregnancy)	
		All fresh, under 30 years All fresh, 38–40 years	

**Table B.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	Overall rate (17.6) used	HFEA data 1995–99 (see Table 11.4)
	All frozen	Overall rate (11.5) used	HFEA data 1995–99 (see Table 11.2)
Ectopic pregnancy	All	Overall rate (0.5) used	HFEA data 1995–99 (see Table 11.4)
Miscarriage	All	Overall rate (2.7) used	HFEA data 1995–99 (see Table 11.5)
Discontinuation	All fresh	40.0–50.0 (including pregnancy) 20 (without pregnancy)	FIVNAT 1998 <sup>779</sup>
	All fresh, under 30 years	17.7	Mardesic et al. 1984 <sup>780</sup>
	All fresh, 38–40 years	50.0	
OHSS	All	0.2–1.0	Various <sup>586–588</sup>

### 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 B.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 11.1 to 11.5). A detailed description of the clinical effectiveness data used in this model is presented in Table B.4.

## B.3 Costs used in the economic models

Treatment costs were estimated using a variety of published and unpublished sources of data. Table B.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 UK-based economic evaluation studies that report resource use and unit costs as well as a cumulative mean cost estimate. 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 £1,000 and the highest around £2,500. The HFEA reported on its website that the cost of an IVF cycle is around £1,771 excluding drug costs. The HFEA also reported on its website that the cost of an ICSI cycle is £1,936 (without drugs).

A UK study<sup>1143</sup> reported the cost of a stimulated cycle of IVF to be around £4,250 and a natural cycle to be around £898. An earlier study reported the cost per couple of IVF to range from £1,786 to £5,749 and a single cycle to cost £1,100.<sup>13</sup> Another UK study undertaken earlier in the 1990s reported a cost of IVF to be £1,005 for stimulated IVF.<sup>707</sup>

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 to 1,000, depending on the drugs used. We used three costs in our models. The baseline cost was £2,771 (£1,771, which includes the costs associated with health services use and counselling, plus £1,000 for drugs); a lower value of £1,771 (the cost without drugs); and a higher value of £3,500 (£2,500,

**Table B.5** Cost data used in the in vitro fertilisation treatment models

Procedure or event	Baseline estimate	Source of data	Range of estimates found in published studies or other sources	Source of data
IVF without drugs per fresh cycle	£1,771	HFEA internet site 2002	£1,000 to £2,500 £1,786 (stimulated IVF) £1,717 to £2,233	Upper and lower limits of private clinic costs reported by Fertility Confidential Nargund et al., 2001 (UK) <sup>1143</sup> Phillips et al., 2000 (UK) <sup>13</sup>
Frozen embryo transfer	£666	HFEA internet site 2002	£300 to £760	Private clinic costs published on the Internet 2003
IVF drugs per attempt: Urinary FSH hMG	Range £320 to £490		Menogon® (Ferring) £10.64 per 75 units 30 doses: £319 35 doses: £372 Menopur® (Ferring) £14 per 75 units 30 doses: £420 35 doses £490 Merional® (Denflect) £13.95 per 75 units 30 doses: £419 35 doses: £488 Gonal-F® (Serono) £26.25 30 doses £788 35 doses £919 Puregon® (Organon) £20.15 per 50 units 30 doses £907 35 doses £1,058	<i>BNF</i> September 2003 <sup>181</sup>
Recombinant FSH	Range £790 to £1100			
OHSS	£800	Daya et al., 2001 (Canada) <sup>552</sup>		
Cost of ICSI	£1936	HFEA internet site 2002	£2077 £3121	Phillips et al 2000 (UK) <sup>13</sup> Granberg 1996 (Sweden) <sup>1144</sup>
Ectopic pregnancy	£769	NHS reference cost 2001 for upper genital tract (intermediate procedures; nearest relevant cost)		
Miscarriage	£233.64	NHS reference cost 2001		

which was the highest value reported in the Fertility Confidential survey, plus £1,000 for drugs). We also explored the impact of assuming an even higher cost of £5,000 per IVF cycle (£4,000 plus £1,000 for drugs). The cost for an ICSI cycle in our model was £2,936 (£1,936, plus £1,000 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 B.5.

