Fertility: assessment and treatment for people with fertility problems

Appendices A – O

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

Commissioned by the National Institute for Health and Clinical Excellence

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This guideline has been fully funded by NICE. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient.

Implementation of this guidance is the responsibility of local commissioners and/or providers

Contents

Appendix A Scope

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

SCOPE

1 Guideline title

Fertility: assessment and management (update)

1.1 Short title

Fertility

2 The remit

This is an update of 'Fertility'', NICE clinical guideline 11 (2004), available from www.nice.org.uk/guidance/CG11. See section 4.3.1 for details of which sections will be updated.

3 Clinical need for the guideline

3.1 Epidemiology

a) Infertility can be primary, in people who have never conceived, or secondary, in people who have previously conceived. It is estimated that infertility affects one in six heterosexual 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 population per year. It appears that whilst there has been a small increase in the prevalence fertility problems since the original guideline even more people now seek help for such problems than in the past. Since the publication of the 2004 guideline more NHS funding has been made available for fertility services.

b) The causes of primary infertility in the UK occur in the following approximate proportions:

- unexplained infertility (no identified male or female cause), 25%
- ovulatory disorders, 20%
- tubal damage, 15%
- factors in the male causing infertility, 30%
- uterine or peritoneal, 10%.

In about one third of cases disorders are found in both the man and the woman. Other factors may play a role, including uterine or endometrial factors, gamete or embryo defects, and any other pelvic condition such as endometriosis.

c) Making a diagnosis serves two purposes. By identifying the cause(s) of the problem it allows appropriate options for treatment to be discussed. It also provides infertile people with a prognosis. For infertility, the situation has changed with the introduction of assisted reproduction: in vitro fertilisation (IVF) treatment has become the ultimate treatment modality for all types of infertility. About 1.5% of babies born in the UK were conceived using assisted reproduction (see section 3.2 f).

3.2 Current practice

a) Infertility affects approximately 17% of heterosexual couples. Its psychological impact can be severe in some cases.

b) For heterosexual couples having unprotected regular intercourse, failure to conceive after 12 months is commonly taken as an indication for further assessment. Within that time about 85% of couples will conceive spontaneously. For non-heterosexuals where conception is being attempted using methods of donor insemination, and in the absence of any known cause of infertility, the majority of successful conceptions will have occurred within 6 cycles. Failure to conceive after that period is commonly taken as an indication for further assessment.

c) NHS funding for investigation of infertility is generally available but there is wide variation and often limited access to NHS-funded treatment, particularly assisted reproduction techniques. Generally the management can be shared, at least in the early stages of investigation, between the GP and hospital-based specialist services.

d) The provision of effective and appropriate investigations for men and women is critical to the operation of an infertility service. These investigations include semen analysis, assessing ovulation, assessing tubal damage, assessing uterine abnormalities and screening for infections such as Chlamydia trachomatis and susceptibility to rubella.

e) There are three main types of infertility treatment:

- medical treatment (for example, use of drugs for ovulation induction)
- surgical treatment (for example, laparoscopy for ablation of endometriosis)
- assisted reproduction techniques.

f) Assisted reproduction includes all treatments that deal with means of conception other than normal coitus. It frequently involves the handling of gametes or embryos. The existing NICE clinical guideline on fertility, published in 2004, provided a comprehensive coverage of the subject and allowed for a more evidence-based approach to investigation and management of infertility. However, its implementation has been variable.

g) The aim of this update is to revise recommendations on the topics listed in section 4.3.1 below in the light of new evidence and make recommendations in areas where there is important new evidence.

4 The guideline

The guideline development process is described in detail on the NICE website (see section 6, ‘Further information’).

This scope defines what the guideline will (and will not) examine, and what the guideline developers will consider. The scope is based on the referral from the Department of Health.

The areas that will be addressed by the guideline are described in the following sections.

4.1 Population

4.1.1 Groups that will be covered

a) People with explained or unexplained infertility.

b) Some specific patient subgroups that may need specific consideration in their treatment or care have been identified. These include:

- people in same-sex relationships who have unexplained infertility after donor insemination;

- people who are unable to, or would find it very difficult to, or who have been advised not to have heterosexual intercourse;

- people with conditions or disabilities that require specific consideration in relation to methods of conception.

c) People who are preparing for cancer treatment who may wish to preserve their fertility.

4.2 Healthcare setting

All settings in which care is funded by the NHS.

4.3 Clinical management

4.3.1 Key clinical issues that will be covered

a) Tests for ovarian reserve.

b) Multifactorial prediction of success to determine clinical and cost effectiveness criteria for IVF treatment.

c) Effectiveness of different embryo/blastocyst transfer strategies as part of IVF treatment - number of embryos.

d) Effectiveness of different embryo/blastocyst transfer strategies as part of IVF treatment - timing of transfer.

e) Effectiveness of ovulation induction agents used in treatment programmes for infertility.

f) Effectiveness of intrauterine insemination, with or without ovulation induction agents.

g) Effectiveness of mild versus conventional IVF treatment.

h) Cryopreservation and vitrification.

i) Sperm washing.

j) Cross-references to related guidance (including the World Health Organization reference values for semen analysis and the Human Fertility and Embryology Authority code of practice) will also be updated.

4.3.2 Clinical issues that will not be covered

a) Multiple or recurrent miscarriage.

b) Surrogacy.

4.4 Main outcomes

a) Live full-term singleton birth.

b) Patient satisfaction.

c) Anxiety and/or depression.

d) Multiple births.

e) Fetal abnormalities.

f) Adverse pregnancy outcome (ectopic pregnancy, miscarriage, fetal growth restriction, spontaneous preterm delivery, perinatal death, pre-eclampsia, and gestational diabetes).

g) Ovarian hyperstimulation syndrome (OHSS).

h) Long-term effects on the woman of ovulation induction.

i) Long-term effects on children born as a result of assisted reproduction techniques.

j) Health-related quality of life – restricted to people seeking treatment for infertility.

4.5 Economic aspects

Developers will take into account both clinical and cost effectiveness when making recommendations involving a choice between alternative interventions. A review of the economic evidence will be conducted and analyses will be carried out as appropriate. The preferred unit of effectiveness for NICE guidelines is the quality-adjusted life year (QALY), and the costs considered will usually be only from an NHS and personal social services (PSS) perspective. Further detail on the methods can be found in 'The guidelines manual' (see ‘Further information’).

In the case of fertility treatment, QALYs may be less suitable. A baby who might be conceived as a result of IVF will experience no loss in health-related quality of life if treatment is not offered. For couples, the psychological distress of ongoing infertility could be considered within a QALY framework but this would not be straightforward and data to inform this may be lacking.

4.6 Status

4.6.1 Scope

This is the final scope.

4.6.2 Timing

The development of the guideline recommendations will begin in October 2010.

5 Related NICE guidance

5.1 Published guidance

5.1.1 NICE guidance to be partially updated

This guideline will update and replace parts of the following NICE guidance:

Fertility. NICE clinical guideline 11 (2004). Available from www.nice.org.uk/guidance/CG11.

5.1.2 Other related NICE guidance

- Weight management before, during and after pregnancy. NICE public health guidance 27 (2010). Available from www.nice.org.uk/guidance/PH27.
- Quitting smoking in pregnancy and following childbirth. NICE public health guidance 26 (2010). Available from www.nice.org.uk/guidance/PH26.
- Maternal and child nutrition. NICE public health guidance 11 (2008). Available from www.nice.org.uk/guidance/PH11.
- Antenatal care. NICE clinical guideline 62 (2003). Available from www.nice.org.uk/guidance/CG62.

5.2 Guidance under development

NICE is currently developing the following related guidance (details available from the NICE website):

- Multiple pregnancy. NICE clinical guideline. Publication expected September 2011.
- Pain and bleeding in early pregnancy. NICE clinical guideline. Publication expected November 2012.

6 Further information

Information on the guideline development process is provided in:

- ‘How NICE clinical guidelines are developed: an overview for stakeholders the public and the NHS’

‘The guidelines manual’.

These are available from the NICE website (www.nice.org.uk/GuidelinesManual). Information on the progress of the guideline will also be available from the NICE website (www.nice.org.uk).

Appendix B Stakeholders

A Little Wish
Abbott Laboratories
Association of Biomedical Andrologists
Association of British Healthcare Industries
Association of Clinical Embryologists
Association of Clinical Pathologists
Barnsley Hospital NHS Foundation Trust
Barts and The London Centre for Reproductive Medicine
Beckman Coulter
Birmingham Infertility Forum
Bradford District Care Trust
British Acupuncture Council
British Association for Counselling and Psychotherapy
British Association for Sexual Health and HIV
British Association of Urological Surgeons
British Dietetic Association
British Fertility Society
British Medical Association
British Medical Journal
British National Formulary
British Psychological Society
British Society for Human Genetics
British Society for Paediatric Endocrinology and Diabetes
BSEC
Cambridge Temperature Concepts Ltd
Cambridge University Hospitals NHS Foundation Trust
Camden Link
Cardiff and Vale University Health Board
Cardiff University
CARE Fertility
Care Quality Commission (CQC)
Central & North West London NHS Foundation Trust
Central London Community Healthcare
Chesterfield Royal Hospital NHS Foundation Trust

Christian Medical Fellowship
CIS' ters
Cleft Lip and Palate Association
Cochrane Menstrual Disorders and Subfertility Group
Coeliac UK
Commission for Social Care Inspection
Cook Medical Inc.
Daisy Network
Department for Communities and Local Government
Department of Health
Department of Health, Social Services and Public Safety - Northern Ireland
Dorset Primary Care Trust
Downs Syndrome Research Foundation
Equality and Human Rights Commission
Faculty of Public Health
Faculty of Sexual and Reproductive Healthcare
Ferring Pharmaceuticals
Fertility Friends
Fibroid Network Charity
George Eliot Hospital NHS Trust
Gloucestershire Hospitals NHS Foundation Trust
Gloucestershire LINk
Great Western Hospitals NHS Foundation Trust
Greater Manchester and Cheshire Cancer Network
Hayward Medical Communications
Health Protection Agency
Health Quality Improvement Partnership
Healthcare Improvement Scotland
Hologic Inc.
Human Fertilisation Embryology Authority
Infertility Network UK
Innermost Secrets Ltd
Institute for Womens Health
Institute of Biomedical Science
iQudos
IVF Hammersmith
IVF Wales
KCARE
King's College Hospital - Weston Education Centre

Lambeth Community Health
Lancashire Care NHS Foundation Trust
Leeds Primary Care Trust (aka NHS Leeds)
Lincolnshire Teaching Primary Care Trust
Liverpool Community Health
Liverpool Primary Care Trust
Liverpool Women's NHS Foundation Trust
Lothian University Hospitals Trust
Luton and Dunstable Hospital NHS Trust
Maternity Action
Maternity Services Action Group
Medicines and Healthcare products Regulatory Agency
Merck Serono
Merck Sharp & Dohme UK Ltd
Mid and West Regional Maternity Service Liasion Committee
Midwives Information and Resource Service
Ministry of Defence
MRC Clinical Trials Unit
Multiple Births Foundation
National Clinical Guideline Centre
National Collaborating Centre for Cancer
National Collaborating Centre for Mental Health
National Infertility Awareness Campaign
National Institute for Health Research - Health Technology Assessment Programme
National Obesity Forum
National Patient Safety Agency
National Pharmacy Association
National Public Health Service for Wales
National Treatment Agency for Substance Misuse
NHS Bournemouth and Poole
NHS Clinical Knowledge Summaries
NHS Connecting for Health
NHS Darlington
NHS Direct
NHS Fetal Anomaly Screening Programme
NHS Forth Valley
NHS Plus
NHS Sefton
NHS Sheffield

NHS Warwickshire Primary Care Trust
NHS Worcestershire
NICE - CPHE
NICE - IMPLEMENTATION CONSULTANT Region - East
NICE - IMPLEMENTATION CO-ORDINATION for info
NICE - PPIP
NICE - R&D for info
NICE - Technical Appraisals
North Tees and Hartlepool NHS Foundation Trust
North West London Perinatal Network
Nottingham City Hospital
Nuture Antenatal
Obstetric Anaesthetists' Association
Oxfordshire Primary Care Trust
Patients Watchdog
Pelvic Pain Support Network
PERIGON Healthcare Ltd
Pfizer
Press for Change
Progress Educational Trust
Public Health Wales NHS Trust
Queen's University Belfast
RAF Families Federation
Randox Laboratories
Royal Berkshire NHS Foundation Trust
Royal College of Anaesthetists
Royal College of General Practitioners
Royal College of General Practitioners in 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 Paediatrics and Child Health - Gastroenterology, Hepatology and Nutrition
Royal College of Pathologists
Royal College of Physicians
Royal College of Psychiatrists
Royal College of Psychiatrists in Scotland
Royal College of Radiologists
Royal College of Surgeons of England

Royal Cornwall Hospitals NHS Trust
Royal Pharmaceutical Society
Royal Society of Medicine
Royal Surrey County Hospital NHS Trust
Sandwell Primary Care Trust
Schering-Plough Ltd
Scottish Intercollegiate Guidelines Network
Sheffield Teaching Hospitals NHS Foundation Trust
Sickle Cell Society
Social Care Institute for Excellence
Society and College of Radiographers
Society for Endocrinology
Solent Healthcare
South Asian Health Foundation
South Devon Healthcare NHS Foundation Trust
Southampton University Hospitals Trust
Southern Health & Social Care Trust
SPD Swiss Precision Diagnostics GmbH
Stockport Primary Care Trust
Teenage Cancer Trust
Teenagers and Young Adults with Cancer
The Association for Clinical Biochemistry
The British In Vitro Diagnostics Association
The Rotherham NHS Foundation Trust
The University of Glamorgan
Twins and Multiple Births Association
UK Clinical Pharmacy Association
United Chiropractic Association
United Lincolnshire Hospitals NHS
VBAC Information and Support
Verity
Welsh Government
Welsh Scientific Advisory Committee
West Hertfordshire Primary Care Trust
Western Cheshire Primary Care Trust
Western Health and Social Care Trust
Wirral University Teaching Hospital NHS Foundation Trust
Women's Health Partnership
York Hospitals NHS Foundation Trust

Yorkshire & The Humber Specialised Commissioning Group

Appendix C Declarations of interest

All GDG members' interests were recorded on declaration forms provided by NICE. The form covered consultancies, fee-paid work, shareholdings, fellowships and support from the healthcare industry. GDG members' interests are listed in this section.

Table C.1 GDG members' declarations of interest

GDG member	Interest
Tom Treasure	None
Susan Bewley	Co-editor of RCOG study group on reproductive ageing
	Published editorial to the BMJ on "Maternal mortality paradoxes" regarding a paper in Human Reproduction showing high MMR in IVF
	Invited to speak at a conference in December 2011
	Written a letter on PCOS medicine and has published commentary on RBM online
	Undertook consultancy for RAND Corporation regarding fertility regulation across Europe (2009)
Siladitya Bhattacharya	Department received financial support from producing infertility related products
	BMJ publication on the outcomes of single vs double embryo transfer
	Accommodation and travel supported to attend an international conference (May 2011)
	Submitted a letter to the New England Journal of Medicine on family planning
	Departmental support for seminars from Merck Serono and Ferring
	Member of PIGO reproductive medicine council which has received funding from Merck Serono
	Editor for Cochrane and Human Reproduction update
	Sitting on the WHO fertility group as a technical advisor and is editing a book for the RCOG on fertility
	Attended a conference and meeting supported by pharmaceutical industries (Jan 2012)
Kate Brian	Author of four non-fiction books on fertility and IVF
	Received travelling expenses for attending a one-day conference sponsored by Merck Serono
	Member of staff at Infertility Network UK

GDG member	Interest
Tim Child	Received lunch and car transfers at an event in Geneva hosted by a pharmaceutical company
	Received accommodation and registration as a speaker in Canada, provided by the organisation committee.
	Received an educational grant from a pharmaceutical company that produces gonadotrophins
Melanie Davies	Present at a departmental meeting with pharma representatives
	Clinical advisor to HFEA
Stephen Harbottle	Sponsored by Research Instruments Ltd as an invited speaker at a conference in Taiwan, in Jan 2011
	Sponsored to attend a number of speaking engagements in Malaysia and Cuba
	Invited to speak at the ACG winter meeting, sponsored by ACG
	Offered funding from two companies to attend ESHRS 2011
	Lectured in IVF to junior doctors in Bury St Edmonds, in a role for Cambridge NHS Trust
	Involved in the review of the Association of Biomedical Andrologists (ABA) guidelines for good practice
	Appointed as the chair of the NEQAS Embryo Assurance Scheme
	Invited to speak at the Jordanian society of reproductive medicine in March 2012 about electronic procedure witnessing, funded by Research Instruments
Helen Kendrew	Invited to sit on the organising committee for a conference and will be receiving travelling expenses in respect of this (March 2011)
	Refrigerator purchased by Ferring for her fertility centre
	Received a bursary and expenses for a workshop held in Stockholm
	ESHRE member and sat on steering committee where her travel and expenses were paid for by Merck Serono
	Trustee at BFS
	Trustee at the INUK
	Member of steering committee for “INSIGHTS” – organised by Merck Serono
Clare Lewis-Jones	Presented at the Fertility Show on NHS funding for IVF treatment
	Chair of Infertility Network UK
Clare Searle	Part of a team that approved the fertility guideline for the Hertfordshire area
Peter Taylor	Spoken at a number of events to managers of various pharmaceutical companies
	Attended pharmaceutical-funded independent consulting group discussing fertility.
	Joined NIAC, hosted by INUK

Table C.2 NCC staff members’ declarations of interest

NCC-WCH staff	Interest
All staff	None declared

Table C.3 External advisors' declarations of interest

External advisor	Interest
Allan Pacey	Carried out paid consultancy for Merck Serono
	Ongoing consultancies with University College London Hospitals NHS Foundation Trust in connection with its andrology laboratory
	Ongoing medico-legal work with Beachcroft LLP
	Ongoing research income from Research Councils, charities and donations
	Has regularly made statements to press about a variety of fertility issues
	Involved in the production of two television programmes
David Hawkins	None declared
Debbie Lawlor	None declared
Scott Nelson	Received honorarium and travel awards from Merck Serono, Ferring and Roche Diagnostics for lectures and participation in Advisory Boards
	Grants from the Wellcome Trust, MRC, Chief Scientist Office and the Cross Research Councils Fund
	Glasgow University has a contractual agreement with GCRM Ltd for the provision of medical services related to assisted conception. Glasgow University also has a self-funded assisted conception service. The income from both of these contracts is used to fund research

Table C.4 Peer reviewers' declarations of interest

Peer reviewer	Interest
Adam Balen	Research grants, consultancy fees and lecture fees received in the last five years from Ferring Pharmaceuticals, Merck Serono, Organon and Preglem
Rachel Cutting	None declared
Joanne Lord	None declared
Antony Rutherford	Occasional Advisory Board Member for Ferring UK

Appendix D Review protocols

Chapter 6. Investigation of fertility problems and management strategies

Fertility (Update) Review Protocol – Tests for ovarian reserve

	Details	Additional comments
Review question	How accurate are tests of ovarian reserve in predicting pregnancy and its outcomes for women with infertility undergoing ovulation induction or ovarian stimulation treatment assisted reproduction (including unexplained infertility and IVF)	
Objectives	To determine the accuracy of measures of ovarian reserve in predicting pregnancy rates and outcomes in women undergoing treatment for infertility.	
Language	English	
Study design	Predictive accuracy studies evaluating clinical outcomes: randomised controlled trials (RCTs) cohort studies case–control studies	The proposed methodological approach is to identify those predictors which give a high accuracy using an area under the curve method to report the predictive accuracy of those tests meeting the criteria for part 1
Status	Published papers	
Population	Infertile women undergoing ovulation induction, ovarian stimulation, or assisted reproduction (including IVF treatment)	
Intervention	Measurement of:	

	Details	Additional comments
	basal follicle stimulating hormone (FSH)	
	clomifene citrate challenge	
	gonadotrophin-releasing hormone (GnRH) agonist stimulation	
	basal estradiol (E2)	
	inhibin B	
	anti-Mullerian hormone (AMH)	
	ultrasound antral follicle count (AFC)	
	ultrasound ovarian volume	
	ovarian blood flow	
	combinations of the above measures	
	confounders including age, BMI, prescreening of patients	
Comparator or reference standard	NA	As we are proceeding with predictive accuracy the 'disease' 'no disease' columns will be outcomes as below and 'test positive' and 'test negative' rows will be the cut-offs specified in the tests.
Outcomes	Live birth	
	Clinical pregnancy	
	Low response to ovarian stimulation/ovulation induction	
	High response to ovarian stimulation/ovulation induction	
	Cycle cancellation rates	
Other criteria for inclusion/ exclusion of studies	Exclude non-human studies	
Search strategies	Searches to cover all terms mentioned under population, intervention and comparator	

	Details	Additional comments
Review strategies	Evidence will be assessed for quality according to the process described in the NICE guidelines manual (January 2009) A list of excluded studies will be provided following weeding Evidence tables and an evidence profile will be used to summarise the evidence	
Equality	Equalities issues will be assessed according to the processes described in the NICE guidelines manual (January 2009) and the NICE equality scheme and action plan (2010 – 2013)	

Fertility (Update) Review Protocol – Sperm washing and viral transmission.

	Details	Additional comments
Review question	What is the effectiveness and safety of different interventions (including sperm washing) to reduce the risk of viral transmission from the male to the female in couples who are trying to conceive?	Incorporates sperm preparation
Objectives	To determine the effectiveness and safety of interventions including sperm washing for men who are positive to HIV, hepatitis B, and hepatitis C in couples who are trying to conceive To include consideration of: the risk of hepatitis C transmission during normal sexual intercoursethe role of interventions other than sperm washing (eg medical treatment of HIV in male partner, vaccination of female partner with HBV male partner) esting sperm before use in IUI, IVF or ICSI (emphasising that sperm washing is a risk-reduction strategy, not a risk-elimination strategy) association between sperm washing and ICSI (rather than conventional IVF)	Effectiveness will focus on the outcome of the interventions and subsequent attempts at conception using normal intercourse, IUI, IVF and ICSI. Safety will focus on transmission of the viral infection to the woman or child The NICE antenatal care guideline addresses screening for such viruses, and prevention of mother-to-child transmission where effective interventions exist
Language	English	
Study design	Randomised controlled trials (RCTs) Cohort studies	There are unlikely to be any RCTs comparing IUI, IVF or ICSI with and without sperm washing because of

	Details	Additional comments
	Case–control studies	the risk of viral transmission with unwashed sperm
	Case series	Evaluation of effectiveness and safety is likely to focus on observational studies (cohort studies and case-control studies) GDG to consider including case series if there are very few controlled/comparative studies for effectiveness or safety
Status	Published papers	
Population	Women who are trying to conceive with male partners who are positive for HIV, hepatitis B, or hepatitis C	
Intervention	IUI, IVF or ICSI using washed sperm, other interventions to reduce viral load in male partner and normal sexual intercourse (especially HIV)	
Comparisons	Head-to-head comparisons of any of the interventions listed above Comparison with spontaneous conception (natural sexual intercourse)	There may be no comparative studies involving spontaneous conception because of the risk of viral transmission with unwashed sperm
Outcomes	Viral transmission rates - to woman or child Post-wash testing Live singleton birth Pre-term birth Multiple pregnancies resulting in live birth Clinical pregnancy rate Adverse pregnancy outcomes (ncluding miscarriages, ectopic pregnancies, intrauterine deaths, fetal abnormalities)	GDG to consider outcome categories in scope and prioritise up to 7 for consideration in this question
Other criteria for inclusion/ exclusion of studies	Exclude non-human studies	

	Details	Additional comments
Search strategies	Searches to cover all terms mentioned under population, intervention and comparator	GDG to list any specific terms to be included in searches for this question, and to provide bibliographic details of key papers that they expect to be identified in the search
Review strategies	Evidence will be assessed for quality according to the process described in the NICE guidelines manual (January 2009) A list of excluded studies will be provided following weeding Evidence tables and an evidence profile will be used to summarise the evidence	
Equality	The 2004 guidance included advice for people with special considerations around fertility such as HIV. The updated scope explicitly extends the population to include those with Hepatitis B&C: “People with conditions that require specific consideration in relation to methods of conception, such as HIV, hepatitis B, hepatitis C, and treatment for cancer.” In the case of infectious diseases it is not a question of infertility but methods to prevent virus transmission both to the partner and potential offspring (such as sperm washing) for which there is no existing NICE guidance. We are aware of our obligation to make sure any discussion in the GDG or ensuing guidance, seeks to redress the effects of these conditions.	

Chapter 8. Ovulation Disorders

Fertility (Update) Review Protocol – Question 4B – Group I WHO women

	Details	GDG comments
Review question	What is the effectiveness and safety of ovulation induction strategies in women with WHO Group I Ovulation Disorders?	To update section 7.1, 7.2, 7.4, 7.6, 7.8, 7.9, 7.11 and 7.12 of the 2004 guideline.
Objectives	To determine the effectiveness and short term adverse events associated with agents used for women with WHO Group I Ovulation Disorders	
Language	English	
Study design	Randomised controlled trials (RCTs) Cohort studies Case–control studies	Note: Evaluation of effectiveness will be restricted to published systematic reviews of RCTs and other RCTs Published systematic reviews may be 'unpicked' to identify individual studies for inclusion in meta-analyses undertaken as part of guideline development Evaluation of safety/outcome is likely to include studies other than RCTs
Status	Published papers	
Population	Anovulatory women: WHO Classification of Ovulation Disorders Group I Subgroup to include High BMI (>/=30) Low BMI (<18)	Also known as hypothalamic amenorrhoea or hypogonadotrophic hypogonadism Papers using mixed sample will be discussed with topic group members case by case.
Intervention	WHO Group 1 treatments to achieve ovulation induction: Drugs Gonadotrophins (uFSH or rFSH, human menopausal gonadotrophin [hMG] and luteinising hormone [LH]) gonadotrophinsPulsatile GnRH ('GnRH Pump') GnRH analogues (agonists and antagonists) + gonadotrophins and dopamine	Paper using combinations of induction agents will be discussed with the topic group case by case. Discussion at GDG about the impact of taking time for losing or gaining weight and taking time which brings in an age threshold.

	Details	GDG comments
	agonists (cabergoline and bromocriptine)	
	Aromatase inhibitors	
	Lifestyle interventions	
	e.g. adjusting weight, appropriate exercise exercise	
Comparisons	Comparator for drug (TBC)	Document confounders such as BMI and age in the studies.
	Any drug on the above intervention list for WHO Group 1	
	Comparator for Lifestyle Intervention	
	Any other lifestyle intervention	
	Any drug from WHO Group 1 list above	
	Placebo	
	No treatment	
	Expectant management	
Outcomes	Live birth.	
	Clinical pregnancy	
	Adverse pregnancy outcome	
	Multiple births	
	Ovarian hyperstimulation syndrome (OHSS)	
	Congenital abnormalities	
	Patient satisfaction	
	Health-related quality of life – restricted to people seeking treatment for infertility.	
	Anxiety and/or depression.	

	Details	GDG comments
Other criteria for inclusion/ exclusion of studies	Exclude non-human studies	
Search strategies	Searches to cover all terms mentioned under population, intervention and comparator	
Review strategies	Evidence will be assessed for quality according to the process described in the NICE guidelines manual (January 2009) A list of excluded studies will be provided following weeding Evidence tables and an evidence profile will be used to summarise the evidence	
Equality	Equalities issues will be assessed according to the processes described in the NICE guidelines manual (January 2009) and the NICE equality scheme and action plan (2010 – 2013)	Note for NCC: any specific equalities considerations to add from Equalities Impact Assessment?

Fertility (Update) Review Protocol – Question 4C - Group II WHO women

	Details	GDG comments
Review question	What is the effectiveness and safety of ovulation induction strategies in women with WHO Group II Ovulation Disorders?	To update section 7.1, 7.2, 7.4, 7.6, 7.8, 7.9, 7.11 and 7.12 of the 2004 guideline.
Objectives	To determine the effectiveness and short term adverse events associated with agents used for women with WHO Group II Ovulation Disorders	
Language	English	
Study design	Randomised controlled trials (RCTs) Cohort studies Case–control studies	Note: Evaluation of effectiveness will be restricted to published systematic reviews of RCTs and other RCTs Published systematic reviews may be 'unpicked' to identify individual studies for inclusion in meta-analyses undertaken as part of guideline development

	Details	GDG comments
		Evaluation of safety/outcome is likely to include studies other than RCTs
Status	Published papers	
Population	Anovulatory women: WHO Classification of Ovulation Disorders Group 2: Subgroups to include Poor response to clomiphene (Clomiphene-resistant PCOS) High BMI Low BMI	Also known as hypothalamic pituitary dysfunction and includes PCOS. Papers using mixed sample will be discussed with topic group members case by case.
Intervention	WHO Group 2 treatments to achieve ovulation induction: Drugs: clomifene metformin gonadotrophins (uFSH or rFSH, human menopausal gonadotrophin [hMG] and luteinising hormone [LH]) GnRH analogues (agonists and antagonists) + gonadotrophins dopamine agonists (cabergoline and bromocriptine) aromatase inhibitors Surgery Lifestyle interventions e.g. adjusting weight, appropriate exercise Other strategies No treatment Expectant management	Paper using combinations of induction agents will be discussed with the topic group case by case. Note for NCC team: need to remember cost of monitoring which has to be undertaken alongside the treatment.

	Details	GDG comments
Comparisons	Comparator for ovulation induction drugs: anti-oestrogens (clomiphene citrate or tamoxifen) Placebo No treatment Expectant management Comparator for ovarian surgery: Ovarian surgery (drilling/electrocautery/diathermy) Comparator for Lifestyle Intervention Any other lifestyle intervention Any drug from WHO Group 2 list above and clomiphene/tamoxifen Placebo No treatment Expectant management Any ovarian surgery	Document any bias such as BMI and age in the studies in RCT studies Document any confounders such as BMI and age in the studies in non-randomised studies
Outcomes	Live full-term singleton birth. Clinical pregnancy Adverse pregnancy outcomes Multiple births Ovarian hyperstimulation syndrome (OHSS) Fetal abnormalities Patient satisfaction Health-related quality of life – restricted to people seeking treatment for infertility. Anxiety and/or depression.	

	Details	GDG comments
Other criteria for inclusion/ exclusion of studies	Exclude non-human studies	
Search strategies	Searches to cover all terms mentioned under population, intervention and comparator	
Review strategies	Evidence will be assessed for quality according to the process described in the NICE guidelines manual (January 2009) A list of excluded studies will be provided following weeding Evidence tables and an evidence profile will be used to summarise the evidence	
Equality	Equalities issues will be assessed according to the processes described in the NICE guidelines manual (January 2009) and the NICE equality scheme and action plan (2010 – 2013)	Note for NCC: any specific equalities considerations to add from Equalities Impact Assessment?

Chapter 12. Intrauterine insemination

Fertility (Update) Review Protocol – IUI

	Details	Additional comments
Review question	What is the effectiveness of intrauterine insemination (IUI)?	To update Section 10.2 of the full guideline (IUI for unexplained infertility; pp 75-76), Section 10.6 (cost effectiveness of stimulated versus unstimulated IUI; pp78-79) and Section 10.7 (cost effectiveness of different ovulation induction drug regimens in IUI; pp79-80), and the corresponding part of the unnumbered section at the start of Chapter 11 (p 83) Add in rationale of why not including other 2 groups
Objectives	To determine the effectiveness of IUI with and without ovarian stimulation, compared with expectant management in couples with unexplained infertility, mild male factor or endometriosis	
Language	English	
Study design	Randomised controlled trials (RCTs)	Evaluation of effectiveness will be restricted to published systematic reviews of RCTs and other RCTs Published systematic reviews may be 'unpicked' to identify individual studies for inclusion in meta-analyses undertaken as part of guideline development
Status	Published papers	
Population	People with unexplained infertility, mild male factor or endometriosis.	
Intervention	Unstimulated single IUI (no ovulation induction agents used)	The recommendation in the original guideline was for IUI without ovarian stimulation (because the latter was associated with a higher multiple pregnancy rate)
Comparisons	Expectant management Stimulated single IUI (ovulation induction agents used)	Timed intercourse not recommended so not used as a comparator.

	Details	Additional comments
Outcomes	1. Live full-term singleton birth 2. Clinical pregnancy rate 4. Adverse pregnancy outcome (including miscarriage, ectopic, stillbirth, preterm delivery) 5. Multiple births 6. Ovarian hyperstimulation syndrome 7. Fetal abnormalities 8. Patient outcomes: clinical symptoms, patient satisfaction, health-related quality of life 9. Anxiety and/or depression	Note for NCC Team: probably need to use the same outcome list as Q4D
Other criteria for inclusion/ exclusion of studies	Exclude non-human studies	
Search strategies	See separate document	
Review strategies	Evidence will be assessed for quality according to the process described in the NICE guidelines manual (January 2009) A list of excluded studies will be provided following weeding Evidence tables and an evidence profile will be used to summarise the evidence	
Equality	Equalities issues with be added once form signed off by NICE	

Chapter 11. Unexplained infertility

Fertility (Update) Review Protocol – Question 4A – unexplained infertility

	Details	GDG comments
Review question	What is the effectiveness of ovarian stimulation strategies in women with unexplained infertility?	To update section 7.1 and 7.12 of the 2004 guideline.
Objectives	To determine the effectiveness associated with ovarian stimulation agents used for women with unexplained infertility.	
Language	English	
Study design	Randomised controlled trials (RCTs)	Note: Evaluation of effectiveness will be restricted to published systematic reviews of RCTs and other RCTs Published systematic reviews may be 'unpicked' to identify individual studies for inclusion in meta-analyses undertaken as part of guideline development Evaluation of safety is likely to include studies other than RCTs
Status	Published papers	
Population	Women with unexplained infertility Subgroups to include • High BMI Age	Women who are infertile but are ovulating and whose partners have normal semen analysis and normal tubal patency Papers using mixed sample will be discussed with topic group members case by case.
Intervention	Ovarian stimulation drugs: anti-oestrogens (clomiphene citrate and tamoxifen - NB consider cost of monitoring) gonadotrophins (uFSH and rFSH, human menopausal gonadotrophin [hMG] and luteinising hormone [LH]) GnRH analogues (agonists and antagonists)	NOTE: There is a need to consider the cost of monitoring the response to the agent Looking at drugs alone, not in conjunction with IUI (question 5)

	Details	GDG comments
	Aromatase inhibitors	
	Combinations of these drugs	
	Placebo	
	No treatment.	
	Expectant management	
Comparisons	Clomiphene citrate.	Clomiphene citrate recommended in 2004 guidance
Outcomes	Live full-term singleton birth.	
	Clinical pregnancy	
	Adverse pregnancy outcome	
	Multiple births	
	Ovarian hyperstimulation syndrome (OHSS)	
	Fetal abnormalities	
	Patient satisfaction	
	Health-related quality of life – restricted to people seeking treatment for infertility.	
	Anxiety and/or depression.	
Other criteria for inclusion/ exclusion of studies	Exclude non-human studies	
Search strategies	Searches to cover all terms mentioned under population, intervention and comparator	
Review strategies	Evidence will be assessed for quality according to the process described in the NICE guidelines manual (January 2009)	
	A list of excluded studies will be provided following weeding	
	Evidence tables and an evidence profile will be used to summarise the evidence	

	Details	GDG comments
Equality	Equalities issues will be assessed according to the processes described in the NICE guidelines manual (January 2009) and the NICE equality scheme and action plan (2010 – 2013)	Note for NCC: any specific equalities considerations to add from Equalities Impact Assessment?

Chapter 14. Access criteria for IVF

Fertility (Update) Review Protocol – IVF prediction

	Details	Additional comments
Review question	How accurate are clinical scoring systems in predicting the outcome of IVF treatment?	To update Section 11.8 of the full guideline (clinical effectiveness and referral for IVF treatment; pp 96-97) Sections 11.2 (female age; pp 84-91), 11.4 (number of previous treatment cycles; pp93-95), 11.5 (pregnancy history; p 95), 11.6 (alcohol, smoking and caffeine consumption; p 95), and 11.7 (body weight; p96) to be removed if evidence is identified in relation to clinical scoring systems that can be used to specify referral criteria for IVF treatment; those sections would otherwise need to be updated as separate subquestions to allow Section 11.8 to be updated
Objectives	To determine the predictive accuracy of scoring systems (or prediction models) incorporating factors that may affect the outcome of IVF treatment (such as ovarian reserve, pregnancy history, number of previous treatment cycles, female age, consumption of alcohol and caffeine, smoking, and body mass index [BMI])	The preference would be to use evidence of ovarian reserve, rather than an indirect measure such as female age, to predict the outcome of IVF treatment. In practical terms given that the ovarian reserve tests have limitations, it may that the ideal predictive model will include socio-demographic, clinical AND ovarian reserve.
Language	English	
Study design	Prediction models	Study design needs further consideration since this is not a standard screening scenario (i.e. pregnancy with IVF treatment is not guaranteed, even if a scoring system predicts that pregnancy is achievable). Prognostic factors are of interest here too
Status	Published papers	
Population	People with infertility	

	Details	Additional comments
Intervention	Probability of success of IVF (pregnancy, live birth, etc) as a function of factors such as:	The factors listed are not exhaustive: scoring systems based on additional/other factors will be considered
	ovarian reserve pregnancy history number of previous treatment cycles	The preference would be to base recommendations on published scoring systems incorporating measures of ovarian reserve, rather than an indirect measures such as female age
	female age consumption of alcohol consumption of caffeine smoking BMI (low and high)	If no suitable (published) prediction models are available attempts may be made to model probabilities (requires further discussion)
	Other factors – partner factors (age, BMI, smoking, EtOH, caffeine), ethnicity, social class, cause of infertility	
	Technical issues – transfer policy,	
Reference standards	Models should be prospectively tested in a separate population.	
Outcomes	Diagnostic accuracy of model in predicting	GDG to prioritise outcomes for consideration
	clinical outcomes: 1. Live full-term singleton birth 2. Preterm delivery rate 3. Adverse pregnancy outcome 4. Multiple births 5. Ovarian hyperstimulation syndrome 6. Fetal abnormalities	Prioritisation of outcomes following GDG voting: Note for NCC team: probably should be the same list of outcomes as for Q4D Need to set a predictive threshold for each outcome (0.8 for AUC-ROC?)

	Details	Additional comments
Other criteria for inclusion/ exclusion of studies	Exclude non-human studies	
Search strategies	Published models predicting IVF success.	To be prepared once review questions finalised Scoping searches suggest 423 publications in Medline only for age, weight and smoking (to answer the overarching question and any subquestions that cannot be answered through evaluation of clinical scoring systems) No Medline estimate for fertility history Need to also include extraction of ovarian reserve data.
Review strategies	Evidence will be assessed for quality according to the process described in the NICE guidelines manual (January 2009) A list of excluded studies will be provided following weeding Evidence tables and an evidence profile will be used to summarise the evidence	
Equality	Maternal age is only one of a number of factors which are correlated with the likelihood of conceiving, Others include maternal BMI, smoking, previous fertility history and measures of ovarian reserve. We will ensure that any recommendations are not biased by age per se.	

Chapter 15. Procedures used during in vitro fertilisation treatment

Fertility (Update) Review Protocol – Question – IVF pre-treatment

	Details	GDG comments
Review question	What is the effectiveness of pre-treatment as part of an ovarian stimulation strategy for women undergoing IVF or ICSI treatment?	
Objectives	To determine the effectiveness and short term adverse events associated with the use of pre-treatment as part of an ovarian stimulation strategy for women undergoing IVF or ICSI treatment.	
Language	English	
Study design	Randomised controlled trials (RCTs) Cohort studies Case–control studies	
Status	Published papers	
Population	Women having IVF/ICSI	
Intervention	Women having IVF/ICSI having pre-treatment with either oral contraceptive pill progesterone estrogen	Paper using combinations of induction agents will be discussed with the topic group case by case. Note for NCC team: need to remember cost of monitoring which has to be undertaken alongside the treatment.
Comparisons	Two options will be compared with the above interventions no pre-treatment different agents/drugs used for pretreatment.	
Outcomes	Live full-term singleton birth. Clinical pregnancy Adverse pregnancy outcomes Multiple births Ovarian hyperstimulation syndrome (OHSS)	

	Details	GDG comments
	Fetal abnormalities	
	Patient satisfaction	
	Health-related quality of life – restricted to people seeking treatment for infertility.	
	Anxiety and/or depression.	
Other criteria for inclusion/ exclusion of studies	Exclude non-human studies	
Search strategies	Searches to cover all terms mentioned under population, intervention and comparator	
Review strategies	Evidence will be assessed for quality according to the process described in the NICE guidelines manual (January 2009)	
	A list of excluded studies will be provided following weeding	
	Evidence tables and an evidence profile will be used to summarise the evidence	
Equality	Equalities issues will be assessed according to the processes described in the NICE guidelines manual (January 2009) and the NICE equality scheme and action plan (2010 – 2013)	Note for NCC: any specific equalities considerations to add from Equalities Impact Assessment?

Fertility (Update) Review Protocol – IVF down regulation

	Details	GDG comments
Review question	What is the effectiveness of down regulation as part of an ovarian stimulation strategy for women undergoing IVF or ICSI treatment?	
Objectives	To determine the effectiveness and short term adverse events associated with down regulation as part of an ovarian stimulation strategy for women undergoing IVF or ICSI treatment**.**	
Language	English	

	Details	GDG comments
Study design	Randomised controlled trials (RCTs)	
	Cohort studies	
	Case–control studies	
Status	Published papers	
Population	Women having IVF/ICSI	
Intervention	No down regulation as part of the ovulation stimulation strategy	
Comparisons	Down regulation with the following (with and without clomifene)	
	GnRH agonists	
	GnRH antagonists	
	Antagonist vs agonist down regulation	
	Different types of down regulation protocol (including long, short, ultra-short and stop protocols)	
Outcomes	Live full-term singleton birth.	
	Clinical pregnancy	
	Adverse pregnancy outcomes	
	Multiple births	
	Ovarian hyperstimulation syndrome (OHSS)	
	Fetal abnormalities	
	Patient satisfaction	
	Health-related quality of life – restricted to people seeking treatment for infertility.	
	Anxiety and/or depression.	
Other criteria for inclusion/ exclusion of studies	Exclude non-human studies	

	Details	GDG comments
Search strategies	Searches to cover all terms mentioned under population, intervention and comparator	
Review strategies	Evidence will be assessed for quality according to the process described in the NICE guidelines manual (January 2009) A list of excluded studies will be provided following weeding Evidence tables and an evidence profile will be used to summarise the evidence	
Equality	Equalities issues will be assessed according to the processes described in the NICE guidelines manual (January 2009) and the NICE equality scheme and action plan (2010 – 2013)	Note for NCC: any specific equalities considerations to add from Equalities Impact Assessment?

Fertility (Update) Review Protocol – IVF ovarian induction

	Details	GDG comments
Review question	What is the effectiveness of different ovarian strategies as part of an ovarian stimulation protocol in women undergoing IVF or ICSI treatment.	
Objectives	To determine the effectiveness and short term adverse events associated with the following strategies as part of an ovarian stimulation protocol in women undergoing IVF or ICSI treatment: Stimulation with gonadotrophins, 'Milder' stimulation, Adjuvant growth hormone and DHEA treatment for women with a previous poor response	
Language	English	
Study design	Randomised controlled trials (RCTs) Cohort studies Case–control studies	

	Details	GDG comments
Status	Published papers	
Population	Women having IVF/ICSI	
Intervention	Stimulation with gonadoptrophins	
Comparisons	Unstimulated cycles	
	Comparison of different forms of gonadotrophins	
	Comparison of different dosages of gonadotrophins	
	'Milder' forms of ovarian stimulation	
	Adjuvant growth hormone and DHEA treatment for women with a previous poor response	
Outcomes	Live full-term singleton birth.	
	Clinical pregnancy	
	Adverse pregnancy outcomes	
	Multiple births	
	Ovarian hyperstimulation syndrome (OHSS)	
	Fetal abnormalities	
	Patient satisfaction	
	Health-related quality of life – restricted to people seeking treatment for infertility.	
	Anxiety and/or depression.	
Other criteria for inclusion/ exclusion of studies	Exclude non-human studies	
Search strategies	Searches to cover all terms mentioned under population, intervention and comparator	

	Details	GDG comments
Review strategies	Evidence will be assessed for quality according to the process described in the NICE guidelines manual (January 2009) A list of excluded studies will be provided following weeding Evidence tables and an evidence profile will be used to summarise the evidence	
Equality	Equalities issues will be assessed according to the processes described in the NICE guidelines manual (January 2009) and the NICE equality scheme and action plan (2010 – 2013)	Note for NCC: any specific equalities considerations to add from Equalities Impact Assessment?

Fertility (Update) Review Protocol – IVF Trigger

	Details	GDG comments
Review question	Which is the most effective ovulation trigger to use as part of an ovarian stimulation strategy for women undergoing IVF or ICSI treatment?	
Objectives	To determine the effectiveness and short term adverse events associated with ovulation triggers used as part of an ovarian stimulation strategy for women undergoing IVF or ICSI treatment.	
Language	English	
Study design	Randomised controlled trials (RCTs) Cohort studies Case–control studies	
Status	Published papers	
Population	Women having IVF/ICSI	
Intervention	Triggering with hCG	
Comparisons	Comparison of different forms of hCG GnRH agonist	

	Details	GDG comments
Outcomes	Live full-term singleton birth. Clinical pregnancy Adverse pregnancy outcomes Multiple births Ovarian hyperstimulation syndrome (OHSS) Fetal abnormalities Patient satisfaction Health-related quality of life – restricted to people seeking treatment for infertility. Anxiety and/or depression.	
Other criteria for inclusion/ exclusion of studies	Exclude non-human studies	
Search strategies	Searches to cover all terms mentioned under population, intervention and comparator	
Review strategies	Evidence will be assessed for quality according to the process described in the NICE guidelines manual (January 2009) A list of excluded studies will be provided following weeding Evidence tables and an evidence profile will be used to summarise the evidence	
Equality	Equalities issues will be assessed according to the processes described in the NICE guidelines manual (January 2009) and the NICE equality scheme and action plan (2010 – 2013)	Note for NCC: any specific equalities considerations to add from Equalities Impact Assessment?

Fertility (Update) Review Protocol – Embryo transfer

	Details	Additional comments
Review question	What is the effectiveness and safety of different embryotransfer strategies?	To update Section 11.3 of the full guideline (number of embryos to be transferred; pp 91-93) and the parts of Section 12.10 that relate to day 2-3 versus day 5-6 transfers (pp 112-114)
Objectives	To determine a, if one or two embryos should be transferred during IVF, and b. if transfer at day 2-3 ('cleavage') is better than at day 5-6 ('blactocyst') and c. if transfer of fresh embryos is more successful than frozen embryos, and d. if a strategy of transfer of a fresh single embryo, followed, if unsuccessful, by a further frozen single embryo is as successful as transfer of one double embryo	To be addressed after questions 4 and 5 (ovulation induction/stimulation and IUI) Consider recording whether 4-5 or 5-6 (possible subgroup analysis)
Language	English	
Study design	Randomised controlled trials (RCTs) Cohort studies Case–control studies National guidelines HFEA and other national databases	Evaluation of effectiveness for timing of transfer will be restricted to published systematic reviews of RCTs and other RCTs or large observational studies
Status	Published papers	
Population	People with infertility	
Intervention	Fresh studies: Single day 2-3 vs Double day 2-3 Single day 2-3 vs Single day 5-6 Double day 2-3 vs Double day 5-6 Single day 5-6 vs Double day 5-6	The interventions listed in relation to timing of transfer are not exhaustive: other transfer times will be considered, depending on the available evidence Consider subgroup analysis by fresh versus frozen cycle transfers Document in the studies past reproductive record,

	Details	Additional comments
	Frozen studies:	age, BMI etc.
	Single day 2-3 vs Double day 2-3	
	Single day 2-3 vs Single day 5-6	
	Double day 2-3 vs Double day 5-6	
	Single day 5-6 vs Double day 5-6	
	Cumulative studies:	
	Cumulative single/single vs double day 2-3	
	Cumulative single/single vs double day 5-6	
Comparisons		First compare to single transfers at different time periods, which of this is deemed to be most effective will then be compared to double on both time periods
Outcomes	1. Live birth rate per cycle	Prioritisation of outcomes:
	2. Multiple pregnancy rate per cycle	Consider reporting anxiety/depression under patient satisfaction
	3. Preterm delivery rate per cycle	'Report per cycle, per patient, per harvest'
	4. Adverse pregnancy outcome (miscarriage, ectopic)	Need to consider fresh vs frozen.(HMcG plans to compare fresh vs fresh)
	5. Clinical pregnancy rate per cycle	
	6. Long-term effects on children born	
	7. Fetal abnormalities	
Other criteria for inclusion/ exclusion of studies	Exclude non-human studies	
Search strategies	See separate document	To be prepared once review questions finalised
		Scoping searches suggest 1157 publications in Medline only for subquestion about how many embryos to be transferred and 444 for subquestion about timing of transfer.

	Details	Additional comments
Review strategies	Evidence will be assessed for quality according to the process described in the NICE guidelines manual (January 2009) A list of excluded studies will be provided following weeding Evidence tables and an evidence profile will be used to summarise the evidence	
Equality	We will ensure that any recommendations are not biased by age per se.	

Fertility (Update) Review Protocol – Question 4C – Luteal Phase support

	Details	GDG comments
Review question	What is the effectiveness of luteal phase support as part of an ovarian stimulation strategy for women undergoing IVF or ICSI treatment?	
Objectives	To determine the effectiveness and short term adverse events associated with different forms of conventional luteal phase support as part of an ovarian stimulation strategy for women undergoing IVF or ICSI treatment.	
Language	English	
Study design	Randomised controlled trials (RCTs) Cohort studies Case–control studies	Note: Evaluation of effectiveness will be restricted to published systematic reviews of RCTs and other RCTs Published systematic reviews may be 'unpicked' to identify individual studies for inclusion in meta-analyses undertaken as part of guideline development Evaluation of safety/outcome is likely to include studies other than RCTs
Status	Published papers	
Population	Women having IVF/ICSI	
Intervention	Progesterone	

	Details	GDG comments
Comparisons	No luteal phase support	
	Other agents/drugs (hCG, progesterone and hCG, progesterone and estrogen, progesterone and GnRH agonist, progesterone and LH)	
	Different duration of support	
Outcomes	Live full-term singleton birth.	
	Clinical pregnancy	
	Adverse pregnancy outcomes	
	Multiple births	
	Ovarian hyperstimulation syndrome (OHSS)	
	Fetal abnormalities	
	Patient satisfaction	
	Health-related quality of life – restricted to people seeking treatment for infertility.	
	Anxiety and/or depression.	
Other criteria for inclusion/ exclusion of studies	Exclude non-human studies	
Search strategies	Searches to cover all terms mentioned under population, intervention and comparator	
Review strategies	Evidence will be assessed for quality according to the process described in the NICE guidelines manual (January 2009)	
	A list of excluded studies will be provided following weeding	
	Evidence tables and an evidence profile will be used to summarise the evidence	
Equality	Equalities issues will be assessed according to the processes described in the NICE guidelines manual (January 2009) and the NICE equality scheme and action plan (2010 – 2013)	Note for NCC: any specific equalities considerations to add from Equalities Impact Assessment?

Chapter 19. People with cancer who wish to preserve fertility

Fertility (Update) Review Protocol – Cryopreservation

	Details	Additional comments
Review question	What is the effectiveness of cryopreservation (including vitrification) in fertility preservation strategies?	To update the parts of Chapter 16 (applications of cryopreservation in cancer treatment) that relate to cryopreservation of semen, embryos, oocytes and ovarian tissue Chapter 16 also includes counselling where cryopreservation is offered; the corresponding evidence and recommendations will not be updated Cryopreservation: The freezing and storage of embryos, sperm, eggs or ovarian tissue for future use in treatment. The technique of controlled-rate slow freezing is well established; vitrification is the term given to a newer form of crypreservation which involves an ultra-rapid freezing process. Cryopreservation is a process, Controlled Rate Freezing (CRF) and Vitrification are 2 discrete methods to facilitate that process
Objectives	To determine the effectiveness of cryopreservation (including vitrification) of semen, embryos, oocytes and ovarian tissue in people with cancer (those who may lose their fertility from their cancer treatment).	This question relates to people who are at risk of infertility from another treatment (including cancer patients) Note from Stephen: The freezing of semen opens another issue as traditionally this is done 'uncontrolled' suspended over a vat of liquid nitrogen vapour. Evidence comparing this technique to linear controlled rate freezing has demonstrated little difference in post thaw viability. Vitrification is only just being evaluated for use with sperm so there will be limited evidence on this topic for this update.
Language	English	

	Details	Additional comments
Study design	Randomised controlled trials (RCTs) Cohort studies Case–control studies	Evaluation of effectiveness of each intervention will be restricted to published systematic reviews of RCTs and other RCTs if there are sufficient studies Published systematic reviews may be 'unpicked' to identify individual studies for inclusion in meta-analyses undertaken as part of guideline development Evaluation of interventions under development is likely to include studies other than RCTs
Status	Published papers	
Population	People with cancer whose condition, or treatment for the condition, may result in reduced fertility or infertility	Population limited to cancer patients because this is the most likely indication for considering the process. Findings of the review can be extrapolated to other populations (see scope)
Intervention	Vitrification of: embryos blastocysts oocytes ovarian tissue	Maturity of oocytes may also be a factor to be considered
Comparator or reference standard	Conventional cryopreservation of: semen (observational studies only) embryos blastocysts oocytes ovarian tissue	

	Details	Additional comments
Outcomes	1. Live full-term singleton birth	Justify why by patient not by cycle for this question
	2. Clinical pregnancy rate	Outcomes to be refined based on what's in the papers
	3. Preterm delivery rate	
	4. Adverse pregnancy outcomes	
	5. Multiple births	
	6. Fetal abnormalities	
	7. Long-term effects on children born as a result of cryopreservation	
	8. Post-thaw viability and abnormal morphology	
Other criteria for inclusion/ exclusion of studies	Exclude non-human studies	
Search strategies	See separate document	To be prepared once review questions finalised
		Scoping searches (Medline only) 398 records.
Review strategies	Evidence will be assessed for quality according to the process described in the NICE guidelines manual (January 2009)	
	A list of excluded studies will be provided following weeding	
	Evidence tables and an evidence profile will be used to summarise the evidence	
Equality	Equalities issues will be detailed once form signed off by NICE	NCC tech team: need to add in

Chapter 20. Long-term safety of assisted reproduction treatments in women with infertility and their children

Fertility (Update) Review Protocol – Long term safety ovulation induction and ovarian stimulation

	Details	GDG comments
Review question	What is the long-term safety of ovulation induction and ovarian stimulation strategies in women with infertility and their children?	To update section 7.1 and 7.12 of the 2004 guideline.
Objectives	To determine the short and long-term adverse events (in the women and their children resulting from treatment) associated with ovulation induction and ovarian stimulation agents used for women with unexplained infertility, ovulatory failure (types 1&2) and those receiving IVF	Short-term adverse events to be summarised in 4a to 4d
Language	English	
Study design	Randomised controlled trials (RCTs) Cohort studies Case–control studies	Note: Evaluation of safety is likely to include both the RCT data for short term safety and Cohort studies will probably given more data for the longer term safety.
Status	Published papers	
Population	Women with unexplained infertility, ovulatory dysfunction (types 1&2) and those receiving IVF and their children	ICSI to be distinguished from 'conventional' IVF in case it has a separate/independent effect on children outcome
Intervention	Drugs listed in protocols for ovarian stimulation in unexplained infertility treatment and IVF and ovulation induction for ovulation disorders Ovarian Surgery Lifestyle interventions	
Comparisons	Reported outcomes in RCT studies will allow comparison of short-term outcomes between treatments Cohort studies will produce descriptive data about longer term outcome.	
Outcomes	Premature mortality (all causes and especially that related to malignancy Future fertility	Importance of distinguishing different pathology/causation

	Details	GDG comments
	Future gynaecological health (including breast, uterine, cervical and ovarian cancer)	
	Future pregnancy outcomes (miscarriage, ectopic pregnancy, pregnancy complications	
	Congenital abnormalities (some may not be recognised at birth)	
	Health-related quality of life – restricted to people seeking treatment for infertility.	
	Long-term effects on children (including diabetes, tumours and autism)	
	Anxiety and/or depression.	
Other criteria for inclusion/ exclusion of studies	Exclude non-human studies	
Search strategies	Searches to cover all terms mentioned under population, intervention and comparator	
Review strategies	Evidence will be assessed for quality according to the process described in the NICE guidelines manual (January 2009)	
	A list of excluded studies will be provided following weeding	
	Evidence tables and an evidence profile will be used to summarise the evidence	
Equality	Equalities issues will be assessed according to the processes described in the NICE guidelines manual (January 2009) and the NICE equality scheme and action plan (2010 – 2013)	

Appendix E Search strategies

Chapter 6. Investigation of fertility problems and management strategies

Tests for ovarian reserve

Database(s): Ovid MEDLINE(R) 1948 to February week 2 2011

Search Strategy: FERT_Q1_ovul_reserve_medline_210211

#	Searches
1	randomized controlled trial.pt.
2	controlled clinical trial.pt.
3	DOUBLE BLIND METHOD/
4	SINGLE BLIND METHOD/
5	RANDOM ALLOCATION/
6	RANDOMIZED CONTROLLED TRIALS/
7	or/1-6
8	((single or double or triple or treble) adj5 (blind$ or mask$)).tw,sh.
9	clinical trial.pt.
10	exp CLINICAL TRIAL/
11	exp CLINICAL TRIALS AS TOPIC/
12	(clinic$ adj5 trial$).tw,sh.
13	PLACEBOS/
14	placebo$.tw,sh.
15	random$.tw,sh.
16	or/8-15
17	or/7,16
18	META ANALYSIS/
19	META ANALYSIS AS TOPIC/
20	meta analysis.pt.
21	(metaanaly$ or meta-analy$ or (meta adj analy$)).tw,sh.
22	(systematic$ adj5 (review$ or overview$)).tw,sh.
23	(methodologic$ adj5 (review$ or overview$)).tw,sh.
24	or/18-23
25	review$.pt.