## B.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 and cost of OHSS per fresh cycle of IVF
- the source of clinical effectiveness data (HFEA or Oxford Fertility Unit).

## B.5 Results

### 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 B.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 (£2,771) are presented in Tables B.6, B.7 and B.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 £6.9 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 (£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. 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 £4.7 million for women aged 24 years, £4.8 million for women aged 35 years and £5.0 million for women aged 39 years.

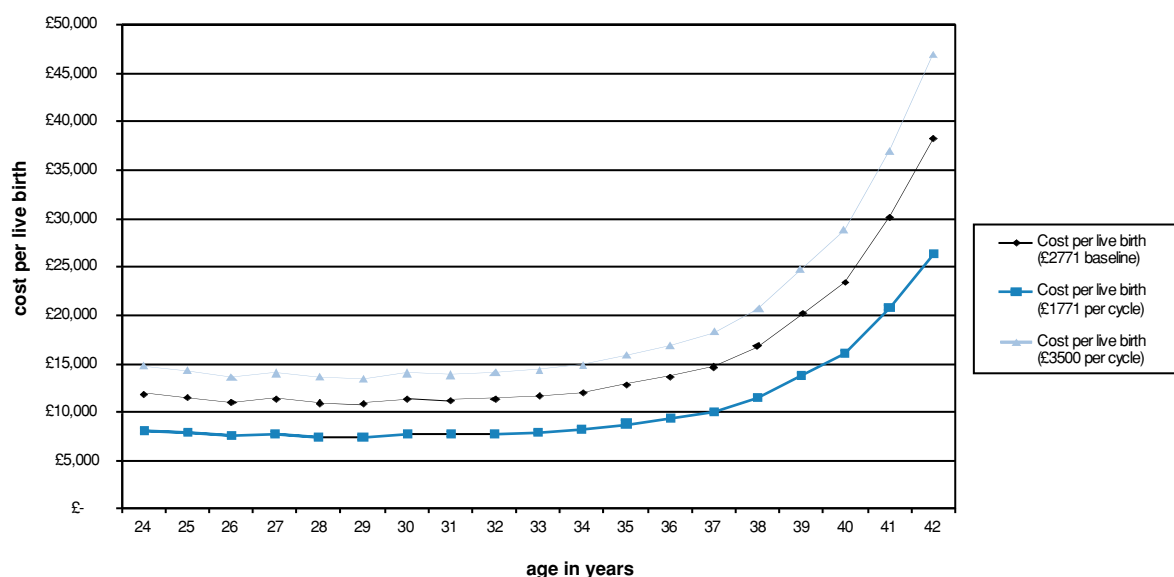


Figure B.3 Age-specific cost per live birth using three cost estimates for a cycle of in vitro fertilisation treatment

**Table B.6** Cost per live birth for women aged 24 years using baseline cost for a cycle of in vitro fertilisation treatment (1000 couples)

Age	24 years	Live birth rate (fresh embryo transfer)	20.68%
Cost	£2,771	Ectopic pregnancy rate	1.09%
Discontinuation rate	17.7%	Miscarriage rate	1.93%
OHSS rate	0.2%	Live birth rate (frozen embryo transfer)	11.1%

	Cycle					
	1	2	3	4	5	6
Cumulative fresh cycles (n)	1000	1607	1976	2200	2336	2414
Cumulative frozen embryo transfer (n)	499	803	987	1099	1167	1208
Cumulative couples with baby (n)	262	421	518	577	612	634
Difference (n)	262	159	97	59	35	22
Cumulative ectopic (n)	11	21	27	30	33	34
Cumulative miscarriage (n)	29	47	57	64	68	70
Cumulative OHSS (n)	2.00	3.21	3.95	4.40	4.67	4.84
Discontinuation (n)	131	79	48	29	18	61
Cumulative discontinuation (n)	138	210	258	287	305	366
Total cost per cycle for 1000 couples (£)	3,124,713	1,897,323	1,152,053	699,525	424,937	258,534
Cumulative cost per cycle for 1000 couples (£)	3,124,713	5,022,036	6,174,089	6,873,614	7,298,551	7,557,085
Cost per live birth (£) (all cycles)	11,917					