26	(medline or medlars or embase or cinahl or cochrane or psycinfo or psychinfo or psychlit or psyclit or "web of science" or "science citation" or scisearch).tw.
27	((hand or manual$) adj2 search$).tw.
28	(electronic database$ or bibliographic database$ or computeri?ed database$ or online database$).tw,sh.
29	(pooling or pooled or mantel haenszel).tw,sh.
30	(peto or dersimonian or der simonian or fixed effect).tw,sh.
31	or/26-30
32	and/25,31
33	exp CASE-CONTROL STUDIES/
34	(case$ adj2 control$).tw.
35	exp COHORT STUDIES/
36	cohort$.tw.
37	or/33-36
38	or/17,24,32,37
39	letter.pt.
40	comment.pt.
41	editorial.pt.
42	historical article.pt.
43	or/39-42
44	38 not 43
45	OVARIAN FUNCTION TESTS/
46	(ovar$ adj3 function$).ti,ab.
47	exp FOLLICLE STIMULATING HORMONE/
48	(follicle stimulating hormone$ or FSH).ti,ab.
49	CLOMIPHENE/
50	clomifene citrate$.ti,ab.
51	((clomiphene or clomifene) adj2 challenge).ti,ab.
52	CCCT.ti,ab.
53	exp GONADOTROPIN-RELEASING HORMONE/
54	(gonadotrophin$ or gonadotropin$).ti,ab.
55	exp ESTRADIOL/
56	E2.ti.
57	exp INHIBINS/
58	"inhibin B".ti,ab.
59	ANTI-MULLERIAN HORMONE/
60	("anti-mullerian" adj (hormone$ or substance$ or factor$)).ti,ab.
61	AMH.ti,ab.
62	exp OVARIAN FOLLICLE/

63	exp CELL COUNT/
64	and/62-63
65	antral follicle count.ti,ab.
66	AFC.ti,ab.
67	exp OVARY/
68	exp IMAGING, THREE-DIMENSIONAL/
69	exp ULTRASONOGRAPHY/
70	or/68-69
71	and/67,70
72	((ovary or ovarian) adj2 (volume or size or sizing)).ti,ab.
73	or/71-72
74	exp OVARY/
75	REGIONAL BLOOD FLOW/
76	BLOOD FLOW VELOCITY/
77	or/75-76
78	and/74,77
79	((ovary or ovarian) adj2 blood flow$).ti,ab.
80	or/45-61,64-66,71,73,78-79
81	exp REPRODUCTIVE TECHNIQUES, ASSISTED/
82	((ovar$ or ovulat$) adj5 (induc$ or stimulat$)).ti,ab.
83	IVF.ti,ab.
84	"in vitro fertili$".ti,ab.
85	INFERTILITY,FEMALE/
86	INFERTILITY/
87	(steril$ or infertil$ or subfertil$ or sub-fertil$ or fecund$ or subfecund$ or sub-fecund$ or assist$ reproduct$).ti,ab.
88	or/81-87
89	and/80,88
90	and/44,89
91	randomized controlled trial.pt.
92	controlled clinical trial.pt.
93	DOUBLE BLIND METHOD/
94	SINGLE BLIND METHOD/
95	RANDOM ALLOCATION/
96	RANDOMIZED CONTROLLED TRIALS/
97	or/91-96
98	((single or double or triple or treble) adj5 (blind$ or mask$)).tw,sh.
99	clinical trial.pt.
100	exp CLINICAL TRIAL/

101	exp CLINICAL TRIALS AS TOPIC/
102	(clinic$ adj5 trial$).tw,sh.
103	PLACEBOS/
104	placebo$.tw,sh.
105	random$.tw,sh.
106	or/98-105
107	or/97,106
108	META ANALYSIS/
109	META ANALYSIS AS TOPIC/
110	meta analysis.pt.
111	(metaanaly$ or meta-analy$ or (meta adj analy$)).tw,sh.
112	(systematic$ adj5 (review$ or overview$)).tw,sh.
113	(methodologic$ adj5 (review$ or overview$)).tw,sh.
114	or/108-113
115	review$.pt.
116	(medline or medlars or embase or cinahl or cochrane or psycinfo or psychinfo or psychlit or psyclit or "web of science" or "science citation" or scisearch).tw.
117	((hand or manual$) adj2 search$).tw.
118	(electronic database$ or bibliographic database$ or computeri?ed database$ or online database$).tw,sh.
119	(pooling or pooled or mantel haenszel).tw,sh.
120	(peto or dersimonian or der simonian or fixed effect).tw,sh.
121	or/116-120
122	and/115,121
123	exp CASE-CONTROL STUDIES/
124	(case$ adj2 control$).tw.
125	exp COHORT STUDIES/
126	cohort$.tw.
127	or/123-126
128	or/107,114,122,127
129	letter.pt.
130	comment.pt.
131	editorial.pt.
132	historical article.pt.
133	or/129-132
134	128 not 133
135	exp FOLLICLE STIMULATING HORMONE/
136	(follicle stimulating hormone$ or FSH).ti,ab.
137	CLOMIPHENE/

138	clomifene citrate$.ti,ab.
139	((clomiphene or clomifene) adj2 challenge).ti,ab.
140	CCCT.ti,ab.
141	exp GONADOTROPIN-RELEASING HORMONE/
142	(gonadotrophin$ or gonadotropin$).ti,ab.
143	exp ESTRADIOL/
144	E2.ti.
145	exp INHIBINS/
146	"inhibin B".ti,ab.
147	ANTI-MULLERIAN HORMONE/
148	("anti-mullerian" adj (hormone$ or substance$ or factor$)).ti,ab.
149	AMH.ti,ab.
150	exp OVARIAN FOLLICLE/
151	exp CELL COUNT/
152	and/150-151
153	antral follicle count.ti,ab.
154	AFC.ti,ab.
155	exp OVARY/
156	exp IMAGING, THREE-DIMENSIONAL/
157	exp ULTRASONOGRAPHY/
158	or/156-157
159	and/155,158
160	((ovary or ovarian) adj2 (volume or size or sizing)).ti,ab.
161	or/159-160
162	exp OVARY/
163	REGIONAL BLOOD FLOW/
164	BLOOD FLOW VELOCITY/
165	or/163-164
166	and/162,165
167	((ovary or ovarian) adj2 blood flow$).ti,ab.
168	or/135-149,152-154,161,166-167
169	exp FOLLICLE STIMULATING HORMONE/
170	(follicle stimulating hormone$ or FSH).ti,ab.
171	or/169-170
172	exp REPRODUCTIVE TECHNIQUES, ASSISTED/
173	((ovar$ or ovulat$) adj5 (induc$ or stimulat$)).ti,ab.
174	IVF.ti,ab.
175	or/172-174
176	and/168,171,175

177	and/134,176
178	90 not 177
179	limit 178 to english language
180	limit 179 to (animals and humans)
181	limit 179 to animals
182	181 not 180
183	**179 not 182**

Database(s): Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations February 18, 2011

Search Strategy: FERT_Q1_ovul_reserve_medline_in_process_210211

#	Searches
1	(ovar$ adj3 function$).ti,ab.
2	(follicle stimulating hormone$ or FSH).ti,ab.
3	(clomifene or clomiphene).ti,ab.
4	CCCT.ti,ab.
5	(gonadotrophin$ or gonadotropin$).ti,ab.
6	(estradiol or oestradiol).ti,ab.
7	E2.ti.
8	"inhibin B".ti,ab.
9	("anti-mullerian" adj (hormone$ or substance$ or factor$)).ti,ab.
10	AMH.ti,ab.
11	antral follicle count.ti,ab.
12	AFC.ti,ab.
13	((ovary or ovarian) adj2 (volume or size or sizing)).ti,ab.
14	((ovary or ovarian) adj2 blood flow$).ti,ab.
15	or/1-14
16	(assist$ adj reproduct$ adj technique$).ti,ab.
17	(artificial$ adj reproduct$ adj technique$).ti,ab.
18	((ovar$ or ovulat$) adj5 (induc$ or stimulat$)).ti,ab.
19	IVF.ti,ab.
20	"in vitro fertili$".ti,ab.
21	(steril$ or infertil$ or subfertil$ or sub-fertil$ or fecund$ or subfecund$ or sub-fecund$ or assist$ reproduct$).ti,ab.
22	or/16-21
23	and/15,22
24	(follicle stimulating hormone$ or FSH).ti,ab.
25	(clomifene or clomiphene).ti,ab.

26	CCCT.ti,ab.
27	(gonadotrophin$ or gonadotropin$).ti,ab.
28	(estradiol or oestradiol).ti,ab.
29	E2.ti.
30	"inhibin B".ti,ab.
31	("anti-mullerian" adj (hormone$ or substance$ or factor$)).ti,ab.
32	AMH.ti,ab.
33	antral follicle count.ti,ab.
34	AFC.ti,ab.
35	((ovary or ovarian) adj2 (volume or size or sizing)).ti,ab.
36	((ovary or ovarian) adj2 blood flow$).ti,ab.
37	or/24-36
38	(follicle stimulating hormone$ or FSH).ti,ab.
39	((ovar$ or ovulat$) adj5 (induc$ or stimulat$)).ti,ab.
40	IVF.ti,ab.
41	or/39-40
42	and/37-38,41
43	23 not 42
44	English.la.
45	and/43-44

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials 1st Quarter 2011

Search Strategy: FERT_Q1_ovul_reserve_cctr_210211

#	Searches
1	randomized controlled trial.pt.
2	controlled clinical trial.pt.
3	DOUBLE BLIND METHOD/
4	SINGLE BLIND METHOD/
5	RANDOM ALLOCATION/
6	RANDOMIZED CONTROLLED TRIALS/
7	or/1-6
8	((single or double or triple or treble) adj5 (blind$ or mask$)).tw,sh.
9	clinical trial.pt.
10	exp CLINICAL TRIAL/
11	exp CLINICAL TRIALS AS TOPIC/
12	(clinic$ adj5 trial$).tw,sh.

13	PLACEBOS/
14	placebo$.tw,sh.
15	random$.tw,sh.
16	or/8-15
17	or/7,16
18	META ANALYSIS/
19	META ANALYSIS AS TOPIC/
20	meta analysis.pt.
21	(metaanaly$ or meta-analy$ or (meta adj analy$)).tw,sh.
22	(systematic$ adj5 (review$ or overview$)).tw,sh.
23	(methodologic$ adj5 (review$ or overview$)).tw,sh.
24	or/18-23
25	review$.pt.
26	(medline or medlars or embase or cinahl or cochrane or psycinfo or psychinfo or psychlit or psyclit or "web of science" or "science citation" or scisearch).tw.
27	((hand or manual$) adj2 search$).tw.
28	(electronic database$ or bibliographic database$ or computeri?ed database$ or online database$).tw,sh.
29	(pooling or pooled or mantel haenszel).tw,sh.
30	(peto or dersimonian or der simonian or fixed effect).tw,sh.
31	or/26-30
32	and/25,31
33	exp CASE-CONTROL STUDIES/
34	(case$ adj2 control$).tw.
35	exp COHORT STUDIES/
36	cohort$.tw.
37	or/33-36
38	or/17,24,32,37
39	letter.pt.
40	comment.pt.
41	editorial.pt.
42	historical article.pt.
43	or/39-42
44	38 not 43
45	OVARIAN FUNCTION TESTS/
46	(ovar$ adj3 function$).ti,ab.
47	exp FOLLICLE STIMULATING HORMONE/
48	(follicle stimulating hormone$ or FSH).ti,ab.
49	CLOMIPHENE/

50	clomifene citrate$.ti,ab.
51	((clomiphene or clomifene) adj2 challenge).ti,ab.
52	CCCT.ti,ab.
53	exp GONADOTROPIN-RELEASING HORMONE/
54	(gonadotrophin$ or gonadotropin$).ti,ab.
55	exp ESTRADIOL/
56	E2.ti.
57	exp INHIBINS/
58	"inhibin B".ti,ab.
59	ANTI-MULLERIAN HORMONE/
60	("anti-mullerian" adj (hormone$ or substance$ or factor$)).ti,ab.
61	AMH.ti,ab.
62	exp OVARIAN FOLLICLE/
63	exp CELL COUNT/
64	and/62-63
65	antral follicle count.ti,ab.
66	AFC.ti,ab.
67	exp OVARY/
68	exp IMAGING, THREE-DIMENSIONAL/
69	exp ULTRASONOGRAPHY/
70	or/68-69
71	and/67,70
72	((ovary or ovarian) adj2 (volume or size or sizing)).ti,ab.
73	or/71-72
74	exp OVARY/
75	REGIONAL BLOOD FLOW/
76	BLOOD FLOW VELOCITY/
77	or/75-76
78	and/74,77
79	((ovary or ovarian) adj2 blood flow$).ti,ab.
80	or/45-61,64-66,71,73,78-79
81	exp REPRODUCTIVE TECHNIQUES, ASSISTED/
82	((ovar$ or ovulat$) adj5 (induc$ or stimulat$)).ti,ab.
83	IVF.ti,ab.
84	"in vitro fertili$".ti,ab.
85	INFERTILITY,FEMALE/
86	INFERTILITY/
87	(steril$ or infertil$ or subfertil$ or sub-fertil$ or fecund$ or subfecund$ or sub-fecund$ or assist$ reproduct$).ti,ab.

88	or/81-87
89	and/80,88
90	and/44,89
91	randomized controlled trial.pt.
92	controlled clinical trial.pt.
93	DOUBLE BLIND METHOD/
94	SINGLE BLIND METHOD/
95	RANDOM ALLOCATION/
96	RANDOMIZED CONTROLLED TRIALS/
97	or/91-96
98	((single or double or triple or treble) adj5 (blind$ or mask$)).tw,sh.
99	clinical trial.pt.
100	exp CLINICAL TRIAL/
101	exp CLINICAL TRIALS AS TOPIC/
102	(clinic$ adj5 trial$).tw,sh.
103	PLACEBOS/
104	placebo$.tw,sh.
105	random$.tw,sh.
106	or/98-105
107	or/97,106
108	META ANALYSIS/
109	META ANALYSIS AS TOPIC/
110	meta analysis.pt.
111	(metaanaly$ or meta-analy$ or (meta adj analy$)).tw,sh.
112	(systematic$ adj5 (review$ or overview$)).tw,sh.
113	(methodologic$ adj5 (review$ or overview$)).tw,sh.
114	or/108-113
115	review$.pt.
116	(medline or medlars or embase or cinahl or cochrane or psycinfo or psychinfo or psychlit or psyclit or "web of science" or "science citation" or scisearch).tw.
117	((hand or manual$) adj2 search$).tw.
118	(electronic database$ or bibliographic database$ or computeri?ed database$ or online database$).tw,sh.
119	(pooling or pooled or mantel haenszel).tw,sh.
120	(peto or dersimonian or der simonian or fixed effect).tw,sh.
121	or/116-120
122	and/115,121
123	exp CASE-CONTROL STUDIES/
124	(case$ adj2 control$).tw.

125	exp COHORT STUDIES/
126	cohort$.tw.
127	or/123-126
128	or/107,114,122,127
129	letter.pt.
130	comment.pt.
131	editorial.pt.
132	historical article.pt.
133	or/129-132
134	128 not 133
135	exp FOLLICLE STIMULATING HORMONE/
136	(follicle stimulating hormone$ or FSH).ti,ab.
137	CLOMIPHENE/
138	clomifene citrate$.ti,ab.
139	((clomiphene or clomifene) adj2 challenge).ti,ab.
140	CCCT.ti,ab.
141	exp GONADOTROPIN-RELEASING HORMONE/
142	(gonadotrophin$ or gonadotropin$).ti,ab.
143	exp ESTRADIOL/
144	E2.ti.
145	exp INHIBINS/
146	"inhibin B".ti,ab.
147	ANTI-MULLERIAN HORMONE/
148	("anti-mullerian" adj (hormone$ or substance$ or factor$)).ti,ab.
149	AMH.ti,ab.
150	exp OVARIAN FOLLICLE/
151	exp CELL COUNT/
152	and/150-151
153	antral follicle count.ti,ab.
154	AFC.ti,ab.
155	exp OVARY/
156	exp IMAGING, THREE-DIMENSIONAL/
157	exp ULTRASONOGRAPHY/
158	or/156-157
159	and/155,158
160	((ovary or ovarian) adj2 (volume or size or sizing)).ti,ab.
161	or/159-160
162	exp OVARY/
163	REGIONAL BLOOD FLOW/

164	BLOOD FLOW VELOCITY/
165	or/163-164
166	and/162,165
167	((ovary or ovarian) adj2 blood flow$).ti,ab.
168	or/135-149,152-154,161,166-167
169	exp FOLLICLE STIMULATING HORMONE/
170	(follicle stimulating hormone$ or FSH).ti,ab.
171	or/169-170
172	exp REPRODUCTIVE TECHNIQUES, ASSISTED/
173	((ovar$ or ovulat$) adj5 (induc$ or stimulat$)).ti,ab.
174	IVF.ti,ab.
175	or/172-174
176	and/168,171,175
177	and/134,176
178	90 not 177

Database(s): EBM Reviews - Cochrane Database of Systematic Reviews 2005 to January 2011, EBM Reviews - Database of Abstracts of Reviews of Effects 1st Quarter 2011

Search Strategy:

#	Searches
1	OVARIAN FUNCTION TESTS.kw.
2	(ovar$ adj3 function$).tw,tx.
3	FOLLICLE STIMULATING HORMONE.kw.
4	(follicle stimulating hormone$ or FSH).tw,tx.
5	CLOMIPHENE.kw.
6	clomifene citrate$.tw,tx.
7	((clomiphene or clomifene) adj2 challenge).tw,tx.
8	CCCT.tw,tx.
9	GONADOTROPIN-RELEASING HORMONE.kw.
10	(gonadotrophin$ or gonadotropin$).tw,tx.
11	ESTRADIOL.kw.
12	E2.ti.
13	INHIBINS.kw.
14	"inhibin B".tw,tx.
15	ANTI-MULLERIAN HORMONE.kw.
16	("anti-mullerian" adj (hormone$ or substance$ or factor$)).tw,tx.
17	AMH.tw,tx.

18	OVARIAN FOLLICLE.kw.
19	CELL COUNT.kw.
20	and/18-19
21	antral follicle count.tw,tx.
22	AFC.tw,tx.
23	OVARY.kw.
24	IMAGING, THREE-DIMENSIONAL.kw.
25	ULTRASONOGRAPHY.kw.
26	or/24-25
27	and/23,26
28	((ovary or ovarian) adj2 (volume or size or sizing)).tw,tx.
29	or/27-28
30	OVARY.kw.
31	REGIONAL BLOOD FLOW.kw.
32	BLOOD FLOW VELOCITY.kw.
33	or/31-32
34	and/30,33
35	((ovary or ovarian) adj2 blood flow$).tw,tx.
36	or/1-17,20-22,27,29,34-35
37	REPRODUCTIVE TECHNIQUES, ASSISTED.kw.
38	((ovar$ or ovulat$) adj5 (induc$ or stimulat$)).tw,tx.
39	IVF.tw,tx.
40	"in vitro fertili$".tw,tx.
41	INFERTILITY,FEMALE.kw.
42	INFERTILITY.kw.
43	(steril$ or infertil$ or subfertil$ or sub-fertil$ or fecund$ or subfecund$ or sub-fecund$ or assist$ reproduct$).tw,tx.
44	or/37-43
45	and/36,44
46	FOLLICLE STIMULATING HORMONE.kw.
47	(follicle stimulating hormone$ or FSH).tw,tx.
48	CLOMIPHENE.kw.
49	clomifene citrate$.tw,tx.
50	((clomiphene or clomifene) adj2 challenge).tw,tx.
51	CCCT.tw,tx.
52	GONADOTROPIN-RELEASING HORMONE.kw.
53	(gonadotrophin$ or gonadotropin$).tw,tx.
54	[exp ESTRADIOL/]
55	E2.ti.

56	INHIBINS.kw.
57	"inhibin B".tw,tx.
58	ANTI-MULLERIAN HORMONE.kw.
59	("anti-mullerian" adj (hormone$ or substance$ or factor$)).tw,tx.
60	AMH.tw,tx.
61	OVARIAN FOLLICLE.kw.
62	CELL COUNT.kw.
63	and/61-62
64	antral follicle count.tw,tx.
65	AFC.tw,tx.
66	OVARY.kw.
67	IMAGING, THREE-DIMENSIONAL.kw.
68	ULTRASONOGRAPHY.kw.
69	or/67-68
70	and/66,69
71	((ovary or ovarian) adj2 (volume or size or sizing)).tw,tx.
72	or/70-71
73	OVARY.kw.
74	REGIONAL BLOOD FLOW.kw.
75	BLOOD FLOW VELOCITY.kw.
76	or/74-75
77	and/73,76
78	((ovary or ovarian) adj2 blood flow$).tw,tx.
79	or/46-60,63-65,72,77-78
80	FOLLICLE STIMULATING HORMONE.kw.
81	(follicle stimulating hormone$ or FSH).tw,tx.
82	or/80-81
83	REPRODUCTIVE TECHNIQUES, ASSISTED.kw.
84	((ovar$ or ovulat$) adj5 (induc$ or stimulat$)).tw,tx.
85	IVF.tw,tx.
86	or/83-85
87	and/79,82,86
88	45 not 87

Database(s): EMBASE 1980 to 2011 Week 07

Search Strategy:FERT_Q1_ovul_reserve_220211

1	CLINICAL TRIALS/
2	(clinic$ adj5 trial$).tw,sh.
3	SINGLE BLIND PROCEDURE/
4	DOUBLE BLIND PROCEDURE/
5	RANDOM ALLOCATION/
6	CROSSOVER PROCEDURE/
7	PLACEBO/
8	placebo$.tw,sh.
9	random$.tw,sh.
10	RANDOMIZED CONTROLLED TRIALS/
11	((single or double or triple or treble) adj (blind$ or mask$)).tw,sh.
12	randomi?ed control$ trial$.tw.
13	or/1-12
14	META ANALYSIS/
15	((meta adj analy$) or metaanalys$ or meta-analy$).tw,sh.
16	(systematic$ adj5 (review$ or overview$)).tw,sh.
17	(methodologic$ adj5 (review$ or overview$)).tw,sh.
18	or/14-17
19	review.pt.
20	(medline or medlars or embase).ab.
21	(scisearch or science citation index).ab.
22	(psychlit or psyclit or psychinfo or psycinfo or cinahl or cochrane).ab.
23	((hand or manual$) adj2 search$).tw.
24	(electronic database$ or bibliographic database$ or computeri?ed database$ or online database$).tw.
25	(pooling or pooled or mantel haenszel).tw.
26	(peto or dersimonian or "der simonian" or fixed effect).tw.
27	or/20-26
28	and/19,27

29	exp CASE CONTROL STUDY/
30	RETROSPECTIVE STUDY/
31	(case$ adj2 control$).tw.
32	COHORT ANALYSIS/
33	LONGITUDINAL STUDY/
34	FOLLOW UP/
35	PROSPECTIVE STUDY/
36	cohort$.tw.
37	or/29-36
38	or/13,18,28,37
39	(book or conference paper or editorial or letter or note or proceeding or short survey).pt.
40	38 not 39
41	FOLLITROPIN/
42	(follicle stimulating hormone$ or FSH).ti,ab.
43	CLOMIFENE/
44	clomifene citrate$.ti,ab.
45	((clomiphene or clomifene) adj2 challenge).ti,ab.
46	CCCT.ti,ab.
47	GONADORELIN/
48	(gonadotrophin$ or gonadotropin$).ti,ab.
49	ESTRADIOL/
50	E2.ti.
51	INHIBIN/
52	"inhibin B".ti,ab.
53	MUELLERIAN INHIBITING FACTOR/
54	("anti-mullerian" adj (hormone$ or substance$ or factor$)).ti,ab.
55	AMH.ti,ab.
56	exp OVARY FOLLICLE/
57	exp CELL COUNT/
58	and/56-57
59	antral follicle count.ti,ab.

60	AFC.ti,ab.
61	exp OVARY/
62	THREE DIMENSIONAL IMAGING/
63	exp ECHOGRAPHY/
64	or/62-63
65	and/61,64
66	((ovary or ovarian) adj2 (volume or size or sizing)).ti,ab.
67	or/65-66
68	exp OVARY/
69	exp BLOOD FLOW/
70	BLOOD FLOW VELOCITY/
71	or/69-70
72	and/68,71
73	((ovary or ovarian) adj2 blood flow$).ti,ab.
74	or/41-55,58-60,67,72-73
75	FEMALE INFERTILITY/
76	exp INFERTILITY THERAPY/
77	((ovar$ or ovulat$) adj5 (induc$ or stimulat$)).ti,ab.
78	IVF.ti,ab.
79	in vitro fertili$.ti,ab.
80	(steril$ or infertil$ or subfertil$ or sub-fertil$ or fecund$ or subfecund$ or sub-fecund$ or assist$ reproduct$).ti,ab.
81	or/75-80
82	and/40,74,81
83	CLINICAL TRIALS/
84	(clinic$ adj5 trial$).tw,sh.
85	SINGLE BLIND PROCEDURE/
86	DOUBLE BLIND PROCEDURE/
87	RANDOM ALLOCATION/
88	CROSSOVER PROCEDURE/
89	PLACEBO/

90	placebo$.tw,sh.
91	random$.tw,sh.
92	RANDOMIZED CONTROLLED TRIALS/
93	((single or double or triple or treble) adj (blind$ or mask$)).tw,sh.
94	randomi?ed control$ trial$.tw.
95	or/83-94
96	META ANALYSIS/
97	((meta adj analy$) or metaanalys$ or meta-analy$).tw,sh.
98	(systematic$ adj5 (review$ or overview$)).tw,sh.
99	(methodologic$ adj5 (review$ or overview$)).tw,sh.
100	or/96-99
101	review.pt.
102	(medline or medlars or embase).ab.
103	(scisearch or science citation index).ab.
104	(psychlit or psyclit or psychinfo or psycinfo or cinahl or cochrane).ab.
105	((hand or manual$) adj2 search$).tw.
106	(electronic database$ or bibliographic database$ or computeri?ed database$ or online database$).tw.
107	(pooling or pooled or mantel haenszel).tw.
108	(peto or dersimonian or "der simonian" or fixed effect).tw.
109	or/102-108
110	and/101,109
111	exp CASE CONTROL STUDY/
112	RETROSPECTIVE STUDY/
113	(case$ adj2 control$).tw.
114	COHORT ANALYSIS/
115	LONGITUDINAL STUDY/
116	FOLLOW UP/
117	PROSPECTIVE STUDY/
118	cohort$.tw.
119	or/111-118

120	or/95,100,110,119
121	(book or conference paper or editorial or letter or note or proceeding or short survey).pt.
122	120 not 121
123	FOLLITROPIN/
124	(follicle stimulating hormone$ or FSH).ti,ab.
125	CLOMIFENE/
126	clomifene citrate$.ti,ab.
127	((clomiphene or clomifene) adj2 challenge).ti,ab.
128	CCCT.ti,ab.
129	GONADORELIN/
130	(gonadotrophin$ or gonadotropin$).ti,ab.
131	ESTRADIOL/
132	E2.ti.
133	INHIBIN/
134	"inhibin B".ti,ab.
135	MUELLERIAN INHIBITING FACTOR/
136	("anti-mullerian" adj (hormone$ or substance$ or factor$)).ti,ab.
137	AMH.ti,ab.
138	exp OVARY FOLLICLE/
139	exp CELL COUNT/
140	and/138-139
141	antral follicle count.ti,ab.
142	AFC.ti,ab.
143	exp OVARY/
144	THREE DIMENSIONAL IMAGING/
145	exp ECHOGRAPHY/
146	or/144-145
147	and/143,146
148	((ovary or ovarian) adj2 (volume or size or sizing)).ti,ab.
149	or/147-148
150	exp OVARY/

151	exp BLOOD FLOW/
152	BLOOD FLOW VELOCITY/
153	or/151-152
154	and/150,153
155	((ovary or ovarian) adj2 blood flow$).ti,ab.
156	or/123-137,140-142,149,154-155
157	FOLLITROPIN/
158	(follicle stimulating hormone$ or FSH).ti,ab.
159	or/157-158
160	exp INFERTILITY THERAPY/
161	((ovar$ or ovulat$) adj5 (induc$ or stimulat$)).ti,ab.
162	IVF.ti,ab.
163	or/160-162
164	and/156,159,163
165	and/122,164
166	82 not 165
167	limit 166 to english language

Cinahl Ebsco FERT_Q1_ovul_reserve_cinahl_220211

#	Query	Limiters/Expanders	Last Run Via	Results	Action
S47	S35 and S45	Limiters - English Language; Exclude MEDLINE records Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	80	Edit S47
S46	S35 and S45	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	404	Edit S46
S45	S36 or S37 or S38 or S39 or S40 or S41 or S42 or S43 or S44	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	5347	Edit S45

S44	TI (artificial* N3 reproduct*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	1	Edit S44
S43	AB (artificial* N3 reproduct*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	12	Edit S43
S42	AB (assist* N3 reproduct*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	361	Edit S42
S41	TI (assist* N3 reproduct*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	325	Edit S41
S40	(MH "INFERTILITY")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	2858	Edit S40
S39	TI (IVF) OR AB (IVF)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	449	Edit S39
S38	AB (ovar* N5 induc*) or AB (ovar* N5 stimulat*) or AB (ovulat* N5 induc*) or AB (ovulat* N5 stimulat*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	252	Edit S38
S37	TI (ovar* N5 induc*) or TI (ovar* N5 stimulat*) or TI (ovulat* N5 induc*) or TI (ovulat* N5 stimulat*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	121	Edit S37
S36	MH REPRODUCTION TECHNIQUES+	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	3073	Edit S36

S35	S15 or S21 or S27 or S34	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	3374	Edit S35
S34	S32 or S33	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	10	Edit S34
S33	TI (ovar* N2 blood flow*) or AB (ovar* N2 blood flow*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	6	Edit S33
S32	S28 and S31	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	8	Edit S32
S31	S29 or S30	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	8714	Edit S31
S30	MH BLOOD FLOW VELOCITY	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	1687	Edit S30
S29	MH BLOOD CIRCULATION+	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	7540	Edit S29
S28	MH OVARY	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	634	Edit S28
S27	S24 or S25 or S26	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	66	Edit S27

S26	AB (ovar* N2 volume) or AB (ovar* N2 siz*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	27	Edit S26
S25	TI (ovar* N2 volume) or TI (ovar* N2 siz*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	10	Edit S25
S24	S22 and S23	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	38	Edit S24
S23	MH ULTRASONOGRAPHY+	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	20793	Edit S23
S22	MH OVARY	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	634	Edit S22
S21	S18 or S19 or S20	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	298	Edit S21
S20	TI (AFC) or AB (AFC)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	291	Edit S20
S19	TI (antral follicle count) or AB (antral follicle count)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	8	Edit S19
S18	S16 and S17	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	1	Edit S18

S17	MH CELL COUNT+	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	5093	Edit S17
S16	MH OVARY	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	634	Edit S16
S15	S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	3033	Edit S15
S14	TI (AMH) or AB (AMH)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	21	Edit S14
S13	AB (anti-mullerian N2 hormone*) or AB (anti-mullerian N2 substance*) or AB (anti-mullerian N2 factor*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	10	Edit S13
S12	TI (anti-mullerian N2 hormone*) or TI (anti-mullerian N2 substance*) or TI (anti-mullerian N2 factor*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	8	Edit S12
S11	TI (inhibin B) or AB (inhibin B)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	29	Edit S11
S10	TI (E2)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	184	Edit S10
S9	MH ESTRADIOL	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	1326	Edit S9

S8	TI (gonadotrophin* or gonadotropin*) or AB (gonadotrophin* or gonadotropin*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	652	Edit S8
S7	MH GONADORELIN+	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	539	Edit S7
S6	TI (CCCT) or AB (CCCT)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	1	Edit S6
S5	TI(clomiphene N2 challenge) or TI (clomifene N2 challenge) or AB (clomiphene N2 challenge) or AB (clomifene N2 challenge)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	5	Edit S5
S4	TI (clomifene citrate*) or AB (clomifene citrate*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	5	Edit S4
S3	MH CLOMIPHENE	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	127	Edit S3
S2	TI (FSH or follicle stimulating hormone*) or AB (FSH or follicle stimulating hormone*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	365	Edit S2
S1	MH FOLLICLE-STIMULATING HORMONE	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	470	

Sperm washing and viral transmission.