**Table B.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 embryo transfer)	18.61%
Cost	£2,771	Ectopic pregnancy rate	0.44%
Discontinuation rate	17.7%	Miscarriage rate	2.89%
OHSS rate	0.2%	Live birth rate (frozen embryo transfer)	10.9%

	Cycle					
	1	2	3	4	5	6
Cumulative fresh cycles (n)	1000	1624	2013	2256	2407	2502
Cumulative frozen embryo transfer (n)	513	833	1033	1157	1236	1284
Cumulative couples with baby (n)	242	393	487	546	582	605
Difference (n)	242	151	94	59	36	23
Cumulative ectopic (n)	49	11	13	14	14	
Cumulative miscarriage (n)	44	71	88	99	105	110
Cumulative OHSS (n)	2.00	3.25	4.03	4.51	4.81	5.0
Discontinuation (n)	134	84	52	33	20	72
Cumulative discontinuation (n)	138	218	270	303	323	395
Total cost per cycle for 1000 couples (£)	3,129,769	1,952,383	1,217,917	759,750	474,383	297,152
Cumulative cost per cycle for 1000 couples (£)	3,129,769	5,082,153	6,300,070	7,059,820	7,534,203	7,831,355
Cost per live birth (all cycles) (£)	12,931					

**Table B.8** Cost per live birth for women aged 39 years using baseline cost for a cycle of in vitro fertilisation treatment (1000 couples)

	Age	39 years	Live birth rate (fresh embryo transfer)	10.73%
	Cost	£2,771	Ectopic pregnancy rate	0.34%
	Discontinuation rate	17.7%	Miscarriage rate	3.03%
	OHSS rate	0.2%	Live birth rate (frozen embryo transfer)	8.9%

	Cycle					
	1	2	3	4	5	6
Cumulative fresh cycles (n)	1000	1693	2173	2506	2737	2899
Cumulative frozen embryo transfer (n)	569	963	1236	1425	1559	1651
Cumulative couples with baby (n)	158	267	343	396	430	455
Difference (n)	158	109	76	53	34	26
Cumulative ectopic (n)	3	7	10	11	13	14
Cumulative miscarriage (n)	48	81	103	119	130	138
Cumulative OHSS (n)	2.00	3.39	4.35	5.01	5.47	5.80
Discontinuation (n)	149	103	72	50	35	136
Cumulative discontinuation (n)	138	252	324	374	408	545
Total cost per cycle for 1000 couples (£)	3,166,701	2,194,692	1,521,039	1,054,161	732,231	512,101
Cumulative cost per cycle for 1000 couples (£)	3,166,701	5,361,393	6,882,432	7,936,593	8,668,823	9,180,924
Cost per live birth (all cycles) (£)	20,056					

### 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 B.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, respectively. These costs reflect the varying live birth rates by number of previous unsuccessful IVF cycles (see Table 11.6). 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. Using an even higher cost of £5,000 for IVF treatment resulted in costs per live birth of £27,528, £29,129, £26,650 and £25,826).

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 B.10 (women aged less than 39 years) and B.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 11.7); the

**Table B.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

HFEA	Cycle			
	1	2	3	4
Cumulative fresh cycles (n)	1000	673	459	307
Births (n)	182	116	86	59
Ectopic pregnancies (0.5%) (n)	5	3	2	2
Miscarriages (2.7%) (n)	27	18	12	8
Couples discontinuing treatment (n)	145	99	66	0
Discontinuation rate	17.7%			
Cumulative births	182	298	384	444
Cumulative miscarriages	27	45	58	66
Cumulative discontinuing (n)	145	243	309	309
Cumulative cycles (n)	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 birth (£)	15,281	16,169	14,793	14,336
Cumulative cost per cycle for 1000 couples (£)	2,781,153	4,653,465	5,929,340	6,781,977
Cumulative couples with a baby (%)	18	30	38	44

cost per live birth for the third cycle of treatment is not 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.