Database(s): Ovid MEDLINE(R) 1950 to September Week 2 2010

Search Strategy: FERT_Q8_sperm_washing_medline_240910

#	Searches
1	exp SPERMATOZOA/
2	exp STERILIZATION/
3	and/1-2
4	(sperm$ adj3 (wash$ or disinfect$ or clean$)).ti,ab.
5	exp SPERMATOZOA/
6	exp Disease Transmission, Infectious/pc [Prevention & Control]
7	and/5-6
8	SEMEN/
9	CELL SEPARATION/
10	and/8-9
11	"sperm-washing".ti,ab.
12	or/3-4,7,10-11
13	ACQUIRED IMMUNODEFICIENCY SYNDROME/ or HIV SEROPOSITIVITY/
14	(hiv adj seropositiv$).ti,ab.
15	exp HEPATITIS, CHRONIC/ or HEPATITIS/ or exp HEPATITIS C/ or exp HEPATITIS C, CHRONIC/ or exp HEPATITIS B/ or exp HEPATITIS B, CHRONIC/ or exp HEPATITIS B VIRUS/
16	hepatitis.ti,ab.
17	CYTOMEGALOVIRUS/
18	exp CYTOMEGALOVIRUS INFECTIONS/
19	cytomegalovir$.ti,ab.
20	or/13-19
21	and/12,20
22	limit 21 to english language
23	limit 21 to (animals and humans)
24	limit 21 to animals
25	24 not 23
26	22 not 25

Database(s): Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations September 24, 2010

Search Strategy: FERT_Q8_sperm_washing_medline_in_process_270910

#	Searches
1	(sperm$ adj3 (wash$ or disinfect$ or clean$ or sterili$)).ti,ab.
2	"sperm-washing".ti,ab.
3	or/1-2
4	human immunodeficiency virus$.ti,ab.
5	HIV.ti,ab.
6	hepatitis.ti,ab.
7	cytomegalovir$.ti,ab.
8	or/4-7
9	and/3,8

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials 3rd Quarter 2010

Search Strategy: FERT_Q8_sperm_washing_cctr_270910

#	Searches
1	exp SPERMATOZOA/
2	exp STERILIZATION/
3	and/1-2
4	(sperm$ adj3 (wash$ or disinfect$ or clean$)).ti,ab.
5	exp SPERMATOZOA/
6	exp Disease Transmission, Infectious/pc [Prevention & Control]
7	and/5-6
8	SEMEN/
9	CELL SEPARATION/
10	and/8-9
11	"sperm-washing".ti,ab.
12	or/3-4,7,10-11
13	ACQUIRED IMMUNODEFICIENCY SYNDROME/ or HIV SEROPOSITIVITY/
14	(hiv adj seropositiv$).ti,ab.
15	exp HEPATITIS, CHRONIC/ or HEPATITIS/ or exp HEPATITIS C/ or exp HEPATITIS C, CHRONIC/ or exp HEPATITIS B/ or exp HEPATITIS B, CHRONIC/ or exp HEPATITIS B VIRUS/
16	hepatitis.ti,ab.

17	CYTOMEGALOVIRUS/
18	exp CYTOMEGALOVIRUS INFECTIONS/
19	cytomegalovir$.ti,ab.
20	or/13-19
21	and/12,20

Database(s): EBM Reviews - Cochrane Database of Systematic Reviews 2005 to September 2010, EBM Reviews - Database of Abstracts of Reviews of Effects 3rd Quarter 2010

Search Strategy: FERT_Q8_sperm_washing_cdsrdare_270910

#	Searches
1	SPERMATOZOA.kw.
2	STERILIZATION.kw.
3	and/1-2
4	(sperm$ adj3 (wash$ or disinfect$ or clean$)).tw,tx.
5	SPERMATOZOA.kw.
6	DISEASE TRANSMISSION, INFECTIOUS.kw.
7	and/5-6
8	SEMEN.kw.
9	CELL SEPARATION.kw.
10	and/8-9
11	"sperm-washing".tw,tx.
12	or/3-4,7,10-11
13	(ACQUIRED IMMUNODEFICIENCY SYNDROME or HIV SEROPOSITIVITY).kw.
14	(hiv adj seropositiv$).tw,tx.
15	(HEPATITIS, CHRONIC or HEPATITIS or HEPATITIS C or HEPATITIS C, CHRONIC or HEPATITIS B or HEPATITIS B, CHRONIC or HEPATITIS B VIRUS).kw.
16	hepatitis.tw,tx.
17	CYTOMEGALOVIRUS.kw.
18	CYTOMEGALOVIRUS INFECTIONS.kw.
19	cytomegalovir$.tw,tx.
20	or/13-19
21	and/12,20

Database(s): EMBASE 1980 to 2010 Week 37

Search Strategy: FERT_Q8_sperm_washing_embase_240910

#	Searches
1	(sperm$ adj3 (wash$ or disinfect$ or clean$)).ti,ab.
2	"sperm-washing".ti,ab.
3	or/1-2
4	exp HUMAN IMMUNODEFICIENCY VIRUS INFECTION/
5	(hiv adj seropositiv$).ti,ab.
6	HEPATITIS B/
7	exp HEPATITIS C/
8	hepatitis.ti,ab.
9	HUMAN CYTOMEGALOVIRUS/
10	exp CYTOMEGALOVIRUS INFECTIONS/
11	cytomegalovir$.ti,ab.
12	or/4-11
13	and/3,12
14	limit 13 to english language

Cinahl FERT_Q8_sperm_washing_cinahl_270910

#	Query
S5	S1 or S2 or S3 or S4
S4	TI (sperm* N3 sterili*) or AB (sperm* N3 sterili*)
S3	TI (sperm* N3 clean*) or AB (sperm* N3 clean*)
S2	TI (sperm* N3 disinfect*) or AB (sperm* N3 disinfect*)
S1	TI (sperm* N3 wash*) or AB (sperm* N3 wash*)

Database(s): Ovid MEDLINE(R) 1948 to July Week 4 2011

Search Strategy: FERT_Q8a_HIV_medline_050811

#	Searches
1	ANTIRETROVIRAL THERAPY, HIGHLY ACTIVE/
2	HAART.ti,ab.
3	(highly adj active antiretroviral therap$).ti,ab.
4	antiretroviral$.ti,ab.

5	or/1-4
6	VIRAL LOAD/
7	((viral or virus$) adj2 (load$ or titer$ or titre$ or burden$)).ti,ab.
8	or/6-7
9	and/5,8
10	exp FERTILIZATION/
11	fertili$.ti,ab.
12	COITUS/
13	(intercourse or coital or coitus).ti,ab.
14	(conception or conceiv$).ti,ab.
15	or/10-14
16	exp HIV Infections/tm [Transmission]
17	(transmit$ or transmission$).ti,ab.
18	HIV SEROPOSITIVITY/
19	seroconver$.ti,ab.
20	or/16-19
21	(pre adj exposure prophyla$).ti,ab.
22	PrEP.ti,ab.
23	prevent$.ti.
24	or/21-23
25	and/9,15
26	and/20,25
27	and/15,20,24
28	and/5,27
29	or/26,28

Database(s): Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations August 04, 2011

Search Strategy: FERT_Q8a_HIV_medline_in_process_050811

#	**Searches**
1	HAART.tw,tx.
2	(highly adj active antiretroviral therap$).tw,tx.
3	antiretroviral$.tw,tx.
4	or/1-3
5	((viral or virus$) adj2 (load$ or titer$ or titre$ or burden$)).tw,tx.
6	and/4-5
7	fertili$.tw,tx.
8	(intercourse or coital or coitus).tw,tx.
9	(conception or conceiv$).tw,tx.
10	or/7-9
11	(HIV or AIDS).tw,tx.
12	(transmit$ or transmission$).tw,tx.
13	seropositiv$.ti,ab.
14	seroconver$.tw,tx.
15	or/11-14
16	and/6,10,15
17	(pre adj exposure prophyla$).tw,tx.
18	PrEP.tw,tx.
19	prevent$.ti.
20	or/17-19
21	and/10,15,20
22	or/16,21

EBM Reviews - Cochrane Central Register of Controlled Trials 3rd Quarter 2011

Search Strategy: FERT_Q8a_HIV_cctr_050811

#	**Searches**
1	ANTIRETROVIRAL THERAPY, HIGHLY ACTIVE/
2	HAART.ti,ab.
3	(highly adj active antiretroviral therap$).ti,ab.
4	antiretroviral$.ti,ab.
5	or/1-4
6	VIRAL LOAD/
7	((viral or virus$) adj2 (load$ or titer$ or titre$ or burden$)).ti,ab.
8	or/6-7
9	and/5,8
10	exp FERTILIZATION/
11	fertili$.ti,ab.
12	COITUS/
13	(intercourse or coital or coitus).ti,ab.
14	(conception or conceiv$).ti,ab.
15	or/10-14
16	exp HIV Infections/tm [Transmission]
17	(transmit$ or transmission$).ti,ab.
18	HIV SEROPOSITIVITY/
19	seroconver$.ti,ab.
20	or/16-19
21	(pre adj exposure prophyla$).ti,ab.
22	PrEP.ti,ab.
23	prevent$.ti.
24	or/21-23
25	and/9,15
26	and/20,25
27	and/15,20,24
28	and/5,27

29	or/26,28

Database(s): EBM Reviews - Cochrane Database of Systematic Reviews 2005 to July 2011, EBM Reviews - Database of Abstracts of Reviews of Effects 3rd Quarter 2011

Search Strategy: FERT_Q8a_HIV_cdsrdare_050811

#	**Searches**
1	ANTIRETROVIRAL THERAPY, HIGHLY ACTIVE.kw.
2	HAART.tw,tx.
3	(highly adj active antiretroviral therap$).tw,tx.
4	antiretroviral$.tw,tx.
5	or/1-4
6	VIRAL LOAD.kw.
7	((viral or virus$) adj2 (load$ or titer$ or titre$ or burden$)).tw,tx.
8	or/6-7
9	and/5,8
10	FERTILIZATION.kw.
11	fertili$.tw,tx.
12	COITUS.kw.
13	(intercourse or coital or coitus).tw,tx.
14	(conception or conceiv$).tw,tx.
15	or/10-14
16	HIV INFECTIONS.kw.
17	(transmit$ or transmission$).tw,tx.
18	HIV SEROPOSITIVITY.kw.
19	seroconver$.tw,tx.
20	or/16-19
21	(pre adj exposure prophyla$).tw,tx.
22	PrEP.tw,tx.
23	prevent$.ti.
24	or/21-23
25	and/9,15

26	and/20,25
27	and/15,20,24
28	and/5,27
29	or/26,28

Database(s): Embase 1980 to 2011 Week 31

Search Strategy: FERT_Q8a_HIV_embase_080811

#	**Searches**
1	HIGHLY ACTIVE ANTIRETROVIRAL THERAPY/
2	HAART.ti,ab.
3	antiretroviral$.ti,ab.
4	or/1-3
5	virus load/
6	((viral or virus$) adj2 (load$ or titer$ or titre$ or burden$)).ti,ab.
7	or/5-6
8	and/5,7
9	CONCEPTION/
10	FERTILIZATION/
11	fertili$.ti,ab.
12	COITUS/
13	(intercourse or coital or coitus).ti,ab.
14	(conception or conceiv$).ti,ab.
15	or/9-14
16	exp HUMAN IMMUNODEFICIENCY VIRUS INFECTION/
17	(transmit$ or transmission$).ti,ab.
18	seroconver$.ti,ab.
19	or/16-18
20	(pre adj exposure prophyla$).ti,ab.
21	PrEP.ti,ab.
22	prevent$.ti.
23	or/20-22

24	and/8,15
25	and/19,24
26	and/23-24
27	and/15,19,23
28	and/4,27
29	or/25,28
30	limit 29 to english language

Chapters 8, 11, 14 and 15. Ovulation induction and ovarian stimulation

Database(s): Ovid MEDLINE(R) 1948 to January Week 4 2011

Search Strategy: FERT_Q4_ovul_induct_economic_medline_250111_2

#	Searches
1	costs.tw.
2	cost effective$.tw.
3	economic.tw.
4	or/1-3
5	(metabolic adj cost).tw.
6	((energy or oxygen) adj cost).tw.
7	4 not (5 or 6)
8	randomized controlled trial.pt.
9	controlled clinical trial.pt.
10	DOUBLE BLIND METHOD/
11	SINGLE BLIND METHOD/
12	RANDOM ALLOCATION/
13	RANDOMIZED CONTROLLED TRIALS/
14	or/8-13
15	((single or double or triple or treble) adj5 (blind$ or mask$)).tw,sh.
16	clinical trial.pt.
17	exp CLINICAL TRIAL/
18	exp CLINICAL TRIALS AS TOPIC/
19	(clinic$ adj5 trial$).tw,sh.
20	PLACEBOS/
21	placebo$.tw,sh.
22	random$.tw,sh.
23	or/15-22
24	or/14,23
25	META ANALYSIS/
26	META ANALYSIS AS TOPIC/
27	meta analysis.pt.
28	(metaanaly$ or meta-analy$ or (meta adj analy$)).tw,sh.
29	(systematic$ adj5 (review$ or overview$)).tw,sh.
30	(methodologic$ adj5 (review$ or overview$)).tw,sh.
31	or/25-30
32	review$.pt.
33	(medline or medlars or embase or cinahl or cochrane or psycinfo or psychinfo or psychlit

	or psyclit or "web of science" or "science citation" or scisearch).tw.
34	((hand or manual$) adj2 search$).tw.
35	(electronic database$ or bibliographic database$ or computeri?ed database$ or online database$).tw,sh.
36	(pooling or pooled or mantel haenszel).tw,sh.
37	(peto or dersimonian or der simonian or fixed effect).tw,sh.
38	or/33-37
39	and/32,38
40	exp CASE-CONTROL STUDIES/
41	(case$ adj2 control$).tw.
42	exp COHORT STUDIES/
43	cohort$.tw.
44	or/40-43
45	or/24,31,39,44
46	letter.pt.
47	comment.pt.
48	editorial.pt.
49	historical article.pt.
50	or/46-49
51	45 not 50
52	(fertil$ or steril$ or infertil$ or subfertil$ or sub-fertil$ or fecund$ or subfecund$ or sub-fecund$ or assist$ reproduc$).ti,ab.
53	INFERTILITY, FEMALE/
54	INFERTILITY/
55	FERTILITY/
56	ANOVULATION/
57	OVULATION/ or OVULATION INHIBITION/
58	anovulat$.ti,ab.
59	oligo-ovulation.ti,ab.
60	"oligo ovulation".ti,ab.
61	Oligoovulat$.ti,ab.
62	exp FERTILIZATION IN VITRO/
63	IVF.ti,ab.
64	"in vitro fertili$".ti,ab.
65	"in?vitro fertili$".ti,ab.
66	ICSI.ti,ab.
67	Amenorrhea/
68	amenorrh$.ti,ab.
69	Hypogonadism/

70	(hypothalamic adj3 amenorrh$).ti,ab.
71	(hypogonadotro$ adj3 hypogonadism).ti,ab.
72	or/52-71
73	exp FERTILITY AGENTS, FEMALE/
74	exp GONADOTROPINS, PITUITARY/
75	(uFSH or rFSH or LH or hMG).ti,ab.
76	(gonadotrophin$ or gonadotropi$).ti,ab.
77	GnRH.ti,ab.
78	exp GONADOTROPIN-RELEASING HORMONE/
79	GnRHa.ti,ab.
80	(zoladex or synarel or decapeptyl).ti,ab.
81	exp DOPAMINE AGENTS/
82	(dopamin$ adj3 (agonist$ or agent$)).ti,ab.
83	BROMOCRIPTINE/
84	(cabergoline or bromocriptine).ti,ab.
85	AROMATASE INHIBITORS/ or AMINOGLUTETHIMIDE/ or FADROZOLE/
86	TESTOLACTONE/
87	(teslac or anastrozole or arimidex or letrozole or femara or exemestane or aromasin or vorozole or rivizor or formestane or lentaron or afema).ti,ab.
88	(aromatase adj3 inhibit$).ti,ab.
89	exp LIFE STYLE/
90	(life?style adj3 (change$ or adjustment$ or interven$)).ti,ab.
91	exp BODY WEIGHT CHANGES/
92	EXERCISE/
93	((reduc$ or decreas$ or stop$ or ceas$) adj3 exercis$).ti,ab.
94	exp ESTROGEN RECEPTOR MODULATORS/ or CLOMIPHENE/ or TAMOXIFEN/
95	(anti?estrogen$ or anti?oestrogen$).ti,ab.
96	(clomiphene or clomifene or tamoxifen).ti,ab.
97	METFORMIN/
98	(metformin or glucophage).ti,ab.
99	exp OVARY/su
100	((ovary or ovaries or ovarian) adj3 (drill$ or electrocauter$ or diatherm$)).ti,ab.
101	LAPAROSCOPY/
102	exp DIATHERMY/
103	and/101-102
104	(LOD or LOE).ti,ab.
105	exp ELECTROCOAGULATION/
106	exp GROWTH HORMONE/
107	(growth adj2 hormone$).ti,ab.

108	DEHYDROEPIANDROSTERONE/
109	DHEA.ti,ab.
110	or/73-100,103-109
111	and/51,72,110
112	limit 111 to english language
113	limit 112 to (animals and humans)
114	limit 112 to animals
115	114 not 113
116	112 not 115
117	and/7,116

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials 4th Quarter 2010

Search Strategy: FERT_Q4_ovul_induct_economic_cctr_250111_2

#	Searches
1	costs.tw.
2	cost effective$.tw.
3	economic.tw.
4	or/1-3
5	(metabolic adj cost).tw.
6	((energy or oxygen) adj cost).tw.
7	4 not (5 or 6)
8	(fertil$ or steril$ or infertil$ or subfertil$ or sub-fertil$ or fecund$ or subfecund$ or sub-fecund$ or assist$ reproduc$).ti,ab.
9	INFERTILITY, FEMALE/
10	INFERTILITY/
11	FERTILITY/
12	ANOVULATION/
13	OVULATION/ or OVULATION INHIBITION/
14	anovulat$.ti,ab.
15	oligo-ovulation.ti,ab.
16	"oligo ovulation".ti,ab.
17	Oligoovulat$.ti,ab.
18	exp FERTILIZATION IN VITRO/
19	IVF.ti,ab.
20	"in vitro fertili$".ti,ab.
21	"in?vitro fertili$".ti,ab.
22	ICSI.ti,ab.

23	Amenorrhea/
24	amenorrh$.ti,ab.
25	Hypogonadism/
26	(hypothalamic adj3 amenorrh$).ti,ab.
27	(hypogonadotro$ adj3 hypogonadism).ti,ab.
28	or/8-27
29	exp FERTILITY AGENTS, FEMALE/
30	exp GONADOTROPINS, PITUITARY/
31	(uFSH or rFSH or LH or hMG).ti,ab.
32	(gonadotrophin$ or gonadotropi$).ti,ab.
33	GnRH.ti,ab.
34	exp GONADOTROPIN-RELEASING HORMONE/
35	GnRHa.ti,ab.
36	(zoladex or synarel or decapeptyl).ti,ab.
37	exp DOPAMINE AGENTS/
38	(dopamin$ adj3 (agonist$ or agent$)).ti,ab.
39	BROMOCRIPTINE/
40	(cabergoline or bromocriptine).ti,ab.
41	AROMATASE INHIBITORS/ or AMINOGLUTETHIMIDE/ or FADROZOLE/
42	TESTOLACTONE/
43	(teslac or anastrozole or arimidex or letrozole or femara or exemestane or aromasin or vorozole or rivizor or formestane or lentaron or afema).ti,ab.
44	(aromatase adj3 inhibit$).ti,ab.
45	exp LIFE STYLE/
46	(life?style adj3 (change$ or adjustment$ or interven$)).ti,ab.
47	exp BODY WEIGHT CHANGES/
48	EXERCISE/
49	((reduc$ or decreas$ or stop$ or ceas$) adj3 exercis$).ti,ab.
50	exp ESTROGEN RECEPTOR MODULATORS/ or CLOMIPHENE/ or TAMOXIFEN/
51	(anti?estrogen$ or anti?oestrogen$).ti,ab.
52	(clomiphene or clomifene or tamoxifen).ti,ab.
53	METFORMIN/
54	(metformin or glucophage).ti,ab.
55	exp OVARY/su
56	((ovary or ovaries or ovarian) adj3 (drill$ or electrocauter$ or diatherm$)).ti,ab.
57	LAPAROSCOPY/
58	exp DIATHERMY/
59	and/57-58
60	(LOD or LOE).ti,ab.

61	exp ELECTROCOAGULATION/
62	exp GROWTH HORMONE/
63	(growth adj2 hormone$).ti,ab.
64	DEHYDROEPIANDROSTERONE/
65	DHEA.ti,ab.
66	or/29-56,59-65
67	and/28,66
68	and/7,67

Database(s): EMBASE 1980 to 2011 Week 04

Search Strategy: FERT_Q4_ovul_induct_economic_embase_250111_2

#	Searches
1	costs.tw.
2	cost effective$.tw.
3	economic.tw.
4	or/1-3
5	(metabolic adj cost).tw.
6	((energy or oxygen) adj cost).tw.
7	4 not (5 or 6)
8	CLINICAL TRIALS/
9	(clinic$ adj5 trial$).tw,sh.
10	SINGLE BLIND PROCEDURE/
11	DOUBLE BLIND PROCEDURE/
12	RANDOM ALLOCATION/
13	CROSSOVER PROCEDURE/
14	PLACEBO/
15	placebo$.tw,sh.
16	random$.tw,sh.
17	RANDOMIZED CONTROLLED TRIALS/
18	((single or double or triple or treble) adj (blind$ or mask$)).tw,sh.
19	randomi?ed control$ trial$.tw.
20	or/8-19
21	META ANALYSIS/
22	((meta adj analy$) or metaanalys$ or meta-analy$).tw,sh.
23	(systematic$ adj5 (review$ or overview$)).tw,sh.
24	(methodologic$ adj5 (review$ or overview$)).tw,sh.
25	or/21-24

26	review.pt.
27	(medline or medlars or embase).ab.
28	(scisearch or science citation index).ab.
29	(psychlit or psyclit or psychinfo or psycinfo or cinahl or cochrane).ab.
30	((hand or manual$) adj2 search$).tw.
31	(electronic database$ or bibliographic database$ or computeri?ed database$ or online database$).tw.
32	(pooling or pooled or mantel haenszel).tw.
33	(peto or dersimonian or "der simonian" or fixed effect).tw.
34	or/27-33
35	and/26,34
36	exp CASE CONTROL STUDY/
37	RETROSPECTIVE STUDY/
38	(case$ adj2 control$).tw.
39	COHORT ANALYSIS/
40	LONGITUDINAL STUDY/
41	FOLLOW UP/
42	PROSPECTIVE STUDY/
43	cohort$.tw.
44	or/36-43
45	or/20,25,35,44
46	(book or conference paper or editorial or letter or note or proceeding or short survey).pt.
47	45 not 46
48	(fertil$ or steril$ or infertil$ or subfertil$ or sub-fertil$ or fecund$ or subfecund$ or sub-fecund$ or assist$ reproduc$).ti,ab.
49	infertility/ or female infertility/ or subfertility/
50	FERTILITY/
51	exp OVARY INSUFFICIENCY/
52	OVULATION/
53	anovulat$.ti,ab.
54	oligo-ovulation.ti,ab.
55	"oligo ovulation".ti,ab.
56	Oligoovulat$.ti,ab.
57	FERTILIZATION IN VITRO/
58	IVF.ti,ab.
59	"in vitro fertili$".ti,ab.
60	"in?vitro fertili$".ti,ab.
61	ICSI.ti,ab.
62	INTRACYTOPLASMIC SPERM INJECTION/

63	AMENORRHEA/
64	amenorrh$.ti,ab.
65	HYPOGONADISM/
66	HYPOGONADOTROPIC HYPOGONADISM/
67	hypogona$.ti,ab.
68	or/48-67
69	exp FERTILITY PROMOTING AGENT/
70	(uFSH or rFSH or LH or hMG).ti,ab.
71	(gonadotrophin$ or gonadotropin$).ti,ab.
72	GnRH$.ti,ab.
73	(zoladex or synarel or decapeptyl).ti,ab.
74	DOPAMINE RECEPTOR STIMULATING AGENT/
75	(dopamin$ adj3 (agonist$ or agent$)).ti,ab.
76	BROMOCRIPTINE/
77	CABERGOLINE/
78	(cabergoline or bromocriptine).ti,ab.
79	AROMATASE INHIBITOR/ or AMINOGLUTETHIMIDE/ or AMINOGLUTETHIMIDE DERIVATIVE/ or AMINOGLUTETHIMIDE PHOSPHATE/ or ANASTROZOLE/ or EXEMESTANE/ or FADROZOLE/ or LETROZOLE/ or TESTOLACTONE/
80	(teslac or femara or aromasin or rivizor or lentaron or afema).ti,ab.
81	(aromatase adj3 inhibitor$).ti,ab.
82	LIFESTYLE MODIFICATION/
83	BODY WEIGHT/ or LEAN BODY WEIGHT/ or WEIGHT CONTROL/ or WEIGHT FLUCTUATION/ or WEIGHT GAIN/ or WEIGHT REDUCTION/
84	weight.ti,ab.
85	exp EXERCISE/
86	((reduc$ or decreas$ or stop$ or ceas$) adj3 exercis$).ti,ab.
87	ANTIESTROGEN/ or CLOMIFENE/ or CLOMIFENE CITRATE/ or TAMOXIFEN/ or TAMOXIFEN AZIRIDINE/ or TAMOXIFEN CITRATE/ or TAMOXIFEN DERIVATIVE/
88	(anti?estrogen$ or anti?oestrogen$).ti,ab.
89	(clomiphene or clomifene or tamoxifen).ti,ab.
90	METFORMIN/
91	(metformin or glucophage).ti,ab.
92	((ovary or ovaries or ovarian) adj3 (drill$ or electrocauter$ or diatherm$)).ti,ab.
93	exp OVARY/su
94	DIATHERMY/
95	LAPAROSCOPIC SURGERY/
96	LAPAROSCOPY/

97	or/95-96
98	and/94,97
99	(LOD or LOE).ti,ab.
100	ELECTROCOAGULATION/
101	exp GROWTH HORMONE/
102	(growth adj2 hormone$).ti,ab.
103	PRASTERONE/
104	DHEA.ti,ab.
105	or/69-93,98-104
106	and/47,68,105
107	limit 106 to english language
108	and/7,107

Database(s): EBM Reviews - Health Technology Assessment 1st Quarter 2011

Search Strategy: FERT_Q4_ovul_induct_economic_hta_250111_2

#	Searches
1	(fertil$ or steril$ or infertil$ or subfertil$ or sub-fertil$ or fecund$ or subfecund$ or sub-fecund$ or assist$ reproduc$).tw.
2	INFERTILITY, FEMALE/
3	INFERTILITY/
4	FERTILITY/
5	ANOVULATION/
6	OVULATION/ or OVULATION INHIBITION/
7	anovulat$.tw.
8	oligo-ovulation.tw.
9	"oligo ovulation".tw.
10	Oligoovulat$.tw.
11	exp FERTILIZATION IN VITRO/
12	IVF.tw.
13	"in vitro fertili$".tw.
14	"in?vitro fertili$".tw.
15	ICSI.tw.
16	Amenorrhea/
17	amenorrh$.tw.
18	Hypogonadism/
19	(hypothalamic adj3 amenorrh$).tw.
20	(hypogonadotro$ adj3 hypogonadism).tw.

21	or/1-20
22	exp FERTILITY AGENTS, FEMALE/
23	exp GONADOTROPINS, PITUITARY/
24	(uFSH or rFSH or LH or hMG).tw.
25	(gonadotrophin$ or gonadotropi$).tw.
26	GnRH.tw.
27	exp GONADOTROPIN-RELEASING HORMONE/
28	GnRHa.tw.
29	(zoladex or synarel or decapeptyl).tw.
30	exp DOPAMINE AGENTS/
31	(dopamin$ adj3 (agonist$ or agent$)).tw.
32	BROMOCRIPTINE/
33	(cabergoline or bromocriptine).tw.
34	AROMATASE INHIBITORS/ or AMINOGLUTETHIMIDE/ or FADROZOLE/
35	TESTOLACTONE/
36	(teslac or anastrozole or arimidex or letrozole or femara or exemestane or aromasin or vorozole or rivizor or formestane or lentaron or afema).tw.
37	(aromatase adj3 inhibit$).tw.
38	exp LIFE STYLE/
39	(life?style adj3 (change$ or adjustment$ or interven$)).tw.
40	exp BODY WEIGHT CHANGES/
41	EXERCISE/
42	((reduc$ or decreas$ or stop$ or ceas$) adj3 exercis$).tw.
43	exp ESTROGEN RECEPTOR MODULATORS/ or CLOMIPHENE/ or TAMOXIFEN/
44	(anti?estrogen$ or anti?oestrogen$).tw.
45	(clomiphene or clomifene or tamoxifen).tw.
46	METFORMIN/
47	(metformin or glucophage).tw.
48	exp OVARY/su
49	((ovary or ovaries or ovarian) adj3 (drill$ or electrocauter$ or diatherm$)).tw.
50	LAPAROSCOPY/
51	exp DIATHERMY/
52	and/50-51
53	(LOD or LOE).tw.
54	exp ELECTROCOAGULATION/
55	exp GROWTH HORMONE/
56	(growth adj2 hormone$).tw.
57	DEHYDROEPIANDROSTERONE/
58	DHEA.tw.

59	or/22-49,52-58
60	and/21,59

Database(s): EBM Reviews - NHS Economic Evaluation Database 1st Quarter 2011

Search Strategy: FERT_Q4_ovul_induct_economic_nhseed_250111_2

#	Searches
1	(fertil$ or steril$ or infertil$ or subfertil$ or sub-fertil$ or fecund$ or subfecund$ or sub-fecund$ or assist$ reproduc$).tw.
2	INFERTILITY, FEMALE/
3	INFERTILITY/
4	FERTILITY/
5	ANOVULATION/
6	OVULATION/ or OVULATION INHIBITION/
7	anovulat$.tw.
8	oligo-ovulation.tw.
9	"oligo ovulation".tw.
10	Oligoovulat$.tw.
11	exp FERTILIZATION IN VITRO/
12	IVF.tw.
13	"in vitro fertili$".tw.
14	"in?vitro fertili$".tw.
15	ICSI.tw.
16	Amenorrhea/
17	amenorrh$.tw.
18	Hypogonadism/
19	(hypothalamic adj3 amenorrh$).tw.
20	(hypogonadotro$ adj3 hypogonadism).tw.
21	or/1-20
22	exp FERTILITY AGENTS, FEMALE/
23	exp GONADOTROPINS, PITUITARY/
24	(uFSH or rFSH or LH or hMG).tw.
25	(gonadotrophin$ or gonadotropi$).tw.
26	GnRH.tw.
27	exp GONADOTROPIN-RELEASING HORMONE/
28	GnRHa.tw.
29	(zoladex or synarel or decapeptyl).tw.
30	exp DOPAMINE AGENTS/

31	(dopamin$ adj3 (agonist$ or agent$)).tw.
32	BROMOCRIPTINE/
33	(cabergoline or bromocriptine).tw.
34	AROMATASE INHIBITORS/ or AMINOGLUTETHIMIDE/ or FADROZOLE/
35	TESTOLACTONE/
36	(teslac or anastrozole or arimidex or letrozole or femara or exemestane or aromasin or vorozole or rivizor or formestane or lentaron or afema).tw.
37	(aromatase adj3 inhibit$).tw.
38	exp LIFE STYLE/
39	(life?style adj3 (change$ or adjustment$ or interven$)).tw.
40	exp BODY WEIGHT CHANGES/
41	EXERCISE/
42	((reduc$ or decreas$ or stop$ or ceas$) adj3 exercis$).tw.
43	exp ESTROGEN RECEPTOR MODULATORS/ or CLOMIPHENE/ or TAMOXIFEN/
44	(anti?estrogen$ or anti?oestrogen$).tw.
45	(clomiphene or clomifene or tamoxifen).tw.
46	METFORMIN/
47	(metformin or glucophage).tw.
48	exp OVARY/su
49	((ovary or ovaries or ovarian) adj3 (drill$ or electrocauter$ or diatherm$)).tw.
50	LAPAROSCOPY/
51	exp DIATHERMY/
52	and/50-51
53	(LOD or LOE).tw.
54	exp ELECTROCOAGULATION/
55	exp GROWTH HORMONE/
56	(growth adj2 hormone$).tw.
57	DEHYDROEPIANDROSTERONE/
58	DHEA.tw.
59	or/22-49,52-58
60	and/21,59

Database(s): Ovid MEDLINE(R) 1948 to July Week 1 2011

Search Strategy: FERT_Q4_ovul_induct_medline_rerun1_180711

#	**Searches**
1	randomized controlled trial.pt.
2	controlled clinical trial.pt.
3	DOUBLE BLIND METHOD/
4	SINGLE BLIND METHOD/
5	RANDOM ALLOCATION/
6	RANDOMIZED CONTROLLED TRIALS/
7	or/1-6
8	((single or double or triple or treble) adj5 (blind$ or mask$)).tw,sh.
9	clinical trial.pt.
10	exp CLINICAL TRIAL/
11	exp CLINICAL TRIALS AS TOPIC/
12	(clinic$ adj5 trial$).tw,sh.
13	PLACEBOS/
14	placebo$.tw,sh.
15	random$.tw,sh.
16	or/8-15
17	or/7,16
18	META ANALYSIS/
19	META ANALYSIS AS TOPIC/
20	meta analysis.pt.
21	(metaanaly$ or meta-analy$ or (meta adj analy$)).tw,sh.
22	(systematic$ adj5 (review$ or overview$)).tw,sh.
23	(methodologic$ adj5 (review$ or overview$)).tw,sh.
24	or/18-23
25	review$.pt.
26	(medline or medlars or embase or cinahl or cochrane or psycinfo or psychinfo or psychlit or psyclit or "web of science" or "science citation" or scisearch).tw.
27	((hand or manual$) adj2 search$).tw.

28	(electronic database$ or bibliographic database$ or computeri?ed database$ or online database$).tw,sh.
29	(pooling or pooled or mantel haenszel).tw,sh.
30	(peto or dersimonian or der simonian or fixed effect).tw,sh.
31	or/26-30
32	and/25,31
33	exp CASE-CONTROL STUDIES/
34	(case$ adj2 control$).tw.
35	exp COHORT STUDIES/
36	cohort$.tw.
37	or/33-36
38	or/17,24,32,37
39	letter.pt.
40	comment.pt.
41	editorial.pt.
42	historical article.pt.
43	or/39-42
44	38 not 43
45	(fertil$ or steril$ or infertil$ or subfertil$ or sub-fertil$ or fecund$ or subfecund$ or sub-fecund$ or assist$ reproduc$).ti,ab.
46	INFERTILITY, FEMALE/
47	INFERTILITY/
48	FERTILITY/
49	ANOVULATION/
50	OVULATION/ or OVULATION INHIBITION/
51	POLYCYSTIC OVARY SYNDROME/
52	PCOS.ti,ab.
53	anovulat$.ti,ab.
54	(polycystic adj2 ovar$).ti,ab.
55	oligo-ovulation.ti,ab.
56	"oligo ovulation".ti,ab.
57	Oligoovulat$.ti,ab.

58	exp FERTILIZATION IN VITRO/
59	IVF.ti,ab.
60	"in vitro fertili$".ti,ab.
61	"in?vitro fertili$".ti,ab.
62	ICSI.ti,ab.
63	AMENORRHEA/
64	amenorrh$.ti,ab.
65	HYPOGONADISM/
66	(hypothalamic adj3 amenorrh$).ti,ab.
67	(hypogonadotro$ adj3 hypogonadism).ti,ab.
68	or/45-67
69	exp FERTILITY AGENTS, FEMALE/
70	exp GONADOTROPINS, PITUITARY/
71	(uFSH or rFSH or LH or hMG).ti,ab.
72	(gonadotrophin$ or gonadotropi$).ti,ab.
73	GnRH.ti,ab.
74	exp GONADOTROPIN-RELEASING HORMONE/
75	GnRHa.ti,ab.
76	(zoladex or synarel or decapeptyl).ti,ab.
77	exp ESTROGENS/
78	exp PROGESTERONE/
79	(oestrogen$ or estrogen$ or progesterone$).ti,ab.
80	exp CONTRACEPTIVES, ORAL/
81	OCP.ti,ab.
82	(contraceptive adj pill$).ti,ab.
83	exp DOPAMINE AGENTS/
84	(dopamin$ adj3 (agonist$ or agent$)).ti,ab.
85	BROMOCRIPTINE/
86	(cabergoline or bromocriptine).ti,ab.
87	AROMATASE INHIBITORS/ or AMINOGLUTETHIMIDE/ or FADROZOLE/
88	TESTOLACTONE/

89	(teslac or anastrozole or arimidex or letrozole or femara or exemestane or aromasin or vorozole or rivizor or formestane or lentaron or afema).ti,ab.
90	(aromatase adj3 inhibit$).ti,ab.
91	exp LIFE STYLE/
92	(life?style adj3 (change$ or adjustment$ or interven$)).ti,ab.
93	exp BODY WEIGHT CHANGES/
94	EXERCISE/
95	((reduc$ or decreas$ or stop$ or ceas$) adj3 exercis$).ti,ab.
96	exp ESTROGEN RECEPTOR MODULATORS/ or CLOMIPHENE/ or TAMOXIFEN/
97	(anti?estrogen$ or anti?oestrogen$).ti,ab.
98	(clomiphene or clomifene or tamoxifen).ti,ab.
99	METFORMIN/
100	(metformin or glucophage).ti,ab.
101	exp OVARY/su
102	((ovary or ovaries or ovarian) adj3 (drill$ or electrocauter$ or diatherm$)).ti,ab.
103	LAPAROSCOPY/
104	exp DIATHERMY/
105	and/103-104
106	and/101,105
107	or/102,106
108	(LOD or LOE).ti,ab.
109	exp ELECTROCOAGULATION/
110	exp GROWTH HORMONE/
111	(growth adj2 hormone$).ti,ab.
112	DEHYDROEPIANDROSTERONE/
113	DHEA.ti,ab.
114	or/69-100,107-113
115	(pretreatment adj phase$).ti,ab.
116	(pre adj treatment adj phase$).ti,ab.
117	(down adj regulation).ti,ab.
118	DOWN-REGULATION/

119	exp OVULATION INDUCTION/
120	((ovarian or ovaries) adj2 stimulat$).ti,ab.
121	trigger$.ti,ab.
122	(luteal adj phase adj2 support$).ti,ab.
123	(pre adj stimulat$).ti,ab.
124	prestimulat$.ti,ab.
125	or/115-124
126	or/114,125
127	and/68,126
128	and/44,127
129	limit 128 to english language
130	limit 129 to (animals and humans)
131	limit 129 to animals
132	131 not 130
133	129 not 132
134	limit 133 to yr="2010 -Current"

Database(s): Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations July 15, 2011

Search Strategy: FERT_Q4_ovul_induct_medline_in_process_rerun1_180711

#	**Searches**
1	(fertil$ or steril$ or infertil$ or subfertil$ or sub-fertil$ or fecund$ or subfecund$ or sub-fecund$ or assist$ reproduc$).ti,ab.
2	anovulat$.ti,ab.
3	oligo-ovulation.ti,ab.
4	"oligo ovulation".ti,ab.
5	Oligoovulat$.ti,ab.
6	IVF.ti,ab.
7	"in vitro fertili$".ti,ab.
8	"in?vitro fertili$".ti,ab.
9	ICSI.ti,ab.
10	amenorrh$.ti,ab.

11	(hypogonadotro$ adj3 hypogonadism).ti,ab.
12	(hypothalamic adj3 amenorrh$).ti,ab.
13	or/1-12
14	(uFSH or rFSH or LH or hMG).ti,ab.
15	(gonadotrophin$ or gonadotropin$).ti,ab.
16	GnRH.ti,ab.
17	GnRHa.ti,ab.
18	(zoladex or synarel or decapeptyl).ti,ab.
19	(dopamin$ adj3 (agonist$ or agent$)).ti,ab.
20	(cabergoline or bromocriptine).ti,ab.
21	(teslac or anastrozole or arimidex or letrozole or femara or exemestane or aromasin or vorozole or rivizor or formestane or lentaron or afema).ti,ab.
22	(aromatase adj3 inhibit$).ti,ab.
23	testolactone.ti,ab.
24	(life?style adj3 (change$ or adjustment$ or interven$)).ti,ab.
25	((reduc$ or decreas$ or stop$ or ceas$) adj3 exercis$).ti,ab.
26	(anti?estrogen$ or anti?oestrogen$).ti,ab.
27	(clomiphene or clomifene or tamoxifen).ti,ab.
28	(metformin or glucophage).ti,ab.
29	((ovary or ovaries or ovarian) adj3 (drill$ or electrocauter$ or diatherm$)).ti,ab.
30	(LOD or LOE).ti,ab.
31	(growth adj2 hormone$).ti,ab.
32	dehydroepiandrosterone.ti,ab.
33	DHEA.ti,ab.
34	(pretreatment adj phase$).ti,ab.
35	(pre adj treatment adj phase$).ti,ab.
36	(down adj regulation).ti,ab.
37	((ovarian or ovaries) adj2 stimulat$).ti,ab.
38	trigger$.ti,ab.
39	(luteal adj phase adj2 support$).ti,ab.
40	(pre adj stimulat$).ti,ab.

41	prestimulat$.ti,ab.
42	or/14-41
43	and/13,42
44	limit 43 to yr="2010 -Current"

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials 3rd Quarter 2011

Search Strategy: FERT_Q4_ovul_induct_cctr_rerun1_180711

#	**Searches**
1	(fertil$ or steril$ or infertil$ or subfertil$ or sub-fertil$ or fecund$ or subfecund$ or sub-fecund$ or assist$ reproduc$).ti,ab.
2	INFERTILITY, FEMALE/
3	INFERTILITY/
4	FERTILITY/
5	ANOVULATION/
6	OVULATION/ or OVULATION INHIBITION/
7	POLYCYSTIC OVARY SYNDROME/
8	PCOS.ti,ab.
9	anovulat$.ti,ab.
10	(polycystic adj2 ovar$).ti,ab.
11	oligo-ovulation.ti,ab.
12	"oligo ovulation".ti,ab.
13	Oligoovulat$.ti,ab.
14	exp FERTILIZATION IN VITRO/
15	IVF.ti,ab.
16	"in vitro fertili$".ti,ab.
17	"in?vitro fertili$".ti,ab.
18	ICSI.ti,ab.
19	AMENORRHEA/
20	amenorrh$.ti,ab.
21	HYPOGONADISM/

22	(hypothalamic adj3 amenorrh$).ti,ab.
23	(hypogonadotro$ adj3 hypogonadism).ti,ab.
24	or/1-23
25	exp FERTILITY AGENTS, FEMALE/
26	exp GONADOTROPINS, PITUITARY/
27	(uFSH or rFSH or LH or hMG).ti,ab.
28	(gonadotrophin$ or gonadotropi$).ti,ab.
29	GnRH.ti,ab.
30	exp GONADOTROPIN-RELEASING HORMONE/
31	GnRHa.ti,ab.
32	(zoladex or synarel or decapeptyl).ti,ab.
33	exp ESTROGENS/
34	exp PROGESTERONE/
35	(oestrogen$ or estrogen$ or progesterone$).ti,ab.
36	exp CONTRACEPTIVES, ORAL/
37	OCP.ti,ab.
38	(contraceptive adj pill$).ti,ab.
39	exp DOPAMINE AGENTS/
40	(dopamin$ adj3 (agonist$ or agent$)).ti,ab.
41	BROMOCRIPTINE/
42	(cabergoline or bromocriptine).ti,ab.
43	AROMATASE INHIBITORS/ or AMINOGLUTETHIMIDE/ or FADROZOLE/
44	TESTOLACTONE/
45	(teslac or anastrozole or arimidex or letrozole or femara or exemestane or aromasin or vorozole or rivizor or formestane or lentaron or afema).ti,ab.
46	(aromatase adj3 inhibit$).ti,ab.
47	exp LIFE STYLE/
48	(life?style adj3 (change$ or adjustment$ or interven$)).ti,ab.
49	exp BODY WEIGHT CHANGES/
50	EXERCISE/
51	((reduc$ or decreas$ or stop$ or ceas$) adj3 exercis$).ti,ab.

52	exp ESTROGEN RECEPTOR MODULATORS/ or CLOMIPHENE/ or TAMOXIFEN/
53	(anti?estrogen$ or anti?oestrogen$).ti,ab.
54	(clomiphene or clomifene or tamoxifen).ti,ab.
55	METFORMIN/
56	(metformin or glucophage).ti,ab.
57	exp OVARY/su
58	((ovary or ovaries or ovarian) adj3 (drill$ or electrocauter$ or diatherm$)).ti,ab.
59	LAPAROSCOPY/
60	exp DIATHERMY/
61	and/59-60
62	and/57,61
63	or/58,62
64	(LOD or LOE).ti,ab.
65	exp ELECTROCOAGULATION/
66	exp GROWTH HORMONE/
67	(growth adj2 hormone$).ti,ab.
68	DEHYDROEPIANDROSTERONE/
69	DHEA.ti,ab.
70	or/25-56,63-69
71	(pretreatment adj phase$).ti,ab.
72	(pre adj treatment adj phase$).ti,ab.
73	(down adj regulation).ti,ab.
74	DOWN-REGULATION/
75	exp OVULATION INDUCTION/
76	((ovarian or ovaries) adj2 stimulat$).ti,ab.
77	trigger$.ti,ab.
78	(luteal adj phase adj2 support$).ti,ab.
79	(pre adj stimulat$).ti,ab.
80	prestimulat$.ti,ab.
81	or/71-80
82	or/70,81

83	and/24,82
84	limit 83 to yr="2010 -Current"

Database(s): EBM Reviews - Cochrane Database of Systematic Reviews 2005 to June 2011, EBM Reviews - Database of Abstracts of Reviews of Effects 3rd Quarter 2011

Search Strategy: FERT_Q4_ovul_induct_cdsrdare_rerun1_200711

#	**Searches**
1	(fertil$ or steril$ or infertil$ or subfertil$ or sub-fertil$ or fecund$ or subfecund$ or sub-fecund$ or assist$ reproduc$).tw,tx.
2	INFERTILITY, FEMALE.kw.
3	INFERTILITY.kw.
4	FERTILITY.kw.
5	ANOVULATION.kw.
6	(OVULATION or OVULATION INHIBITION).kw.
7	anovulat$.tw,tx.
8	oligo-ovulation.tw,tx.
9	"oligo ovulation".tw,tx.
10	Oligoovulat$.tw,tx.
11	FERTILIZATION IN VITRO.kw.
12	IVF.tw,tx.
13	"in vitro fertili$".tw,tx.
14	"in?vitro fertili$".tw,tx.
15	ICSI.tw,tx.
16	AMENORRHEA.kw.
17	amenorrh$.tw,tx.
18	HYPOGONADISM.kw.
19	(hypothalamic adj3 amenorrh$).tw,tx.
20	(hypogonadotro$ adj3 hypogonadism).tw,tx.
21	or/1-20
22	FERTILITY AGENTS, FEMALE.kw.
23	GONADOTROPINS, PITUITARY.kw.

24	(uFSH or rFSH or LH or hMG).tw,tx.
25	(gonadotrophin$ or gonadotropi$).tw,tx.
26	GnRH.tw,tx.
27	GONADOTROPIN-RELEASING HORMONE.kw.
28	GnRHa.tw,tx.
29	(zoladex or synarel or decapeptyl).tw,tx.
30	ESTROGENS.kw.
31	PROGESTERONE.kw.
32	(oestrogen$ or estrogen$ or progesterone$).tw,tx.
33	CONTRACEPTIVES, ORAL.kw.
34	OCP.tw,tx.
35	(contraceptive adj pill$).ti,ab.
36	DOPAMINE AGENTS.kw.
37	(dopamin$ adj3 (agonist$ or agent$)).tw,tx.
38	BROMOCRIPTINE.kw.
39	(cabergoline or bromocriptine).tw,tx.
40	(AROMATASE INHIBITORS or AMINOGLUTETHIMIDE or FADROZOLE).kw.
41	TESTOLACTONE.kw.
42	(teslac or anastrozole or arimidex or letrozole or femara or exemestane or aromasin or vorozole or rivizor or formestane or lentaron or afema).tw,tx.
43	(aromatase adj3 inhibit$).tw,tx.
44	LIFE STYLE.kw.
45	(life?style adj3 (change$ or adjustment$ or interven$)).tw,tx.
46	BODY WEIGHT CHANGES.kw.
47	EXERCISE.kw.
48	((reduc$ or decreas$ or stop$ or ceas$) adj3 exercis$).tw,tx.
49	(ESTROGEN RECEPTOR MODULATORS or CLOMIPHENE or TAMOXIFEN).kw.
50	(anti?estrogen$ or anti?oestrogen$).tw,tx.
51	(clomiphene or clomifene or tamoxifen).tw,tx.
52	METFORMIN.kw.
53	(metformin or glucophage).tw,tx.

54	or/22-53
55	OVARY.kw.
56	((ovary or ovaries or ovarian) adj3 (drill$ or electrocauter$ or diatherm$)).tw,tx.
57	LAPAROSCOPY.kw.
58	DIATHERMY.kw.
59	and/57-58
60	and/55,59
61	or/56,60
62	(LOD or LOE).tw,tx.
63	ELECTROCOAGULATION.kw.
64	GROWTH HORMONE.kw.
65	(growth adj2 hormone$).tw,tx.
66	DEHYDROEPIANDROSTERONE.kw.
67	DHEA.tw,tx.
68	(pretreatment adj phase$).tw,tx.
69	(pre adj treatment adj phase$).tw,tx.
70	(down adj regulation).tw,tx.
71	DOWN-REGULATION.kw.
72	OVULATION INDUCTION.kw.
73	((ovarian or ovaries) adj2 stimulat$).tw,tx.
74	trigger$.tw,tx.
75	(luteal adj phase adj2 support$).tw,tx.
76	or/62-75
77	or/54,61,76
78	and/21,77
79	limit 78 to last 2 years

Database(s): Embase 1980 to 2011 Week 28

Search Strategy: FERT_Q4_ovul_induct_embase_rerun1_210711

#	**Searches**
1	CLINICAL TRIALS/
2	(clinic$ adj5 trial$).tw,sh.
3	SINGLE BLIND PROCEDURE/
4	DOUBLE BLIND PROCEDURE/
5	RANDOM ALLOCATION/
6	CROSSOVER PROCEDURE/
7	PLACEBO/
8	placebo$.tw,sh.
9	random$.tw,sh.
10	RANDOMIZED CONTROLLED TRIALS/
11	((single or double or triple or treble) adj (blind$ or mask$)).tw,sh.
12	randomi?ed control$ trial$.tw.
13	or/1-12
14	META ANALYSIS/
15	((meta adj analy$) or metaanalys$ or meta-analy$).tw,sh.
16	(systematic$ adj5 (review$ or overview$)).tw,sh.
17	(methodologic$ adj5 (review$ or overview$)).tw,sh.
18	or/14-17
19	review.pt.
20	(medline or medlars or embase).ab.
21	(scisearch or science citation index).ab.
22	(psychlit or psyclit or psychinfo or psycinfo or cinahl or cochrane).ab.
23	((hand or manual$) adj2 search$).tw.
24	(electronic database$ or bibliographic database$ or computeri?ed database$ or online database$).tw.
25	(pooling or pooled or mantel haenszel).tw.
26	(peto or dersimonian or "der simonian" or fixed effect).tw.
27	or/20-26

28	and/19,27
29	exp CASE CONTROL STUDY/
30	RETROSPECTIVE STUDY/
31	(case$ adj2 control$).tw.
32	COHORT ANALYSIS/
33	LONGITUDINAL STUDY/
34	FOLLOW UP/
35	PROSPECTIVE STUDY/
36	cohort$.tw.
37	or/29-36
38	or/13,18,28,37
39	(book or conference paper or editorial or letter or note or proceeding or short survey).pt.
40	38 not 39
41	(fertil$ or steril$ or infertil$ or subfertil$ or sub-fertil$ or fecund$ or subfecund$ or sub-fecund$ or assist$ reproduc$).ti,ab.
42	infertility/ or female infertility/ or subfertility/
43	FERTILITY/
44	exp OVARY INSUFFICIENCY/
45	OVULATION/
46	anovulat$.ti,ab.
47	oligo-ovulation.ti,ab.
48	"oligo ovulation".ti,ab.
49	Oligoovulat$.ti,ab.
50	FERTILIZATION IN VITRO/
51	IVF.ti,ab.
52	"in vitro fertili$".ti,ab.
53	"in?vitro fertili$".ti,ab.
54	ICSI.ti,ab.
55	INTRACYTOPLASMIC SPERM INJECTION/
56	AMENORRHEA/
57	amenorrh$.ti,ab.

58	HYPOGONADISM/
59	HYPOGONADOTROPIC HYPOGONADISM/
60	hypogona$.ti,ab.
61	or/41-60
62	exp FERTILITY PROMOTING AGENT/
63	(uFSH or rFSH or LH or hMG).ti,ab.
64	(gonadotrophin$ or gonadotropin$).ti,ab.
65	GnRH$.ti,ab.
66	(zoladex or synarel or decapeptyl).ti,ab.
67	exp ESTROGEN/
68	PROGESTERONE/
69	(oestrogen$ or estrogen$ or progesterone$).ti,ab.
70	exp ORAL CONTRACEPTIVE AGENT/
71	OCP.ti,ab.
72	(contraceptive adj pill$).ti,ab.
73	DOPAMINE RECEPTOR STIMULATING AGENT/
74	(dopamin$ adj3 (agonist$ or agent$)).ti,ab.
75	BROMOCRIPTINE/
76	CABERGOLINE/
77	(cabergoline or bromocriptine).ti,ab.
78	AROMATASE INHIBITOR/ or AMINOGLUTETHIMIDE/ or AMINOGLUTETHIMIDE DERIVATIVE/ or AMINOGLUTETHIMIDE PHOSPHATE/ or ANASTROZOLE/ or EXEMESTANE/ or FADROZOLE/ or LETROZOLE/ or TESTOLACTONE/
79	(teslac or femara or aromasin or rivizor or lentaron or afema).ti,ab.
80	(aromatase adj3 inhibitor$).ti,ab.
81	LIFESTYLE MODIFICATION/
82	BODY WEIGHT/ or LEAN BODY WEIGHT/ or WEIGHT CONTROL/ or WEIGHT FLUCTUATION/ or WEIGHT GAIN/ or WEIGHT REDUCTION/
83	weight.ti,ab.
84	exp EXERCISE/
85	((reduc$ or decreas$ or stop$ or ceas$) adj3 exercis$).ti,ab.

86	ANTIESTROGEN/ or CLOMIFENE/ or CLOMIFENE CITRATE/ or TAMOXIFEN/ or TAMOXIFEN AZIRIDINE/ or TAMOXIFEN CITRATE/ or TAMOXIFEN DERIVATIVE/
87	(anti?estrogen$ or anti?oestrogen$).ti,ab.
88	(clomiphene or clomifene or tamoxifen).ti,ab.
89	METFORMIN/
90	(metformin or glucophage).ti,ab.
91	or/62-90
92	((ovary or ovaries or ovarian) adj3 (drill$ or electrocauter$ or diatherm$)).ti,ab.
93	exp OVARY/su
94	DIATHERMY/
95	LAPAROSCOPIC SURGERY/
96	LAPAROSCOPY/
97	or/95-96
98	and/94,97
99	or/92,98
100	(LOD or LOE).ti,ab.
101	ELECTROCOAGULATION/
102	exp GROWTH HORMONE/
103	(growth adj2 hormone$).ti,ab.
104	PRASTERONE/
105	DHEA.ti,ab.
106	(pretreatment adj phase$).ti,ab.
107	(pre adj treatment adj phase$).ti,ab.
108	(down adj regulation).ti,ab.
109	DOWN REGULATION/
110	OVULATION INDUCTION/
111	((ovarian or ovaries) adj2 stimulat$).ti,ab.
112	trigger$.ti,ab.
113	(luteal adj phase adj2 support$).ti,ab.
114	(pre adj stimulat$).ti,ab.
115	prestimulat$.ti,ab.