**Table B.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	2	3
Cycles starting with 1000 couples (n)	1000	626	391
Births (n)	239	152	86
Miscarriages (n)	102	62	38
Couples discontinuing treatment (n)	135	84 n/a	
Discontinuation rate (%)	17.7		
Cumulative births (n)	239	391	476
Cumulative miscarriages (n)	102	164	202
Cumulative discontinuing (n)	135	219 n/a	
Cumulative cycles (n)	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
Cumulative cost per cycle for 1000 couples	2,794,831	4,545,136	5,636,737
Cumulative couples with a baby (%)	23.9	39.1	47.6

**Table B.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	2	3
Cycles starting with 1000 couples (n)	1000	739	549
Births (n)	102	72	120
Miscarriages (n)	194	261	88
Couples discontinuing treatment (n)	159	0	n/a
Discontinuation rate (%)	17.7		
Cumulative births (n)	102	174	294
Cumulative miscarriages (n)	194	455	543
Cumulative discontinuing (n)	159	159	n/a
Cumulative cycles (n)	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 live birth	27,611	28,938	12,825
Cumulative cost per cycle for 1000 couples	2,816,326	4,890,855	6,433,465
Cumulative couples with a baby (%)	10.2	17.4	29.4

#### *Changing the incidence rate and cost of treating ovarian hyperstimulation syndrome*

Using the baseline IVF model (live birth rates of 17.7% for fresh embryo transfers and 11.5% for frozen embryo transfers, ectopic pregnancy rate of 0.5%, miscarriage rate of 2.7%, discontinuation rate of 17.6%, cost per fresh IVF cycle of £2,771, cost per frozen embryo transfer £666, OHSS incidence rate of 0.2%, and OHSS treatment cost of £800), the overall cost per live birth was £13,301. Increasing the OHSS incidence rate to 1% led to an overall cost per live birth of £13,328, while decreasing the cost of treating OHSS to £350 (a UK private sector estimate) led to an overall cost per live birth of £13,309. These results indicate that the rate and cost of OHSS are not important factors in the overall cost-effectiveness of IVF. The lack of robust cost data for the treatment of OHSS is less important than the lack of robust data for the cost of an IVF cycle.

#### *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 review of this evidence shows far higher cost-effectiveness ratios (cost of IVF per delivery) in the USA (as might be expected), but similar results in Scandinavian countries.<sup>1145</sup> The data reported below are for the year 1994:

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

#### **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 B.12. The table show that the cost per live birth was £14,002. 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.

**Table B.12** Cost per live birth using baseline cost for intracytoplasmic sperm injection

All ages		Live birth rate (fresh embryo transfer) (%)	17.6
Cost (£)	2,936	Ectopic pregnancy rate (%)	0.5
Discontinuation rate (%)	17.7	Miscarriage rate (%)	2.7
OHSS rate (%)	0.2	Live birth rate (frozen embryo transfer) (%)	11.5

	Cycle					
	1	2	3	4	5	6
Cumulative fresh cycles (n)	1000	1629	2025	2274	2431	2530
Cumulative frozen embryo transfer (n)	518	843	1048	1177	1260	1311
Cumulative couples with baby (n)	236	384	477	536	572	595
Cumulative ectopic pregnancy	5	10	13	15	16	17
Cumulative Miscarriage	41	67	83	93	100	104
Cumulative OHSS	2.00	3.26	4.05	4.55	4.86	5.06
Discontinuation	135	85	54	34	21	76
Cumulative discontinuation rate	138	220	274	308	329	405
Total cost per cycle for 1000 couples (£)	3,297,974	2,074,920	1,305,436	821,315	517,516	327,892
Cumulative cost per cycle for 1000 couples (£)	3,297,974	5,372,894	6,678,330	7,499,645	8,017,161	8,345,053
<b>Cost per live birth (all cycles) (£)</b>	<b>14,002</b>					