116	or/100-115
117	or/91,99,116
118	and/61,117
119	and/40,118
120	limit 119 to english language
121	limit 120 to yr="2010 -Current"

Cinahl Ebsco

FERT_Q4_ovul_induct_cinahl_rerun1_220711

#	Query
S99	S21 and S95
S98	S21 and S95
S97	S21 and S95
S96	S21 and S95
S95	S93 or S94
S94	S75 or S76 or S77 or S78 or S79 or S80 or S81 or S82 or S83 or S84 or S85 or S86 or S87 or S88 or S89 or S90 or S91 or S92
S93	S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32 or S33 or S34 or S35 or S36 or S37 or S38 or S39 or S40 or S41 or S42 or S43 or S44 or S45 or S46 or S47 or S48 or S49 or S50 or S51 or S52 or S53 or S54 or S55 or S56 or S57 or S58 or S59 or S60 or S61 or S62 or S63 or S64 or S65 or S66 or S67 or S68 or S69 or S70 or S71 or S72
S92	TI (pre-stimulat*) or AB (pre-stimulat*)
S91	AB ("luteal phase support")
S90	TI ("luteal phase support")
S89	TI (trigger*) or AB (trigger*)
S88	AB (ovar* N2 stimulat*)
S87	TI (ovar* N2 stimulat*)

S86	(MH "OVULATION INDUCTION")
S85	TI (down-regulat*) or AB (down-regulat*)
S84	TI (pre-treatment) or AB (pre-treatment)
S83	TI (DHEA) or AB (DHEA)
S82	(MH "PRASTERONE")
S81	AB (growth N2 hormone*)
S80	TI (growth N2 hormone*)
S79	(MH "HUMAN GROWTH HORMONE")
S78	(MH "ELECTROCOAGULATION+")
S77	AB (LOD) or AB (LOE)
S76	TI (LOD) or TI (LOE)
S75	S73 and S74
S74	(MH "DIATHERMY")
S73	(MH "LAPAROSCOPY")
S72	AB (drill* or electrocauter* or diatherm*)
S71	TI (drill* or electrocauter* or diatherm*)
S70	(MH "OVARY/SU")
S69	AB (metformin) or AB (glucophage)
S68	TI (metformin) or TI (glucophage)
S67	(MH "METFORMIN")
S66	AB (tamoxifene) or AB (clomiphene) or AB (clomifene)
S65	TI (tamoxifene) or TI (clomiphene) or TI (clomifene)
S64	TI (anti-oestrogen*) or AB (anti-oestrogen*)
S63	TI (anti-estrogen*) or AB (anti-estrogen*)

S62	(MH "ESTROGEN RECEPTOR MODULATORS") OR (MH "ESTROGEN ANTAGONISTS+")
S61	TI (exercis*) or AB (exercis*)
S60	(MH "EXERCISE")
S59	(MH "BODY WEIGHT CHANGES+")
S58	AB (life-style N3 interven*)
S57	TI (life-style N3 interven*)
S56	AB (life-style N3 adjustment*)
S55	TI (life-style N3 adjustment*)
S54	AB (life-style N3 change*)
S53	TI (life-style N3 change*)
S52	(MH "LIFE STYLE+")
S51	AB (aminoglutethimide or testolactone or teslac or arimidex or letrozole or femara or exemestane or aromasin or vorozole or rivizor or formestane or lentaron or fadrozole or afema)
S50	TI (aminoglutethimide or testolactone or teslac or arimidex or letrozole or femara or exemestane or aromasin or vorozole or rivizor or formestane or lentaron or fadrozole or afema)
S49	AB (aromatase N3 inhibitor*)
S48	TI (aromatase N3 inhibitor*)
S47	(MH "AROMATASE INHIBITORS+")
S46	AB (cabergoline) or AB (bromocriptine)
S45	TI (cabergoline) or TI (bromocriptine)
S44	(MH "BROMOCRIPTINE")
S43	TI (dopamine N3 agents*) or AB (dopamine N3 agents*)
S42	TI (dopamine N3 agonist*) or AB (dopamine N3 agonist*)
S41	(MH "DOPAMINE AGENTS+")
S40	TI (contraceptive N3 pill*) or AB (contraceptive N3 pill*)

S39	TI (OCP) or AB (OCP)
S38	(MH "CONTRACEPTIVES, ORAL+")
S37	AB (oestrogen* or estrogen* or progesterone*)
S36	TI (oestrogen* or estrogen* or progesterone*)
S35	(MH "PROGESTERONE+")
S34	(MH "ESTROGENS+")
S33	AB (zoladex) or AB (synarel) or AB (decapeptyl)
S32	Ti (zoladex) or TI (synarel) or TI (decapeptyl)
S31	TI (GnRH) or AB (GnRH)
S30	(MH "GONADORELIN+")
S29	TI (GnRHa) or AB (GnRHa)
S28	AB (gonadotrophin* or gonadotropin*)
S27	TI (gonadotrophin* or gonadotropin*)
S26	TI (hMG) or AB (hMG)
S25	TI (rFSH) or AB (rFSH)
S24	TI (uFSH) or AB (uFSH)
S23	(MH "GONADOTROPINS, PITUITARY+")
S22	(MH "FERTILITY AGENTS+") OR (MH "MENSTRUATION INDUCING AGENTS+")
S21	S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20
S20	TI (polycystic) or AB (polycystic)
S19	(MH "POLYCYSTIC OVARY SYNDROME")
S18	(MH "HYPOGONADISM+")
S17	TI (amenorrh*) or AB (amenorrh*)
S16	(MH "AMENORRHEA")

S15	AB (intracytoplasmic sperm injection*)
S14	TI (intracytoplasmic sperm injection*)
S13	TI (ICSI) or AB (ICSI)
S12	TI (in vitro fertili*) or AB (in vitro fertili*)
S11	TI (IVF) or AB (IVF)
S10	(MH "FERTILIZATION IN VITRO")
S9	TI (oligo-ovulat*) or AB (oligo-ovulat*)
S8	TI (anovulat*) or AB (anovulat*)
S7	(MH "OVULATION")
S6	(MH "FERTILITY")
S5	TI (assist* reproduc*) or AB (assist* reproduc*)
S4	(MH "INFERTILITY RISK (Saba CCC)")
S3	(MH "INFERTILITY")
S2	AB (fertil* or steril* or infertil* or sub-fertil* or fecund* or sub-fecund*)
S1	TI (fertil* or steril* or infertil* or sub-fertil* or fecund* or sub-fecund*)

Chapter 12. Intrauterine insemination

Database(s): Ovid MEDLINE(R) 1948 to December Week 4 2010

Search Strategy: FERT_Q5_IUI_unexplained_medline_110111

1	randomized controlled trial.pt.	293371
2	controlled clinical trial.pt.	80564
3	DOUBLE BLIND METHOD/	106239
4	SINGLE BLIND METHOD/	14251
5	RANDOM ALLOCATION/	69106
6	RANDOMIZED CONTROLLED TRIALS/	68959
7	or/1-6	495350
8	((single or double or triple or treble) adj5 (blind$ or mask$)).tw,sh.	104562
9	clinical trial.pt.	453342
10	exp CLINICAL TRIAL/	613768
11	exp CLINICAL TRIALS AS TOPIC/	231993
12	(clinic$ adj5 trial$).tw,sh.	155483
13	PLACEBOS/	28751
14	placebo$.tw,sh.	136466
15	random$.tw,sh.	640587
16	or/8-15	1107607
17	or/7,16	1112379
18	META ANALYSIS/	25913
19	META ANALYSIS AS TOPIC/	10611
20	meta analysis.pt.	25913
21	(metaanaly$ or meta-analy$ or (meta adj analy$)).tw,sh.	45242
22	(systematic$ adj5 (review$ or overview$)).tw,sh.	26971
23	(methodologic$ adj5 (review$ or overview$)).tw,sh.	2308
24	or/18-23	64734
25	review$.pt.	1546249
26	(medline or medlars or embase or cinahl or cochrane or psycinfo or psychinfo or psychlit or psyclit or "web of science" or "science citation" or scisearch).tw.	41194
27	((hand or manual$) adj2 search$).tw.	4355
28	(electronic database$ or bibliographic database$ or computeri?ed database$ or online database$).tw,sh.	7245
29	(pooling or pooled or mantel haenszel).tw,sh.	34887
30	(peto or dersimonian or der simonian or fixed effect).tw,sh.	1806
31	or/26-30	78513
32	and/25,31	35859
33	or/24,32	83855

34	letter.pt.	689425
35	case report.tw.	151951
36	comment.pt.	420615
37	editorial.pt.	263457
38	historical article.pt.	265519
39	or/34-38	1423449
40	17 not 39	1070067
41	33 not 39	79185
42	or/40-41	1111107
43	(fertil$ or steril$ or infertil$ or subfertil$ or sub-fertil$ or fecund$ or subfecund$ or sub-fecund$ or assist$ reproduc$).ti,ab.	166866
44	INFERTILITY, FEMALE/	20500
45	INFERTILITY/	7578
46	ANOVULATION/	1796
47	anovulat$.ti,ab.	3893
48	oligo-ovulation.ti,ab.	41
49	"oligo ovulation".ti,ab.	41
50	Oligoovulat$.ti,ab.	36
51	or/43-50	177445
52	exp Insemination, Artificial/	8960
53	(artificial$ adj3 inseminat$).ti,ab.	4413
54	(IUI or SIUI).ti,ab.	909
55	or/52-54	10656
56	and/51,55	5011
57	and/42,56	726
58	limit 57 to english language	696
59	limit 58 to (animals and humans)	4
60	limit 58 to animal	259
61	60 not 59	255
62	58 not 61	441

Database(s): Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations January 07, 2011

Search Strategy: FERT_Q5_IUI_unexplained_medline_in_process_100111

#	Searches
1	(fertil$ or steril$ or infertil$ or subfertil$ or sub-fertil$ or fecund$ or subfecund$ or sub-fecund$ or assist$ reproduc$).ti,ab.
2	anovulat$.ti,ab.

3	oligo-ovulation.ti,ab.
4	"oligo ovulation".ti,ab.
5	Oligoovulat$.ti,ab.
6	or/1-5
7	(artificial$ adj3 inseminat$).ti,ab.
8	(IUI or SIUI).ti,ab.
9	or/7-8
10	and/6,9

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials 4th Quarter 2010

Search Strategy: FERT_Q5_IUI_unexplained_cctr_100111

#	Searches
1	(fertil$ or steril$ or infertil$ or subfertil$ or sub-fertil$ or fecund$ or subfecund$ or sub-fecund$ or assist$ reproduc$).ti,ab.
2	INFERTILITY, FEMALE/
3	INFERTILITY/
4	ANOVULATION/
5	anovulat$.ti,ab.
6	oligo-ovulation.ti,ab.
7	"oligo ovulation".ti,ab.
8	Oligoovulat$.ti,ab.
9	or/1-8
10	exp INSEMINATION, ARTIFICIAL/
11	(artificial$ adj3 inseminat$).ti,ab.
12	(IUI or SIUI).ti,ab.
13	or/10-12
14	and/9,13

Database(s): EBM Reviews - Cochrane Database of Systematic Reviews 2005 to December 2010, EBM Reviews - Database of Abstracts of Reviews of Effects 4th Quarter 2010

Search Strategy: FERT_Q5_IUI_unexplained_cdsrdare_110111

#	Searches
1	(fertil$ or steril$ or infertil$ or subfertil$ or sub-fertil$ or fecund$ or subfecund$ or sub-fecund$ or assist$ reproduc$).tw,tx.
2	INFERTILITY, FEMALE.kw.

3	INFERTILITY.kw.
4	ANOVULATION.kw.
5	anovulat$.tw,tx.
6	oligo-ovulation.tw,tx.
7	"oligo ovulation".tw,tx.
8	Oligoovulat$.tw,tx.
9	or/1-8
10	INSEMINATION, ARTIFICIAL.kw.
11	(artificial$ adj3 inseminat$).ti,ab.
12	(IUI or SIUI).ti,ab.
13	or/10-12
14	and/9,13

Database(s): EMBASE 1980 to 2011 Week 01

Search Strategy: FERT_Q5_IUI_unexplained_embase_100111

#	Searches
1	CLINICAL TRIALS/
2	(clinic$ adj5 trial$).ti,ab,sh.
3	SINGLE BLIND PROCEDURE/
4	DOUBLE BLIND PROCEDURE/
5	RANDOM ALLOCATION/
6	CROSSOVER PROCEDURE/
7	PLACEBO/
8	placebo$.ti,ab,sh.
9	random$.ti,ab,sh.
10	RANDOMIZED CONTROLLED TRIALS/
11	((single or double or triple or treble) adj (blind$ or mask$)).ti,ab,sh.
12	randomi?ed control$ trial$.tw.
13	or/1-12
14	META ANALYSIS/
15	((meta adj analy$) or metaanalys$ or meta-analy$).ti,ab,sh.
16	(systematic$ adj5 (review$ or overview$)).ti,sh,ab.
17	(methodologic$ adj5 (review$ or overview$)).ti,ab,sh.
18	or/14-17
19	review.pt.

20	(medline or medlars or embase).ab.
21	(scisearch or science citation index).ab.
22	(psychlit or psyclit or psychinfo or psycinfo or cinahl or cochrane).ab.
23	((hand or manual$) adj2 search$).tw.
24	(electronic database$ or bibliographic database$ or computeri?ed database$ or online database$).tw.
25	(pooling or pooled or mantel haenszel).tw.
26	(peto or dersimonian or "der simonian" or fixed effect).tw.
27	or/20-26
28	and/19,27
29	or/18,28
30	(book or conference paper or editorial or letter or note or proceeding or short survey).pt.
31	13 not 30
32	29 not 30
33	or/31-32
34	(fertil$ or steril$ or infertil$ or subfertil$ or sub-fertil$ or fecund$ or subfecund$ or sub-fecund$ or assist$ reproduc$).ti,ab.
35	INFERTILITY/ or FEMALE INFERTILITY/
36	ANOVULATION/
37	anovulat$.ti,ab.
38	oligo-ovulation.ti,ab.
39	Oligoovulat$.ti,ab.
40	or/34-39
41	ARTIFICIAL INSEMINATION/
42	(IUI or SIUI).ti,ab.
43	or/41-42
44	and/40,43
45	and/33,44
46	limit 45 to english language

Cinahl Ebsco

FERT_Q5_IUI_unexplained_cinahl_120111

#	Query	
S18	S10 and S16	

S17	S10 and S16	
S16	S11 or S12 or S13 or S14 or S15	
S15	AB (IUI) or AB (SIUI)	
S14	TI (IUI) or TI (SIUI)	
S13	AB (artificial* N3 inseminat*)	
S12	TI (artificial* N3 inseminat*)	
S11	(MH "INSEMINATION, ARTIFICIAL")	
S10	S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9	
S9	TI (oligoovulat*) or AB (oligoovulat*)	
S8	TI (oligo ovulat*) or AB (oligo ovulat*)	
S7	TI (oligo-ovulat*) or AB (oligo-ovulat*)	
S6	TI (anovulat*) or AB (anovulat*)	
S5	(MH "ANOVULATION")	
S4	(MH "INFERTILITY RISK (Saba CCC)")	
S3	(MH "INFERTILITY")	
S2	AB (fertil* or steril* or infertil* or sub-fertil* or fecund* or sub-fecund*)	
S1	TI (fertil* or steril* or infertil* or sub-fertil* or fecund* or sub-fecund*)	

Chapter 14. Access criteria for IVF

Database(s): Ovid MEDLINE(R) 1948 to February week 3 2011

Search Strategy: Database(s): Ovid MEDLINE(R) 1948 to February week 3 2011

#	Searches
1	exp FERTILIZATION IN VITRO/
2	INFERTILITY/th
3	(IVF or ICSI).ti,ab.
4	in vitro fertili$.ti,ab.
5	or/1-4
6	exp "SENSITIVITY and SPECIFICITY"/
7	exp PROGNOSIS/
8	REPRODUCIBILITY OF RESULTS/
9	exp PREGNANCY RATE/
10	or/6-9
11	((logistic or risk or predict$) adj3 model$).ti.
12	MODELS, BIOLOGICAL/ or MODELS, THEORETICAL/ or MODELS, STATISTICAL/
13	LOGISTIC MODELS/
14	FORECASTING/
15	or/11-14
16	and/5,10,15
17	limit 16 to english language
18	limit 17 to (animals and humans)
19	limit 17 to animals
20	19 not 18
21	17 not 20

Database(s): Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations March 01, 2011

Search Strategy: FERT_Q2_predict_ivf_medline_in_process_020311

#	**Searches**
1	(fertil$ or steril$ or infertil$ or subfertil$ or sub-fertil$ or fecund$ or subfecund$ or sub-fecund$ or assist$ reproduc$).ti,ab.
2	(IVF or ICSI).ti,ab.
3	in vitro fertili$.ti,ab.
4	or/1-3
5	(sensitivity or specificity).ti,ab.
6	prognos$.ti,ab.
7	pregnancy.ti,ab.
8	or/5-7
9	((logistic or risk or predict$) adj3 model$).ti.
10	model$.ti.
11	(forecast$ or predict$).ti,ab.
12	or/9-11
13	and/4,8,12
14	english.la.
15	and/13-14

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials 1st Quarter 2011

Search Strategy: FERT_Q2_predict_ivf_cctr_020311

#	**Searches**
1	exp FERTILIZATION IN VITRO/
2	INFERTILITY/th
3	(IVF or ICSI).ti,ab.
4	in vitro fertili$.ti,ab.
5	or/1-4
6	exp "SENSITIVITY and SPECIFICITY"/
7	exp PROGNOSIS/
8	REPRODUCIBILITY OF RESULTS/

9	exp PREGNANCY RATE/
10	or/6-9
11	((logistic or risk or predict$) adj3 model$).ti.
12	MODELS, BIOLOGICAL/ or MODELS, THEORETICAL/ or MODELS, STATISTICAL/
13	LOGISTIC MODELS/
14	FORECASTING/
15	or/11-14
16	and/5,10,15

Database(s): EBM Reviews - Cochrane Database of Systematic Reviews 2005 to February 2011, EBM Reviews - Database of Abstracts of Reviews of Effects 1st Quarter 2011

Search Strategy: FERT_Q2_predict_ivf_cdsrdare_020311

#	**Searches**
1	FERTILIZATION IN VITRO.kw.
2	INFERTILITY.kw.
3	(IVF or ICSI).tw,tx.
4	in vitro fertili$.tw,tx.
5	or/1-4
6	"SENSITIVITY and SPECIFICITY".kw.
7	PROGNOSIS.kw.
8	REPRODUCIBILITY OF RESULT.kw.
9	PREGNANCY RATE.kw.
10	or/6-9
11	((logistic or risk or predict$) adj3 model$).tw.
12	(MODELS, BIOLOGICAL or MODELS, THEORETICAL or MODELS, STATISTICAL).kw.
13	LOGISTIC MODELS.kw.
14	FORECASTING.kw.
15	or/11-14
16	and/5,10,15

Database(s): EMBASE 1980 to 2011 Week 08

Search Strategy: FERT_Q2_predict_ivf_embase_020311

#	Searches
1	exp INFERTILITY THERAPY/
2	"in vitro fertili$".ti,ab.
3	(IVF or ICSI).ti,ab.
4	or/1-3
5	"SENSITIVITY and SPECIFICITY"/
6	exp PROGNOSIS/
7	REPRODUCIBILITY/
8	exp "PARAMETERS CONCERNING THE FETUS, NEWBORN AND PREGNANCY"/
9	or/5-8
10	((logistic or risk or predict$) adj3 model$).ti.
11	MATHEMATICAL MODEL/ or STATISTICAL MODEL/
12	FORECASTING/
13	or/10-12
14	and/4,9,13

Cinahl Ebsco

FERT_Q2_predict_ivf_cinahl_020311

#	Query	
S21	S7 and S13 and S19	
S20	S7 and S13 and S19	
S19	S14 or S15 or S16 or S17 or S18	
S18	(MH "FORECASTING")	
S17	(MH "MODELS, BIOLOGICAL")	
S16	(MH "MODELS, STATISTICAL")	

S15	AB (model* or risk* or predict* or logistic* or forecast*)	
S14	TI (model* or risk* or predict* or logistic* or forecast*)	
S13	S8 or S9 or S10 or S11 or S12	
S12	AB (pregnan* N3 rate*)	
S11	TI (pregnan* N3 rate*)	
S10	(MH "REPRODUCIBILITY OF RESULTS")	
S9	(MH "PROGNOSIS+")	
S8	(MH "SENSITIVITY and SPECIFICITY")	
S7	S1 or S2 or S3 or S4 or S5 or S6	
S6	AB (in vitro fertili*)	
S5	TI (in vitro fertili*)	
S4	TI (ICSI) or AB (ICSI)	
S3	TI (IVF) or AB (IVF)	
S2	(MH "REPRODUCTION TECHNIQUES+")	
S1	(MH "INFERTILITY CARE (Saba CCC)")	

Chapter 15. Procedures used during in vitro fertilisation treatment

Embryo transfer strategies

Database(s): Ovid MEDLINE(R) 1950 to November Week 3 2010

Search Strategy: FERT_Q3_embryo_transfer_medline_011210 (SRs, RCTs & Cohort studies)

#	Searches
1	randomized controlled trial.pt.
2	controlled clinical trial.pt.
3	DOUBLE BLIND METHOD/
4	SINGLE BLIND METHOD/
5	RANDOM ALLOCATION/
6	RANDOMIZED CONTROLLED TRIALS/
7	or/1-6
8	((single or double or triple or treble) adj5 (blind$ or mask$)).tw,sh.
9	clinical trial.pt.
10	exp CLINICAL TRIAL/
11	exp CLINICAL TRIALS AS TOPIC/
12	(clinic$ adj5 trial$).tw,sh.
13	PLACEBOS/
14	placebo$.tw,sh.
15	random$.tw,sh.
16	or/8-15
17	or/7,16
18	META ANALYSIS/
19	META ANALYSIS AS TOPIC/
20	meta analysis.pt.
21	(metaanaly$ or meta-analy$ or (meta adj analy$)).tw,sh.
22	(systematic$ adj5 (review$ or overview$)).tw,sh.
23	(methodologic$ adj5 (review$ or overview$)).tw,sh.
24	or/18-23
25	review$.pt.
26	(medline or medlars or embase or cinahl or cochrane or psycinfo or psychinfo or psychlit or psyclit or "web of science" or "science citation" or scisearch).tw.
27	((hand or manual$) adj2 search$).tw.
28	(electronic database$ or bibliographic database$ or computeri?ed database$ or online database$).tw,sh.
29	(pooling or pooled or mantel haenszel).tw,sh.
30	(peto or dersimonian or der simonian or fixed effect).tw,sh.

31	or/26-30
32	and/25,31
33	exp COHORT STUDIES/
34	cohort$.tw.
35	or/33-34
36	or/17,24,32,35
37	letter.pt.
38	comment.pt.
39	editorial.pt.
40	historical article.pt.
41	or/37-40
42	36 not 41
43	(fertil$ or steril$ or infertil$ or subfertil$ or sub-fertil$ or fecund$ or subfecund$ or sub-fecund$ or assist$ reproduc$).ti,ab.
44	INFERTILITY, FEMALE/
45	INFERTILITY, MALE/
46	INFERTILITY/
47	ANOVULATION/
48	anovulat$.ti,ab.
49	oligo-ovulation.ti,ab.
50	"oligo ovulation".ti,ab.
51	Oligoovulat$.ti,ab.
52	exp FERTILIZATION IN VITRO/
53	in vitro fert$.ti,ab.
54	IVF.ti,ab.
55	or/43-54
56	exp EMBRYO TRANSFER/
57	((embryo$ or blastocyst$ or cleavage) adj2 (implant$ or transfer$)).ti,ab.
58	(SET or DET).ti,ab.
59	exp EMBRYO IMPLANTATION/
60	or/56-59
61	and/55,60
62	and/42,61
63	limit 62 to english language
64	limit 62 to (animals and humans)
65	limit 63 to animal
66	65 not 64
67	63 not 66

Database(s): Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations November 30, 2010

Search Strategy: FERT_Q3_embryo_transfer_medline_in_process_011210

"	Searches
1	(fertil$ or steril$ or infertil$ or subfertil$ or sub-fertil$ or fecund$ or subfecund$ or sub-fecund$ or assist$ reproduc$).ti,ab.
2	anovulat$.ti,ab.
3	oligo-ovulation.ti,ab.
4	"oligo ovulation".ti,ab.
5	Oligoovulat$.ti,ab.
6	in vitro fert$.ti,ab.
7	IVF.ti,ab.
8	or/1-7
9	((embryo$ or blastocyst$ or cleavage) adj2 (implant$ or transfer$)).ti,ab.
10	(SET or DET).ti,ab.
11	or/9-10
12	and/8,11

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials 4th Quarter 2010

Search Strategy: FERT_Q3_embryo_transfer_cctr_011210

"	Searches
1	(fertil$ or steril$ or infertil$ or subfertil$ or sub-fertil$ or fecund$ or subfecund$ or sub-fecund$ or assist$ reproduc$).ti,ab.
2	INFERTILITY, FEMALE/
3	INFERTILITY, MALE/
4	INFERTILITY/
5	ANOVULATION/
6	anovulat$.ti,ab.
7	oligo-ovulation.ti,ab.
8	"oligo ovulation".ti,ab.
9	Oligoovulat$.ti,ab.
10	exp FERTILIZATION IN VITRO/
11	in vitro fert$.ti,ab.
12	IVF.ti,ab.
13	or/1-12

14	exp EMBRYO TRANSFER/
15	((embryo$ or blastocyst$ or cleavage) adj2 (implant$ or transfer$)).ti,ab.
16	(SET or DET).ti,ab.
17	exp EMBRYO IMPLANTATION/
18	or/14-17
19	and/13,18

Database(s): EBM Reviews - Cochrane Database of Systematic Reviews 2005 to November 2010, EBM Reviews - Database of Abstracts of Reviews of Effects 4th Quarter 2010

Search Strategy: FERT_Q3_embryo_transfer_cdsrdare_011210

#	Searches
1	(fertil$ or steril$ or infertil$ or subfertil$ or sub-fertil$ or fecund$ or subfecund$ or sub-fecund$ or assist$ reproduc$).tw,tx.
2	INFERTILITY, FEMALE.kw.
3	INFERTILITY, MALE.kw.
4	INFERTILITY.kw.
5	ANOVULATION.kw.
6	anovulat$.tw,tx.
7	oligo-ovulation.tw,tx.
8	"oligo ovulation".tw,tx.
9	Oligoovulat$.tw,tx.
10	FERTILIZATION IN VITRO.kw.
11	in vitro fert$.tw,tx.
12	IVF.tw,tx.
13	or/1-12
14	EMBRYO TRANSFER.kw.
15	((embryo$ or blastocyst$ or cleavage) adj2 (implant$ or transfer$)).tw,tx.
16	(SET or DET).tw,tx.
17	EMBRYO IMPLANTATION.kw.
18	or/14-17
19	and/13,18

Database(s): EMBASE 1980 to 2010 Week 47

Search Strategy: : FERT_Q3_embryo_transfer_embase_021210 (SRs, RCTs & Cohort studies)

#	Searches
1	CLINICAL TRIALS/
2	(clinic$ adj5 trial$).tw,sh.
3	SINGLE BLIND PROCEDURE/
4	DOUBLE BLIND PROCEDURE/
5	RANDOM ALLOCATION/
6	CROSSOVER PROCEDURE/
7	PLACEBO/
8	placebo$.tw,sh.
9	random$.tw,sh.
10	RANDOMIZED CONTROLLED TRIALS/
11	((single or double or triple or treble) adj (blind$ or mask$)).tw,sh.
12	randomi?ed control$ trial$.tw.
13	or/1-12
14	META ANALYSIS/
15	((meta adj analy$) or metaanalys$ or meta-analy$).tw,sh.
16	(systematic$ adj5 (review$ or overview$)).tw,sh.
17	(methodologic$ adj5 (review$ or overview$)).tw,sh.
18	or/14-17
19	review.pt.
20	(medline or medlars or embase).ab.
21	(scisearch or science citation index).ab.
22	(psychlit or psyclit or psychinfo or psycinfo or cinahl or cochrane).ab.
23	((hand or manual$) adj2 search$).tw.
24	(electronic database$ or bibliographic database$ or computeri?ed database$ or online database$).tw.
25	(pooling or pooled or mantel haenszel).tw.
26	(peto or dersimonian or "der simonian" or fixed effect).tw.
27	or/20-26
28	and/19,27
29	COHORT ANALYSIS/
30	LONGITUDINAL STUDY/
31	FOLLOW UP/
32	PROSPECTIVE STUDY/
33	cohort$.tw.
34	or/29-33

35	or/13,18,28,34
36	(book or conference paper or editorial or letter or note or proceeding or short survey).pt.
37	35 not 36
38	(fertil$ or steril$ or infertil$ or subfertil$ or sub-fertil$ or fecund$ or subfecund$ or sub-fecund$ or assist$ reproduc$).ti,ab.
39	INFERTILITY/ or FEMALE INFERTILITY/ or SUBFERTILITY/
40	exp OVARY INSUFFICIENCY/
41	anovulat$.ti,ab.
42	oligo-ovulation.ti,ab.
43	"oligo ovulation".ti,ab.
44	Oligoovulat$.ti,ab.
45	FERTILIZATION IN VITRO/
46	"in vitro fertili$".ti,ab.
47	"in?vitro fertili$".ti,ab.
48	or/38-47
49	EMBRYO TRANSFER/
50	((embryo$ or blastocyst$ or cleavage) adj2 (implant$ or transfer$ or transplant$)).ti,ab.
51	(SET or DET).ti,ab.
52	exp NIDATION/
53	or/49-52
54	and/48,53
55	and/37,54
56	limit 55 to english language

Cinahl Ebsco FERT_Q3_embryo_transfer_cinahl_021210

#	Query
S23	S11 and S21
S22	S11 and S21
S21	S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20
S20	TI (nidation) or AB (nidation)
S19	TI (SET) or TI (DET)
S18	TI (blastocyst$ N3 implant*) or AB (blastocyst$ N3 implant*)
S17	TI (blastocyst$ N3 transfer*) or AB (blastocyst$ N3 transfer*)
S16	TI (blastocyst$ N3 transplant*) or AB (blastocyst$ N3 transplant*)
S15	TI (embryo N3 implant*) or AB (embryo N3 implant*)
S14	TI (embryo N3 transfer*) or AB (embryo N3 transfer*)
S13	TI (embryo N3 tranplant*) or AB (embryo N3 tranplant*)