The cost of the PESA/TESA procedure can add to the average cost of a live birth for when sperm retrieval is necessary before ICSI. We did not identify any studies that reported the cost per live birth of ICSI with PESA/TESA in the UK, nor any that reported the cost of the procedure alone. A German study published in 2000 reported a hospital fee of 369 euros (around £250) at one institution,<sup>1146</sup> but no further data were provided to indicate which health care resources were included in the cost. In the UK, private fertility clinics charge a range of prices for PESA/TESA. The lower end of the range of prices published on the internet in November 2003 was £625 and the higher end was around £1,400. A voluntary organisation reported a guide price £1,100 for couples seeking treatment with PESA/TESA ([www.oneinsix.com](http://www.oneinsix.com), accessed 4 November 2003).

**Table B.13** Typical treatment schedule and cost of antagonists and agonists in ovulation induction

Generic/proprietary name	Duration, route and treatment schedule	Dose/day	Days of treatment per cycle (n)	Price and unit advertised in BNF <sup>(B1)</sup> and total cost of antagonist or agonist	Mean dose gonadotrophin	Gonadotrophin days (n)	Price and unit advertised in BNF <sup>(B1)</sup> and total cost of gonadotrophin	Total price (agonist/antagonist plus gonadotrophin)
Antagonists e.g. cetrorelix (brand name: Cetrotide®)	Short Injection	250 micrograms	5 days	Net price 250-microgram vial = £24.00	1500 iu (3000 iu for poorly responding patients)	10	150-unit ampoule of gonal-f = £52.50	With low dose Gonalf: £120 + £525 (Gonal-f) = £645
	5 days of gonadotrophin and then 5 days of gonadotrophin plus antagonist (total 10 days)			£24 x 5 days = £120	150–300 iu/day, depending on patient characteristics	starting on 1st day of cycle	150-unit vial of puregon = £54.43	With high dose Gonalf (or for 300 iu/day): £120 + £1050 = £1170
Agonists e.g. nafarelin (brand name Synarel®)	Long Nasal	200 micrograms in each nostril, twice a day	14 days (minimum duration) to 21 days (maximum duration)	200 micrograms per metered spray. Net price 30-dose unit = £32.28; 60-dose unit = £55.66	1500–3000 iu total	10	At 150 iu/day: £52.50 x 10 days = £525 for gonalf	With low dose Puregon: £120 + £544.30 (Puregon) = £664.30
	Start agonist on 21st day of cycle for 2–3 weeks, then 10 days of gonadotrophin plus agonist (total 24–31 days)	= 800 micrograms per day	plus 10 days while on gonadotrophin	= £87.94 for 90 doses	or 150–300 iu/day		At 300 iu/day (high dose): 2 x 150 units per day x 10 days = £1050 (rounded to nearest £10)	With high dose Puregon: £120 + £1090 = 1210
			= 96 doses (minimum duration)					Range: £645–1170
			= 124 doses (maximum duration)					Minimum duration of agonist, high dose of gonadotrophin: £88 + 1050 = £1138
								Maximum duration of agonist, high dose of gonadotrophin: £111 + £1050 = £1162
								Minimum duration, low dose gonadotrophin: £88 + £535 (mean cost) = £623
								Maximum duration agonist, high dose of gonadotrophin: £111 + £535 = £646
								Range: £623–1138

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A version of this guideline for people with fertility problems, their partners and the public, called Assessment and treatment for people with fertility problems: understanding NICE guidance – information for people with fertility problems, their partners and the public, is also available (reproduced as Appendix A in this version). It can be downloaded from the NICE website ([www.nice.org.uk](http://www.nice.org.uk)) or ordered from the NHS Response Line (0870 155455); quote reference number N0466 for an English version and N0467 for an English and Welsh version.

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