S12	(MH "EMBRYO TRANSFER")
S11	S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10
S10	TI (in vitro fertili*) or AB (in vitro fertili*)
S9	(MH "FERTILIZATION IN VITRO")
S8	(MH "FERTILIZATION IN VITRO")
S7	TI (oligo-ovulat*) or AB (oligo-ovulat*)
S6	TI (anovulat*) or AB (anovulat*)
S5	TI (assist* reproduc*) or AB (assist* reproduc*)
S4	(MH "Infertility Risk (Saba CCC)")
S3	(MH "INFERTILITY")
S2	AB (fertil* or steril* or infertil* or sub-fertil* or fecund* or sub-fecund*)
S1	TI (fertil* or steril* or infertil* or sub-fertil* or fecund* or sub-fecund*)

Chapter 19. People with cancer who wish to preserve fertility

Database(s): Ovid MEDLINE(R) 1948 to April Week 4 2011

Search Strategy: FERT_Q7_cryo_combined_medline_060511

#	Searches
1	randomized controlled trial.pt.
2	controlled clinical trial.pt.
3	DOUBLE BLIND METHOD/
4	SINGLE BLIND METHOD/
5	RANDOM ALLOCATION/
6	RANDOMIZED CONTROLLED TRIALS/
7	or/1-6
8	((single or double or triple or treble) adj5 (blind$ or mask$)).tw,sh.
9	clinical trial.pt.
10	exp CLINICAL TRIAL/
11	exp CLINICAL TRIALS AS TOPIC/
12	(clinic$ adj5 trial$).tw,sh.
13	PLACEBOS/
14	placebo$.tw,sh.
15	random$.tw,sh.
16	or/8-15
17	or/7,16
18	META ANALYSIS/
19	META ANALYSIS AS TOPIC/
20	meta analysis.pt.
21	(metaanaly$ or meta-analy$ or (meta adj analy$)).tw,sh.
22	(systematic$ adj5 (review$ or overview$)).tw,sh.
23	(methodologic$ adj5 (review$ or overview$)).tw,sh.
24	or/18-23
25	review$.pt.
26	(medline or medlars or embase or cinahl or cochrane or psycinfo or psychinfo or psychlit or psyclit or "web of science" or "science citation" or scisearch).tw.
27	((hand or manual$) adj2 search$).tw.
28	(electronic database$ or bibliographic database$ or computeri?ed database$ or online database$).tw,sh.
29	(pooling or pooled or mantel haenszel).tw,sh.
30	(peto or dersimonian or der simonian or fixed effect).tw,sh.
31	or/26-30
32	and/25,31

33	exp CASE-CONTROL STUDIES/
34	(case$ adj2 control$).tw.
35	exp COHORT STUDIES/
36	cohort$.tw.
37	or/33-36
38	or/17,24,32,37
39	letter.pt.
40	comment.pt.
41	editorial.pt.
42	historical article.pt.
43	or/39-42
44	38 not 43
45	exp INFERTILITY/
46	FERTILITY/
47	exp REPRODUCTIVE TECHNIQUES, ASSISTED/
48	(fertil$ or steril$ or infertil$ or subfertil$ or sub-fertil$ or fecund$ or subfecund$ or sub-fecund$ or assist$ reproduc$).ti,ab.
49	or/45-48
50	exp CRYOPRESERVATION/
51	exp TISSUE PRESERVATION/
52	VITRIFICATION/
53	(cryo$ or CRF or vitrif$ or freez$ or frozen or storing or storage or preserv$).ti,ab.
54	or/50-53
55	exp GERM CELLS/
56	exp EMBRYO, MAMMALIAN/
57	SEMEN/
58	OVARY/
59	(sperm$ or semen or embryo$ or blastocyst$ or oocyt$ or ov#cyt$ or ova or ovum or ovar$).ti,ab.
60	or/55-59
61	and/49,54,60
62	limit 61 to english language
63	limit 62 to animals
64	limit 62 to (animals and humans)
65	63 not 64
66	62 not 65
67	and/44,66
68	limit 67 to yr="2010 -Current"

Database(s): Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations May 05, 2011

Search Strategy: FERT_Q7_cryo_combined_mip_060511

1	(fertil$ or steril$ or infertil$ or subfertil$ or sub-fertil$ or fecund$ or subfecund$ or sub-fecund$ or assist$ reproduc$).ti,ab.	7623
2	(cryo$ or CRF or vitrif$ or freez$ or frozen or storing or storage or preserv$).ti,ab.	22331
3	(sperm$ or semen or embryo$ or blastocyst$ or oocyt$ or ov#cyt$ or ova or ovum or ovar$).ti,ab.	17366
4	and/1-3	404
5	limit 4 to yr="2010 -Current"	172

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials 1st Quarter 2011

Search Strategy: FERT_Q7_cryo_combined_cctr_060511

#	Searches
1	exp INFERTILITY/
2	FERTILITY/
3	exp REPRODUCTIVE TECHNIQUES, ASSISTED/
4	(fertil$ or steril$ or infertil$ or subfertil$ or sub-fertil$ or fecund$ or subfecund$ or sub-fecund$ or assist$ reproduc$).ti,ab.
5	or/1-4
6	exp CRYOPRESERVATION/
7	exp TISSUE PRESERVATION/
8	VITRIFICATION/
9	(cryo$ or CRF or vitrif$ or freez$ or frozen or storing or storage or preserv$).ti,ab.
10	or/6-9
11	exp GERM CELLS/
12	exp EMBRYO, MAMMALIAN/
13	SEMEN/
14	OVARY/
15	(sperm$ or semen or embryo$ or blastocyst$ or oocyt$ or ov#cyt$ or ova or ovum or ovar$).ti,ab.
16	or/11-15
17	and/5,10,16
18	limit 17 to yr="2010 -Current"

Database(s): EBM Reviews - Cochrane Database of Systematic Reviews 2005 to April 2011, EBM Reviews - Database of Abstracts of Reviews of Effects 2nd Quarter 2011

Search Strategy: FERT_Q7_cryo_combined_cdsrdare_060511

#	Searches
1	INFERTILITY.kw.
2	FERTILITY.kw.
3	REPRODUCTIVE TECHNIQUES, ASSISTED.kw.
4	(fertil$ or steril$ or infertil$ or subfertil$ or sub-fertil$ or fecund$ or subfecund$ or sub-fecund$ or assist$ reproduc$).tw,tx.
5	or/1-4
6	CRYOPRESERVATION.kw.
7	TISSUE PRESERVATION.kw.
8	VITRIFICATION.kw.
9	(cryo$ or CRF or vitrif$ or freez$ or frozen or storing or storage or preserv$).tw,tx.
10	or/6-9
11	GERM CELLS.kw.
12	EMBRYO, MAMMALIAN.kw.
13	SEMEN.kw.
14	OVARY.kw.
15	(sperm$ or semen or embryo$ or blastocyst$ or oocyt$ or ov#cyt$ or ova or ovum or ovar$).tw,tx.
16	or/11-15
17	and/5,10,16
18	limit 17 to last 2 years

Database(s): EMBASE 1980 to 2011 Week 17

Search Strategy: FERT_Q7_cryo_combined_embase_060511

#	Searches
1	CLINICAL TRIALS/
2	(clinic$ adj5 trial$).tw,sh.
3	SINGLE BLIND PROCEDURE/
4	DOUBLE BLIND PROCEDURE/
5	RANDOM ALLOCATION/
6	CROSSOVER PROCEDURE/
7	PLACEBO/
8	placebo$.tw,sh.
9	random$.tw,sh.

10	RANDOMIZED CONTROLLED TRIALS/
11	((single or double or triple or treble) adj (blind$ or mask$)).tw,sh.
12	randomi?ed control$ trial$.tw.
13	or/1-12
14	META ANALYSIS/
15	((meta adj analy$) or metaanalys$ or meta-analy$).tw,sh.
16	(systematic$ adj5 (review$ or overview$)).tw,sh.
17	(methodologic$ adj5 (review$ or overview$)).tw,sh.
18	or/14-17
19	review.pt.
20	(medline or medlars or embase).ab.
21	(scisearch or science citation index).ab.
22	(psychlit or psyclit or psychinfo or psycinfo or cinahl or cochrane).ab.
23	((hand or manual$) adj2 search$).tw.
24	(electronic database$ or bibliographic database$ or computeri?ed database$ or online database$).tw.
25	(pooling or pooled or mantel haenszel).tw.
26	(peto or dersimonian or "der simonian" or fixed effect).tw.
27	or/20-26
28	and/19,27
29	exp CASE CONTROL STUDY/
30	RETROSPECTIVE STUDY/
31	(case$ adj2 control$).tw.
32	COHORT ANALYSIS/
33	LONGITUDINAL STUDY/
34	FOLLOW UP/
35	PROSPECTIVE STUDY/
36	cohort$.tw.
37	or/29-36
38	or/13,18,28,37
39	(book or conference paper or editorial or letter or note or proceeding or short survey).pt.
40	38 not 39
41	exp INFERTILITY/
42	exp FERTILITY/
43	exp INFERTILITY THERAPY/
44	(fertil$ or steril$ or infertil$ or subfertil$ or sub-fertil$ or fecund$ or subfecund$ or sub-fecund$ or assist$ reproduc$).ti,ab.
45	or/41-44
46	CRYOPRESERVATION/

47	SPERM PRESERVATION/
48	TISSUE PRESERVATION/
49	VITRIFICATION/
50	(cryo$ or CRF or vitrif$ or freez$ or frozen or storing or storage or preserv$).ti,ab.
51	or/46-50
52	exp GERM CELL/
53	EMBRYO/
54	BLASTOCYST/
55	exp SEMEN/
56	exp OVARY/
57	(sperm$ or semen or embryo$ or blastocyst$ or oocyt$ or ov#cyt$ or ova or ovum or ovar$).ti,ab.
58	or/52-57
59	and/45,51,58
60	limit 59 to english language
61	and/40,60
62	limit 61 to yr="2010 -Current"

Cinahl FERT_Q7_cryo_combined_cinahl_060511

	Query
S20	S19
S19	S6 and S11 and S18
S18	S12 or S13 or S14 or S15 or S16 or S17
S17	AB (sperm* or semen or embryo* or blastocyst* or oocyt* or ov?cyt* or ova or ovum or ovar*)
S16	TI (sperm* or semen or embryo* or blastocyst* or oocyt* or ov?cyt* or ova or ovum or ovar*)
S15	MH OVARY
S14	MH SEMEN
S13	MH EMBRYO+
S12	MH GERM CELLS+
S11	S7 or S8 or S9 or S10
S10	AB (cryo* or CRF or vitrif* or freez* or frozen or storing or storage or preserv*)
S9	TI (cryo* or CRF or vitrif* or freez* or frozen or storing or storage or preserv*)
S8	MH TISSUE PRESERVATION+

S7	MH CRYOPRESERVATION+
S6	S1 or S2 or S3 or S4 or S5
S5	AB (fertil* or steril* or infertil* or sub-fertil* or sub#fertil* or fecund* or sub-fecund* or sub#fecund* or assist* reproduc*)
S4	TI (fertil* or steril* or infertil* or sub-fertil* or sub#fertil* or fecund* or sub-fecund* or sub#fecund* or assist* reproduc*)
S3	MH REPRODUCTION TECHNIQUES+
S2	MH FERTILITY
S1	MH INFERTILITY

Chapter 20. Long-term safety of assisted reproduction treatments in women with infertility and their children

Database(s): Ovid MEDLINE(R) 1948 to April Week 4 2011

Search Strategy: FERT_Q4e_safety_women_child_medline_050511

#	Searches
1	(fertil$ or steril$ or infertil$ or subfertil$ or sub-fertil$ or fecund$ or subfecund$ or sub-fecund$ or assist$ reproduc$).ti,ab.
2	INFERTILITY, FEMALE/
3	INFERTILITY/
4	FERTILITY/
5	ANOVULATION/
6	OVULATION/ or OVULATION INHIBITION/
7	anovulat$.ti,ab.
8	oligo-ovulation.ti,ab.
9	"oligo ovulation".ti,ab.
10	Oligoovulat$.ti,ab.
11	exp FERTILIZATION IN VITRO/
12	IVF.ti,ab.
13	"in vitro fertili$".ti,ab.
14	"in?vitro fertili$".ti,ab.
15	ICSI.ti,ab.
16	Amenorrhea/
17	amenorrh$.ti,ab.
18	Hypogonadism/
19	(hypothalamic adj3 amenorrh$).ti,ab.
20	(hypogonadotro$ adj3 hypogonadism).ti,ab.
21	or/1-20
22	exp FERTILIZATION IN VITRO/
23	exp FERTILITY AGENTS, FEMALE/
24	exp GONADOTROPINS, PITUITARY/
25	(uFSH or rFSH or LH or hMG).ti,ab.
26	(gonadotrophin$ or gonadotropi$).ti,ab.

27	GnRH.ti,ab.
28	exp GONADOTROPIN-RELEASING HORMONE/
29	GnRHa.ti,ab.
30	(zoladex or synarel or decapeptyl).ti,ab.
31	exp DOPAMINE AGENTS/
32	(dopamin$ adj3 (agonist$ or agent$)).ti,ab.
33	BROMOCRIPTINE/
34	(cabergoline or bromocriptine).ti,ab.
35	AROMATASE INHIBITORS/ or AMINOGLUTETHIMIDE/ or FADROZOLE/
36	TESTOLACTONE/
37	(teslac or anastrozole or arimidex or letrozole or femara or exemestane or aromasin or vorozole or rivizor or formestane or lentaron or afema).ti,ab.
38	(aromatase adj3 inhibit$).ti,ab.
39	exp LIFE STYLE/
40	(life?style adj3 (change$ or adjustment$ or interven$)).ti,ab.
41	exp BODY WEIGHT CHANGES/
42	EXERCISE/
43	((reduc$ or decreas$ or stop$ or ceas$) adj3 exercis$).ti,ab.
44	exp ESTROGEN RECEPTOR MODULATORS/ or CLOMIPHENE/ or TAMOXIFEN/
45	(anti?estrogen$ or anti?oestrogen$).ti,ab.
46	(clomiphene or clomifene or tamoxifen).ti,ab.
47	METFORMIN/
48	(metformin or glucophage).ti,ab.
49	exp OVARY/su
50	((ovary or ovaries or ovarian) adj3 (drill$ or electrocauter$ or diatherm$)).ti,ab.
51	LAPAROSCOPY/
52	exp DIATHERMY/
53	and/51-52
54	(LOD or LOE).ti,ab.
55	exp ELECTROCOAGULATION/
56	exp GROWTH HORMONE/

57	(growth adj2 hormone$).ti,ab.
58	DEHYDROEPIANDROSTERONE/
59	DHEA.ti,ab.
60	or/22-50,53-59
61	(inciden$ or hazard$).ti.
62	risk$.ti.
63	associat$.ti.
64	or/61-63
65	and/21,60,64
66	exp REPRODUCTIVE TECHNIQUES, ASSISTED/
67	(IVF or ICSI).ti,ab.
68	in vitro fertili?$.ti,ab.
69	or/66-68
70	exp CHILD/
71	exp INFANT/
72	ADOLESCENT/
73	(newborn or neonate or preterm or prematur$ or infant$ or baby or babies or child* or adolescen$ or teenage$).ti,ab.
74	or/70-73
75	risk$.ti.
76	(inciden$ or hazard$).ti.
77	associat$.ti.
78	or/75-77
79	and/69,74,78
80	or/65,79
81	limit 80 to yr="2003 -Current"
82	limit 81 to english language
83	limit 82 to (animals and humans)
84	limit 82 to animals
85	84 not 83
86	82 not 85

Database(s): Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations May 09, 2011

Search Strategy: FERT_Q4e_safety_women_child_MiP_100511

#	**Searches**
1	(fertil$ or steril$ or infertil$ or subfertil$ or sub-fertil$ or fecund$ or subfecund$ or sub-fecund$ or assist$ reproduc$).ti,ab.
2	anovulat$.ti,ab.
3	oligo-ovulation.ti,ab.
4	"oligo ovulation".ti,ab.
5	Oligoovulat$.ti,ab.
6	"in vitro fertili$".ti,ab.
7	"in?vitro fertili$".ti,ab.
8	IVF.ti,ab.
9	ICSI.ti,ab.
10	amenorrh$.ti,ab.
11	hypogonadi$.ti,ab.
12	(hypothalamic adj3 amenorrh$).ti,ab.
13	(hypogonadotro$ adj3 hypogonadism).ti,ab.
14	or/1-13
15	"in vitro fertili$".ti,ab.
16	"in?vitro fertili$".ti,ab.
17	IVF.ti,ab.
18	(uFSH or rFSH or LH or hMG).ti,ab.
19	(gonadotrophin$ or gonadotropi$).ti,ab.
20	GnRH.ti,ab.
21	GnRHa.ti,ab.
22	(zoladex or synarel or decapeptyl).ti,ab.
23	(dopamine adj3 (agent$ or agonist$)).ti,ab.
24	(bromocriptine or cabergoline).ti,ab.
25	(aromatase inhibitor$ or aminoglutethimide or fadrozole).ti,ab.
26	testolactone.ti,ab.
27	(teslac or anastrozole or arimidex or letrozole or femara or exemestane or aromasin or

	vorozole or rivizor or formestane or lentaron or afema).ti,ab.
28	(life?style or life style).ti,ab.
29	weight.ti,ab.
30	((reduc$ or decreas$ or stop$ or ceas$) adj3 exercis$).ti,ab.
31	(?estrogen$ or tamoxifen or clomifen or clomiphene).ti,ab.
32	(anti?estrogen$ or anti?oestrogen$).ti,ab.
33	(metformin or glucophage).ti,ab.
34	((ovary or ovaries or ovarian) adj3 (drill$ or electrocauter$ or diatherm$)).ti,ab.
35	(LOD or LOE).ti,ab.
36	(laparoscop$ or diatherm$).ti,ab.
37	electrocoagulation.ti,ab.
38	(growth adj2 hormone$).ti,ab.
39	dehydroepiandrosterone.ti,ab.
40	DHEA.ti,ab.
41	or/15-40
42	risk$.ti.
43	(inciden$ or hazard$).ti.
44	associat$.ti.
45	or/42-44
46	and/14,41,45
47	((assisted or artificial$) adj3 (concept$ or reproduct$)).ti,ab.
48	(IVF or ICSI).ti,ab.
49	in vitro fertili?$.ti,ab.
50	or/47-49
51	(newborn$ or neonat$ or preterm or prematur$ or infant$ or baby or babies or child* or adolescen$ or teenage$).ti,ab.
52	risk$.ti.
53	(inciden$ or hazard$).ti.
54	associat$.ti.
55	or/52-54
56	and/50-51,55

57	or/46,56

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials 1st Quarter 2011

Search Strategy: FERT_Q4e_safety_women_child_cctr_050511

#	**Searches**
1	(fertil$ or steril$ or infertil$ or subfertil$ or sub-fertil$ or fecund$ or subfecund$ or sub-fecund$ or assist$ reproduc$).ti,ab.
2	INFERTILITY, FEMALE/
3	INFERTILITY/
4	FERTILITY/
5	ANOVULATION/
6	OVULATION/ or OVULATION INHIBITION/
7	anovulat$.ti,ab.
8	oligo-ovulation.ti,ab.
9	"oligo ovulation".ti,ab.
10	Oligoovulat$.ti,ab.
11	exp FERTILIZATION IN VITRO/
12	IVF.ti,ab.
13	"in vitro fertili$".ti,ab.
14	"in?vitro fertili$".ti,ab.
15	ICSI.ti,ab.
16	Amenorrhea/
17	amenorrh$.ti,ab.
18	Hypogonadism/
19	(hypothalamic adj3 amenorrh$).ti,ab.
20	(hypogonadotro$ adj3 hypogonadism).ti,ab.
21	or/1-20
22	exp FERTILIZATION IN VITRO/
23	exp FERTILITY AGENTS, FEMALE/
24	exp GONADOTROPINS, PITUITARY/

25	(uFSH or rFSH or LH or hMG).ti,ab.
26	(gonadotrophin$ or gonadotropi$).ti,ab.
27	GnRH.ti,ab.
28	exp GONADOTROPIN-RELEASING HORMONE/
29	GnRHa.ti,ab.
30	(zoladex or synarel or decapeptyl).ti,ab.
31	exp DOPAMINE AGENTS/
32	(dopamin$ adj3 (agonist$ or agent$)).ti,ab.
33	BROMOCRIPTINE/
34	(cabergoline or bromocriptine).ti,ab.
35	AROMATASE INHIBITORS/ or AMINOGLUTETHIMIDE/ or FADROZOLE/
36	TESTOLACTONE/
37	(teslac or anastrozole or arimidex or letrozole or femara or exemestane or aromasin or vorozole or rivizor or formestane or lentaron or afema).ti,ab.
38	(aromatase adj3 inhibit$).ti,ab.
39	exp LIFE STYLE/
40	(life?style adj3 (change$ or adjustment$ or interven$)).ti,ab.
41	exp BODY WEIGHT CHANGES/
42	EXERCISE/
43	((reduc$ or decreas$ or stop$ or ceas$) adj3 exercis$).ti,ab.
44	exp ESTROGEN RECEPTOR MODULATORS/ or CLOMIPHENE/ or TAMOXIFEN/
45	(anti?estrogen$ or anti?oestrogen$).ti,ab.
46	(clomiphene or clomifene or tamoxifen).ti,ab.
47	METFORMIN/
48	(metformin or glucophage).ti,ab.
49	exp OVARY/su
50	((ovary or ovaries or ovarian) adj3 (drill$ or electrocauter$ or diatherm$)).ti,ab.
51	LAPAROSCOPY/
52	exp DIATHERMY/
53	and/51-52
54	(LOD or LOE).ti,ab.

55	exp ELECTROCOAGULATION/
56	exp GROWTH HORMONE/
57	(growth adj2 hormone$).ti,ab.
58	DEHYDROEPIANDROSTERONE/
59	DHEA.ti,ab.
60	or/22-50,53-59
61	(inciden$ or hazard$).ti.
62	risk$.ti.
63	associat$.ti.
64	or/61-63
65	and/21,60,64
66	exp REPRODUCTIVE TECHNIQUES, ASSISTED/
67	(IVF or ICSI).ti,ab.
68	in vitro fertili?$.ti,ab.
69	or/66-68
70	exp CHILD/
71	exp INFANT/
72	ADOLESCENT/
73	(newborn or neonate or preterm or prematur$ or infant$ or baby or babies or child* or adolescen$ or teenage$).ti,ab.
74	or/70-73
75	risk$.ti.
76	(inciden$ or hazard$).ti.
77	associat$.ti.
78	or/75-77
79	and/69,74,78
80	or/65,79
81	limit 80 to yr="2003 -Current"

Database(s): EBM Reviews - Cochrane Database of Systematic Reviews 2005 to April 2011, EBM Reviews - Database of Abstracts of Reviews of Effects 2nd Quarter 2011

Search Strategy: FERT_Q4e_safety_women_child_cdsrdare_050511

#	**Searches**
1	(fertil$ or steril$ or infertil$ or subfertil$ or sub-fertil$ or fecund$ or subfecund$ or sub-fecund$ or assist$ reproduc$).tw,tx.
2	INFERTILITY, FEMALE.kw.
3	INFERTILITY.kw.
4	FERTILITY.kw.
5	ANOVULATION.kw.
6	(OVULATION or OVULATION INHIBITION).kw.
7	anovulat$.tw,tx.
8	oligo-ovulation.tw,tx.
9	"oligo ovulation".tw,tx.
10	Oligoovulat$.tw,tx.
11	FERTILIZATION IN VITRO.kw.
12	IVF.tw,tx.
13	"in vitro fertili$".tw,tx.
14	"in?vitro fertili$".tw,tx.
15	ICSI.tw,tx.
16	AMENORRHEA.kw.
17	amenorrh$.tw,tx.
18	HYPOGONADISM.kw.
19	(hypothalamic adj3 amenorrh$).tw,tx.
20	(hypogonadotro$ adj3 hypogonadism).tw,tx.
21	or/1-20
22	FERTILIZATION IN VITRO.kw.
23	FERTILITY AGENTS, FEMALE.kw.
24	GONADOTROPINS, PITUITARY.kw.
25	(uFSH or rFSH or LH or hMG).tw,tx.
26	(gonadotrophin$ or gonadotropi$).tw,tx.
27	GnRH.tw,tx.

28	GONADOTROPIN-RELEASING HORMONE.kw.
29	GnRHa.tw,tx.
30	(zoladex or synarel or decapeptyl).tw,tx.
31	DOPAMINE AGENTS.kw.
32	(dopamin$ adj3 (agonist$ or agent$)).tw,tx.
33	BROMOCRIPTINE.kw.
34	(cabergoline or bromocriptine).tw,tx.
35	(AROMATASE INHIBITORS or AMINOGLUTETHIMIDE or FADROZOLE).kw.
36	TESTOLACTONE.kw.
37	(teslac or anastrozole or arimidex or letrozole or femara or exemestane or aromasin or vorozole or rivizor or formestane or lentaron or afema).tw,tx.
38	(aromatase adj3 inhibit$).tw,tx.
39	LIFE STYLE.kw.
40	(life?style adj3 (change$ or adjustment$ or interven$)).tw,tx.
41	BODY WEIGHT CHANGES.kw.
42	EXERCISE.kw.
43	((reduc$ or decreas$ or stop$ or ceas$) adj3 exercis$).tw,tx.
44	(ESTROGEN RECEPTOR MODULATORS or CLOMIPHENE or TAMOXIFEN).kw.
45	(anti?estrogen$ or anti?oestrogen$).tw,tx.
46	(clomiphene or clomifene or tamoxifen).tw,tx.
47	METFORMIN.kw.
48	(metformin or glucophage).tw,tx.
49	OVARY.kw.
50	((ovary or ovaries or ovarian) adj3 (drill$ or electrocauter$ or diatherm$)).tw,tx.
51	LAPAROSCOPY.kw.
52	DIATHERMY.kw.
53	and/51-52
54	(LOD or LOE).tw,tx.
55	ELECTROCOAGULATION.kw.
56	GROWTH HORMONE.kw.
57	(growth adj2 hormone$).tw,tx.

58	DEHYDROEPIANDROSTERONE.kw.
59	DHEA.tw,tx.
60	or/22-50,53-59
61	(inciden$ or hazard$).ti.
62	risk$.ti.
63	associat$.ti.
64	or/61-63
65	and/21,60,64
66	REPRODUCTIVE TECHNIQUES, ASSISTED.kw.
67	(IVF or ICSI).tw,tx.
68	in vitro fertili?$.tw,tx.
69	or/66-68
70	CHILD.kw.
71	INFANT.kw.
72	ADOLESCENT.kw.
73	(newborn or neonate or preterm or prematur$ or infant$ or baby or babies or child* or adolescen$ or teenage$).tw,tx.
74	or/70-73
75	risk$.ti.
76	(inciden$ or hazard$).ti.
77	associat$.ti.
78	or/75-77
79	and/69,74,78
80	or/65,79

Database(s): Embase 1980 to 2011 Week 18

Search Strategy: FERT_Q4e_safety_women_child_embase_100511

#	**Searches**
1	(fertil$ or steril$ or infertil$ or subfertil$ or sub-fertil$ or fecund$ or subfecund$ or sub-fecund$ or assist$ reproduc$).ti,ab.
2	infertility/ or female infertility/ or subfertility/

3	FERTILITY/
4	exp OVARY INSUFFICIENCY/
5	OVULATION/
6	anovulat$.ti,ab.
7	oligo-ovulation.ti,ab.
8	"oligo ovulation".ti,ab.
9	Oligoovulat$.ti,ab.
10	exp INFERTILITY THERAPY/
11	IVF.ti,ab.
12	"in vitro fertili$".ti,ab.
13	"in?vitro fertili$".ti,ab.
14	ICSI.ti,ab.
15	INTRACYTOPLASMIC SPERM INJECTION/
16	AMENORRHEA/
17	amenorrh$.ti,ab.
18	hypogonadi$.ti,ab.
19	(hypothalamic adj3 amenorrh$).ti,ab.
20	(hypogonadotro$ adj3 hypogonadism).ti,ab.
21	or/1-20
22	exp INFERTILITY THERAPY/
23	IVF.ti,ab.
24	"in vitro fertili$".ti,ab.
25	exp FERTILITY PROMOTING AGENT/
26	"in?vitro fertili$".ti,ab.
27	(uFSH or rFSH or LH or hMG).ti,ab.
28	(gonadotrophin$ or gonadotropin$).ti,ab.
29	GnRH$.ti,ab.
30	(zoladex or synarel or decapeptyl).ti,ab.
31	DOPAMINE RECEPTOR STIMULATING AGENT/
32	(dopamin$ adj3 (agonist$ or agent$)).ti,ab.
33	BROMOCRIPTINE/

34	CABERGOLINE/
35	(cabergoline or bromocriptine).ti,ab.
36	LIFESTYLE MODIFICATION/
37	BODY WEIGHT/ or LEAN BODY WEIGHT/ or WEIGHT CONTROL/ or WEIGHT FLUCTUATION/ or WEIGHT GAIN/ or WEIGHT REDUCTION/
38	weight.ti,ab.
39	exp EXERCISE/
40	((reduc$ or decreas$ or stop$ or ceas$) adj3 exercis$).ti,ab.
41	ANTIESTROGEN/ or CLOMIFENE/ or CLOMIFENE CITRATE/ or TAMOXIFEN/ or TAMOXIFEN AZIRIDINE/ or TAMOXIFEN CITRATE/ or TAMOXIFEN DERIVATIVE/
42	(anti?estrogen$ or anti?oestrogen$).ti,ab.
43	(clomiphene or clomifene or tamoxifen).ti,ab.
44	METFORMIN/
45	(metformin or glucophage).ti,ab.
46	((ovary or ovaries or ovarian) adj3 (drill$ or electrocauter$ or diatherm$)).ti,ab.
47	exp OVARY/su
48	DIATHERMY/
49	LAPAROSCOPIC SURGERY/
50	LAPAROSCOPY/
51	or/49-50
52	and/48,51
53	(LOD or LOE).ti,ab.
54	ELECTROCOAGULATION/
55	exp GROWTH HORMONE/
56	(growth adj2 hormone$).ti,ab.
57	PRASTERONE/
58	DHEA.ti,ab.
59	or/22-46,52-58
60	risk$.ti.
61	(inciden$ or hazard$).ti.
62	associat$.ti.

63	or/60-62
64	and/21,59,63
65	exp INFERTILITY THERAPY/
66	(IVF or ICSI).ti,ab.
67	"in vitro fertili$".ti,ab.
68	"in?vitro fertili$".ti,ab.
69	or/65-68
70	exp CHILD/
71	exp INFANT/
72	exp ADOLESCENT/
73	(newborn$ or neonat$ or preterm or prematur$ or infant$ or baby or babies or child* or adolescen$ or teenage$).ti,ab.
74	or/70-73
75	risk$.ti.
76	(inciden$ or hazard$).ti.
77	associat$.ti.
78	or/75-77
79	and/69,74,78
80	or/64,79
81	limit 80 to yr="2003 -Current"
82	limit 81 to english language

Cinahl FERT_Q4e_safety_women_child_cinahl_100511

#	Query
S95	S82 or S93
S94	S82 or S93
S93	S81 and S92
S92	S87 and S91
S91	S88 or S89 or S90

S90	AB (newborn* or neonat* or preterm or prematur* or infant* or baby or babies or child* or adolescen* or teenage*)
S89	TI (newborn* or neonat* or preterm or prematur* or infant* or baby or babies or child* or adolescen* or teenage*)
S88	(MH "ADOLESCENCE+") OR (MH "CHILD+")
S87	S83 or S84 or S85 or S86
S86	TI (in vitro fertili*) or AB (in vitro fertili*)
S85	TI (ICSI) or AB (ICSI)
S84	TI (IVF) or AB (IVF)
S83	(MH "REPRODUCTION TECHNIQUES+")
S82	S76 and S81
S81	S77 or S78 or S79 or S80
S80	TI (associat*)
S79	TI (hazard*)
S78	TI (inciden*)
S77	TI (risk*)
S76	S19 and S75
S75	S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32 or S33 or S34 or S35 or S36 or S37 or S38 or S39 or S40 or S41 or S42 or S43 or S44 or S45 or S46 or S47 or S48 or S49 or S50 or S51 or S52 or S53 or S54 or S55 or S56 or S57 or S58 or S59 or S60 or S61 or S62 or S63 or S66 or S67 or S68 or S69 or S70 or S71 or S72 or S73 or S74
S74	TI (DHEA) or AB (DHEA)
S73	(MH "PRASTERONE")
S72	AB (growth N2 hormone*)
S71	TI (growth N2 hormone*)
S70	(MH "HUMAN GROWTH HORMONE")
S69	(MH "ELECTROCOAGULATION+")

S68	AB (LOD) or AB (LOE)
S67	TI (LOD) or TI (LOE)
S66	S64 and S65
S65	(MH "DIATHERMY")
S64	(MH "LAPAROSCOPY")
S63	AB (drill* or electrocauter* or diatherm*)
S62	TI (drill* or electrocauter* or diatherm*)
S61	(MH "OVARY/SU")
S60	AB (metformin) or AB (glucophage)
S59	TI (metformin) or TI (glucophage)
S58	(MH "METFORMIN")
S57	AB (tamoxifene) or AB (clomiphene) or AB (clomifene)
S56	TI (tamoxifene) or TI (clomiphene) or TI (clomifene)
S55	TI (anti-oestrogen*) or AB (anti-oestrogen*)
S54	TI (anti-estrogen*) or AB (anti-estrogen*)
S53	(MH "ESTROGEN RECEPTOR MODULATORS") OR (MH "ESTROGEN ANTAGONISTS+")
S52	TI (exercis*) or AB (exercis*)
S51	(MH "EXERCISE")
S50	(MH "BODY WEIGHT CHANGES+")
S49	AB (life-style N3 interven*)
S48	TI (life-style N3 interven*)
S47	AB (life-style N3 adjustment*)
S46	TI (life-style N3 adjustment*)
S45	AB (life-style N3 change*)

S44	TI (life-style N3 change*)
S43	(MH "LIFE STYLE+")
S42	AB (aminoglutethimide or testolactone or teslac or arimidex or letrozole or femara or exemestane or aromasin or vorozole or rivizor or formestane or lentaron or fadrozole or afema)
S41	TI (aminoglutethimide or testolactone or teslac or arimidex or letrozole or femara or exemestane or aromasin or vorozole or rivizor or formestane or lentaron or fadrozole or afema)
S40	AB (aromatase N3 inhibitor*)
S39	TI (aromatase N3 inhibitor*)
S38	(MH "AROMATASE INHIBITORS+")
S37	AB (cabergoline) or AB (bromocriptine)
S36	TI (cabergoline) or TI (bromocriptine)
S35	(MH "BROMOCRIPTINE")
S34	TI (dopamine N3 agents*) or AB (dopamine N3 agents*)
S33	TI (dopamine N3 agonist*) or AB (dopamine N3 agonist*)
S32	(MH "DOPAMINE AGENTS+")
S31	AB (zoladex) or AB (synarel) or AB (decapeptyl)
S30	Ti (zoladex) or TI (synarel) or TI (decapeptyl)
S29	TI (GnRH) or AB (GnRH)
S28	(MH "GONADORELIN+")
S27	TI (GnRHa) or AB (GnRHa)
S26	AB (gonadotrophin* or gonadotropin*)
S25	TI (gonadotrophin* or gonadotropin*)
S24	TI (hMG) or AB (hMG)
S23	TI (rFSH) or AB (rFSH)
S22	TI (uFSH) or AB (uFSH)

S21	(MH "GONADOTROPINS, PITUITARY+")
S20	(MH "FERTILITY AGENTS+") OR (MH "MENSTRUATION INDUCING AGENTS+")
S19	S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18
S18	(MH "HYPOGONADISM+")
S17	TI (amenorrh*) or AB (amenorrh*)
S16	(MH "AMENORRHEA")
S15	AB (intracytoplasmic sperm injection*)
S14	TI (intracytoplasmic sperm injection*)
S13	TI (ICSI) or AB (ICSI)
S12	TI (in vitro fertili*) or AB (in vitro fertili*)
S11	TI (IVF) or AB (IVF)
S10	(MH "FERTILIZATION IN VITRO")
S9	TI (oligo-ovulat*) or AB (oligo-ovulat*)
S8	TI (anovulat*) or AB (anovulat*)
S7	(MH "OVULATION")
S6	(MH "FERTILITY")
S5	TI (assist* reproduc*) or AB (assist* reproduc*)
S4	(MH "Infertility Risk (Saba CCC)")
S3	(MH "INFERTILITY")
S2	AB (fertil* or steril* or infertil* or sub-fertil* or fecund* or sub-fecund*)
S1	TI (fertil* or steril* or infertil* or sub-fertil* or fecund* or sub-fecund*)

Appendix F Summary of identified studies

Table F.1 Summary of indentified studies

Question	Review summary
How accurate are tests of ovarian reserve in predicting pregnancy and its outcomes for women with infertility undergoing: ovulation induction treatment; assisted reproduction (including unexplained infertility and IVF).	Search results: 9,192 Ordered/weeded in: 234 Included: 20 Excluded: 214
What is the effectiveness and safety of sperm washing to reduce the risk of viral transmission?	Search results: 402 Ordered/weeded in: 49 Included: 18 Excluded: 30
What is the effectiveness and safety of ovulation induction strategies in women with WHO Group I ovulation disorders?	Search results: 6112 Ordered/weeded in: 36 Included: 0 Excluded: 36
What is the effectiveness and safety of ovulation induction strategies in women with WHO Group II ovulation disorders?	Search results: 945 Ordered/weeded in: 173 Included: 31 Excluded: 142
What is the effectiveness and safety of ovarian stimulation strategies in women with unexplained infertility?	Search results: 634 Ordered/weeded in: 32 Included: 2 Excluded: 30
What is the effectiveness of intrauterine insemination (IUI)?	Search results: 916 Ordered/weeded in: 53 Included: 9 Excluded: 44
How accurate are clinical scoring systems in predicting the outcome of IVF treatment	Search results: 507 Ordered/weeded in: 40 Included: 6 Excluded: 34

Question	Review summary
What is the effectiveness of pre-treatment as part of an ovarian stimulation strategy for women undergoing IVF or ICSI treatment?	Search results: 8278 Ordered/weeded in: 43 Included: 2 Excluded: 41
What is the effectiveness of down regulation as part of an ovarian stimulation strategy for women undergoing IVF or ICSI treatment?	Search results: 8278 Ordered/weeded in: 96 Included: 16 Excluded: 80
What is the effectiveness of different ovarian strategies as part of an ovarian stimulation protocol in women undergoing IVF or ICSI treatment?	Search results: 8278 Ordered/weeded in: 263 Included: 74 Excluded: 189
Which is the most effective ovulation trigger to use as part of an ovarian stimulation strategy for women undergoing IVF or ICSI treatment?	Search results: 8278 Ordered/weeded in: 61 Included: 5 Excluded: 56
What is the effectiveness and safety of different embryo transfer strategies?	Search results: 5982 Ordered/weeded in: 80 Included: 27 Excluded: 53
What is the effectiveness of luteal phase support as part of an ovarian stimulation strategy for women undergoing IVF or ICSI treatment?	Search results: 8278 Ordered/weeded in: 99 Included: 5 Excluded: 94
What is the effectiveness of cryopreservation (including vitrification) in fertility preservation strategies?	Search results: 575 Ordered/weeded in: 25 Included: 10 Excluded: 15 *(Second search)* Search results: 918 Ordered/weeded in: 27 Included: 14 Excluded: 13

Question	Review summary
Safety of ovulation stimulating agents in women and long term effects on children conceived via ART	Search results: 5501 Ordered/weeded in: 5396 Included: 41 Excluded: 53 Unavailable: 5 Duplicate: 3

Appendix G Excluded studies

Chapter 6. Investigation of fertility problems and management strategies

Tests for ovarian reserve

Table G.1 How accurate are tests of ovarian reserve in predicting pregnancy and its outcomes for women with infertility undergoing: ovulation induction treatment; assisted reproduction (including unexplained infertility and IVF)

Bibliographic information	Reason for exclusion
Aboulghar,M.A., Mansour,R.T., Serour,G.I., Al-Inany,H.G., Diagnosis and management of unexplained infertility: An update, Archives of Gynecology and Obstetrics, 267, 177-188, 2003	Summary of Cochrane review
Alviggi,C., Humaidan,P., Howles,C.M., Tredway,D., Hillier,S.G., Biological versus chronological ovarian age: Implications for assisted reproductive technology, Reproductive Biology and Endocrinology, 7, -, 2009	Review
Anderson,R.A., Themmen,A.P.N., Al-Qahtani,A., Groome,N.P., Cameron,D.A., The effects of chemotherapy and long-term gonadotrophin suppression on the ovarian reserve in premenopausal women with breast cancer, Human Reproduction, 21, 2583-2592, 2006	Study does not provide data on outcomes of interest.
Arce,J.C., Balen,A., Platteau,P., Pettersson,G., Andersen,A.N., Mid-luteal progesterone concentrations are associated with live birth rates during ovulation induction, Reproductive Biomedicine Online, 22, 449-456, 2011	Does not present diagnostic accuracy data
Arslan,M., Bocca,S., Mirkin,S., Barroso,G., Stadtmauer,L., Oehninger,S., Controlled ovarian hyperstimulation protocols for in vitro fertilization: Two decades of experience after the birth of Elizabeth Carr, Fertility and Sterility, 84, 555-569, 2005	Not relevant
Baka,S., Makrakis,E., Tzanakaki,D., Konidaris,S., Hassiakos,D., Moustakarias,T., Creatsas,G., Poor responders in IVF: cancellation of a first cycle is not predictive of a subsequent failure, Annals of the New York Academy of Sciences, 1092, 418-425, 2006	Study does not provide data on outcomes of interest.
Balasch,J., Creus,M., Fabregues,F., Carmona,F., Casamitjana,R., Ascaso,C., Vanrell,J.A., Inhibin, follicle-stimulating hormone, and age as predictors of ovarian response in in vitro fertilization cycles stimulated with gonadotropin-releasing hormone agonist-gonadotropin treatment, American Journal of Obstetrics and Gynecology, 175, 1226-1230, 1996	Retrospective study. Study does not provide data on outcomes of interest.

Bibliographic information	Reason for exclusion
Bancsi,L.F., Huijs,A.M., den Ouden,C.T., Broekmans,F.J., Looman,C.W., Blankenstein,M.A., te Velde,E.R., Basal follicle-stimulating hormone levels are of limited value in predicting ongoing pregnancy rates after in vitro fertilization, Fertility and Sterility, 73, 552-557, 2000	Retrospective study.
Barad,D.H., Weghofer,A., Gleicher,N., Age-specific levels for basal follicle-stimulating hormone assessment of ovarian function, Obstetrics and Gynecology, 109, 1404-1410, 2007	Retrospective study.
Barad,D.H., Weghofer,A., Gleicher,N., Comparing anti-Mullerian hormone (AMH) and follicle-stimulating hormone (FSH) as predictors of ovarian function, Fertility and Sterility, 91, 1553-1555, 2009	Correspondence
Blazar,A.S., Lambert-Messerlian,G., Hackett,R., Krotz,S., Carson,S.A., Robins,J.C., Use of in-cycle antimullerian hormone levels to predict cycle outcome, American Journal of Obstetrics and Gynecology, 205, 223-223, 2011	Does not present diagnostic accuracy data
Blumenfeld,Z., Avivi,I., Linn,S., Epelbaum,R., Ben-Shahar,M., Haim,N., Prevention of irreversible chemotherapy-induced ovarian damage in young women with lymphoma by a gonadotrophin-releasing hormone agonist in parallel to chemotherapy, Human Reproduction, 11, 1620-1626, 1996	Study does not provide data on ouctomes of interest.
Bonetti,T.C., Salomao,R., Brunialti,M., Braga,D.P., Borges E Jr, Silva,I.D., Cytokine and hormonal profile in serum samples of patients undergoing controlled ovarian stimulation: interleukin-1beta predicts ongoing pregnancy, Human Reproduction, 25, 2101-2106, 2010	Study does not provide data on outcomes of interest.
Bukman,A., Heineman,M.J., Ovarian reserve testing and the use of prognostic models in patients with subfertility. [85 refs], Human Reproduction Update, 7, 581-590, 2001	Review
Cabrera,R.A., Stadtmauer,L., Mayer,J.F., Gibbons,W.E., Oehninger,S., Follicular phase serum levels of luteinizing hormone do not influence delivery rates in in vitro fertilization cycles down-regulated with a gonadotropin-releasing hormone agonist and stimulated with recombinant follicle-stimulating hormone, Fertility and Sterility, 83, 42-48, 2005	Test of interest were not examined.
Carrera-Rotllan,J., Estrada-Garcia,L., Sarquella-Ventura,J., Prediction of pregnancy in IVF cycles on the fourth day of ovarian stimulation, Journal of Assisted Reproduction and Genetics, 24, 387-394, 2007	Tests of ovarian reserve on women undergoing stimulation.
Chang,C.L., Wang,T.H., Horng,S.G., Wu,H.M., Wang,H.S., Soong,Y.K., The concentration of inhibin B in follicular fluid: Relation to oocyte maturation and embryo development, Human Reproduction, 17, 1724-1728, 2002	Study does not provide data on outcomes of interest.
Chang,M.Y., Chiang,C.H., Hsieh,T.T., Soong,Y.K., Hsu,K.H., Use of the antral follicle count to predict the outcome of assisted reproductive technologies, Fertility and Sterility, 69, 505-510, 1998	Study does not provide data on outcomes of interest.
Check,J.H., Katsoff,B., Brasile,D., Choe,J.K., Amui,J., Pregnancy outcome following in vitro fertilization-embryo transfer (IVF-ET) in women of more advanced reproductive age with elevated serum follicle stimulating hormone (FSH) levels, Clinical and Experimental Obstetrics and Gynecology, 35, 13-15, 2008	Study does not provide data on outcomes of interest.

Bibliographic information	Reason for exclusion
Chiang,C.H., Hsieh,T.T., Chang,M.Y., Shiau,C.S., Hou,H.C., Hsu,J.J., Soong,Y.K., Prediction of pregnancy rate of in vitro fertilization and embryo transfer in women aged 40 and over with basal uterine artery pulsatility index, Journal of Assisted Reproduction and Genetics, 17, 409-414, 2000	Stuidy did not use tests of interest.
Chow,G.E., Criniti,A.R., Soules,M.R., Antral follicle count and serum follicle-stimulating hormone levels to assess functional ovarian age, Obstetrics and Gynecology, 104, 801-804, 2004	Study does not rpovide any data on outcomes of interest. Study makes an estimation of the variation in AFC and FSH.
Chuang,C.C., Chen,C.D., Chao,K.H., Chen,S.U., Ho,H.N., Yang,Y.S., Age is a better predictor of pregnancy potential than basal follicle-stimulating hormone levels in women undergoing in vitro fertilization, Fertility and Sterility, 79, 63-68, 2003	Retrospective study design
Corrigan,E., McLaughlin,E.A., Coulson,C., Ford,W.C., Hull,M.G., The effect of halving the standard dose of cryopreserved semen for donor insemination: a controlled study of conception rates, Human Reproduction, 9, 330-333, 1994	Study provides insufficient data oin outcomes of interest.
Costello,M.F., Hughes,G.J., Garrett,D.K., Hanjani,A., Steigrad,S.J., A spontaneous luteinizing hormone surge is beneficial in women with unexplained infertility undergoing controlled ovarian hyperstimulation without in vitro fertilization, International Journal of Fertility and Womens Medicine, 43, 28-33, 1998	Not relevant
D'Amato,G., Caroppo,E., Pasquadibisceglie,A., Carone,D., Vitti,A., Vizziello,G.M., A novel protocol of ovulation induction with delayed gonadotropin-releasing hormone antagonist administration combined with high-dose recombinant follicle-stimulating hormone and clomiphene citrate for poor responders and women over 35 years, Fertility and Sterility, 81, 1572-1577, 2004	Retrospective study. Study does not provide data on outcomes of interest.
de Carvalho,B.R., Rosa-e-Silva AC, Rosa-e-Silva JC, Dos Reis,R.M., Ferriani,R.A., Silva-de-Sa,M.F., Increased basal FSH levels as predictors of low-quality follicles in infertile women with endometriosis, International Journal of Gynaecology and Obstetrics, 110, 208-212, 2010	Study does not provide data on outcomes of interest.
De,PlacidoG, Alviggi,C., Clarizia,R., Mollo,A., Alviggi,E., Strina,I., Fiore,E., Wilding,M., Pagano,T., Matarase,G., Intra-follicular leptin concentration as a predictive factor for in vitro oocyte fertilization in assisted reproductive techniques, Journal of Endocrinological Investigation, 29, 719-726, 2006	Study does not provide data on outcomes of interest.
Decanter,C., Pigny,P., Lefebvre,C., Thomas,P., Leroy,M., Dewailly,D., Serum inhibin B during controlled ovarian hyperstimulation: an additional criterion for deciding whether to proceed with egg retrieval, Fertility and Sterility, 91, 2419-2425, 2009	Women were already undergoing stimulation when tested.
Dechanet,C., Castelli,C., Reyftmann,L., Coubes,C., Hamamah,S., Hedon,B., Dechaud,H., Anahory,T., Myotonic dystrophy type 1 and PGD: Ovarian stimulation response and correlation analysis between ovarian reserve and genotype, Reproductive Biomedicine Online, #20, 610-618, 2010	Retrospective study.

Bibliographic information	Reason for exclusion
Delvigne,A., Dubois,M., Battheu,B., Bassil,S., Meuleman,C., De,Sutter P., Rodesch,C., Janssens,P., Remacle,P., Gordts,S., The ovarian hyperstimulation syndrome in in-vitro fertilization: a Belgian multicentric study. II. Multiple discriminant analysis for risk prediction, Human Reproduction, 8, 1361-1366, 1993	Study does not provide any data on outcomes of interest. Study examines teh risk of OHSS.
Duleba,A.J., Hausman,N., Jones,E.E., Olive,D.L., Preretrieval predictors of pregnancy in IVF, Journal of Assisted Reproduction and Genetics, 14, -211, 1997	Study does not provide data on outcomes of interest.
Durmusoglu,F., Elter,K., Yoruk,P., Erenus,M., Combining cycle day 7 follicle count with the basal antral follicle count improves the prediction of ovarian response, Fertility and Sterility, 81, 1073-1078, 2004	Tests of ovarian reserve on women undergoing stimulation.
Dzik,A., Lambert-Messerlian,G., Izzo,V.M., Soares,J.B., Pinotti,J.A., Seifer,D.B., Inhibin B response to EFORT is associated with the outcome of oocyte retrieval in the subsequent in vitro fertilization cycle, Fertility and Sterility, 74, 1114-1117, 2000	Study does not provide data on outcomes of interest.
Ebner,T., Sommergruber,M., Moser,M., Shebl,O., Schreier-Lechner,E., Tews,G., Basal level of anti-Mullerian hormone is associated with oocyte quality in stimulated cycles, Human Reproduction, 21, 2022-2026, 2006	Study does not provide data on outcomes of interest.
Ebrahim,A., Rienhardt,G., Morris,S., Kruger,T.F., Lombard,C.J., Van der Merwe,J.P., Follicle stimulating hormone levels on cycle day 3 predict ovulation stimulation response, Journal of Assisted Reproduction and Genetics, 10, 130-136, 1993	Study does not provide data on outcomes of interest.
Eldar,Geva T., Margalioth,E.J., Algur,N.N., Robertson,D.M., Healy,D.L., Serum inhibin B concentrations measured early during FSH administration for IVF/embryo transfer can predict treatment outcome, Human Reproduction, Vol.15, pp.87-88, 2000., -88, 2000	Conference abstract.
Eldar-Geva,T., Ben-Chetrit,A., Spitz,I.M., Rabinowitz,R., Markowitz,E., Mimoni,T., Gal,M., Zylber-Haran,E., Margalioth,E.J., Dynamic assays of inhibin B, anti-Mullerian hormone and estradiol following FSH stimulation and ovarian ultrasonography as predictors of IVF outcome, Human Reproduction, #20, 3178-3183, 2005	Study population is potentially biased
Eldar-Geva,T., Margalioth,E.J., Ben-Chetrit,A., Gal,M., Robertson,D.M., Healy,D.L., Diamant,Y.Z., Spitz,I.M., Serum inhibin B levels measured early during FSH administration for IVF may be of value in predicting the number of oocytes to be retrieved in normal and low responders, Human Reproduction, 17, 2331-2337, 2002	Study does not provide data on outcomes of interest.
Elgindy,E.A., El-Haieg,D.O., El-Sebaey,A., Anti-Mullerian hormone: correlation of early follicular, ovulatory and midluteal levels with ovarian response and cycle outcome in intracytoplasmic sperm injection patients, Fertility and Sterility, 89, 1670-1676, 2008	Study population is potentially biased
El-Halawaty,S., Rizk,A., Kamal,M., Aboulhassan,M., Al-Sawah,H., Noah,O., Al-Inany,H., Clinical significance of serum concentration of anti-Mullerian hormone in obese women with polycystic ovary syndrome, Reproductive Biomedicine Online, 15, 495-499, 2007	Study does n ot provide a definition for poor response.
El-Shawarby,S.A., Khalaf,Y., Age-specific serum FSH concentrations and their correlation with the outcome of ovarian stimulation for IVF, Reproductive Biomedicine Online, 18, 750-755, 2009	Retrospective study.

Bibliographic information	Reason for exclusion
Elter,K., Sismanoglu,A., Durmusoglu,F., Intercycle variabilities of basal antral follicle count and ovarian volume in subfertile women and their relationship to reproductive aging: a prospective study, Gynecological Endocrinology, 20, 137-143, 2005	Study does not provide any data on outcomes of interest. Study is concerned with inter-cycle variability of AFC
Elting,M.W., Kwee,J., Schats,R., Rekers-Mombarg,L.T.M., Schoemaker,J., The rise of estradiol and inhibin B after acute stimulation with follicle-stimulating hormone predict the follicle cohort size in women with polycystic ovary syndrome, regularly menstruating women with polycystic ovaries, and regularly menstruating women with normal ovaries, Journal of Clinical Endocrinology and Metabolism, 86, 1589-1595, 2001	Study does not provide data on outcomes of interest.
El-Toukhy,T., Khalaf,Y., Hart,R., Taylor,A., Braude,P., Young age does not protect against the adverse effects of reduced ovarian reserve--an eight year study, Human Reproduction, 17, 1519-1524, 2002	Retrospective study.
Engels,V., Sanfrutos,L., Perez-Medina,T., Alvarez,P., Zapardiel,I., Godoy-Tundidor,S., Salazar,F.J., Troyano,J., Bajo-Arenas,J.M., Periovulatory follicular volume and vascularization determined by 3D and power Doppler sonography as pregnancy predictors in intrauterine insemination cycles, Journal of Clinical Ultrasound, 39, 243-247, 2011	Did not undertake diagnostic accuracy tests.
Enskog,L., Nilsson,M., Brannstrom, Peripheral blood concentrations of inhibin B are elevated during gonadotrophin stimulation in patients who later develop ovarian OHSS and inhibin A concentrations are elevated after OHSS onset, Human Reproduction, 15, 532-538, 2000	Study does not provide data on outcomes of interest. Study examines predictors of OHSS.
Erdem,M., Erdem,A., Guler,I., Atmaca,S., Role of antral follicle count in controlled ovarian hyperstimulation and intrauterine insemination cycles in patients with unexplained subfertility, Fertility and Sterility, 90, 360-366, 2008	Tests of ovarian reserve on women undergoing stimulation.
Erman,Akar M., Oktay,K., Falling FSH levels predict poor IVF pregnancy rates in patients whom the gonadotropins are withheld, Archives of Gynecology and Obstetrics, 280, 761-765, 2009	Study does not provide any data on the outcomes of interest. Study is a retrospective review of IVF with coasting.
Esposito,M.A., Coutifaris,C., Barnhart,K.T., A moderately elevated day 3 FSH concentration has limited predictive value, especially in younger women, Human Reproduction, 17, 118-123, 2002	AUC data does not meet a priori accuracy levels so thrshold data not used.
Evers,J.L.H., Slaats,P., Land,J.A., Dumoulin,J.C.M., Dunselman,G.A.J., Elevated levels of basal estradiol-17beta predict poor response in patients normal basal levels of follicle-stimulating hormone undergoing in vitro fertilization, Fertility and Sterility, 69, 1010-1014, 1998	Study does not provide data on outcomes of interest.
Faber,B.M., Mayer,J., Cox,B., Jones,D., Toner,J.P., Oehninger,S., Muasher,S.J., Cessation of gonadotropin-releasing hormone agonist therapy combined with high-dose gonadotropin stimulation yields favorable pregnancy results in low responders, Fertility and Sterility, 69, 826-830, 1998	Study does not provide data on outcomes of interest.
Fallat,M.E., Siow,Y., Marra,M., Cook,C., Carrillo,A., Mullerian-inhibiting substance in follicular fluid and serum: a comparison of patients with tubal factor infertility, polycystic ovary syndrome, and endometriosis, Fertility and Sterility, 67, 962-965, 1997	Study does not provide data on outcomes of interest.

Bibliographic information	Reason for exclusion
Fanchin,R., Castelo,Branco A., Kadoch,I.J., Hosny,G., Bagirova,M., Frydman,R., Premenstrual administration of gonadotropin-releasing hormone antagonist coordinates early antral follicle sizes and sets up the basis for an innovative concept of controlled ovarian hyperstimulation, Fertility and Sterility, 81, 1554-1559, 2004	Study does not provide data on outcomes of interest.
Fanchin,R., de,Ziegler D., Olivennes,F., Taieb,J., Dzik,A., Frydman,R., Exogenous follicle stimulating hormone ovarian reserve test (EFORT): a simple and reliable screening test for detecting 'poor responders' in in-vitro fertilization, Human Reproduction, 9, 1607-1611, 1994	Study does not provide data on outcomes of interest.
Fanchin,R., Louafi,N., Mendez,LozanoD, Frydman,N., Frydman,R., Taieb,J., Per-follicle measurements indicate that anti-mullerian hormone secretion is modulated by the extent of follicular development and luteinization and may reflect qualitatively the ovarian follicular status, Fertility and Sterility, 84, 167-173, 2005	Study does not provide data on outcomes of interest.
Fanchin,R., Mendez Lozano,D.H., Louafi,N., chour-Frydman,N., Frydman,R., Taieb,J., Dynamics of serum anti-Mullerian hormone levels during the luteal phase of controlled ovarian hyperstimulation, Human Reproduction, 20, 747-751, 2005	Study does not provide data on outcomes of interest.
Farber,L.A., Ames,J.W., Rush,S., Gal,D., Laparoscopic ovarian transposition to preserve ovarian function before pelvic radiation and chemotherapy in a young patient with rectal cancer, Medgenmed [Computer File]: Medscape General Medicine, 7, 66-, 2005	Study has sample size less than 10
Fawzy,M., Lambert,A., Harrison,R.F., Knight,P.G., Groome,N., Hennelly,B., Robertson,W.R., Day 5 inhibin B levels in a treatment cycle are predictive of IVF outcome, Human Reproduction, 17, 1535-1543, 2002	Study does not provide data on outcomes of interest.
Ficicioglu,C., Kutlu,T., Baglam,E., Bakacak,Z., Early follicular antimullerian hormone as an indicator of ovarian reserve, Fertility and Sterility, 85, 592-596, 2006	Inappropriate definition of low response
Ficicioglu,C., Kutlu,T., Demirbasoglu,S., Mulayim,B., The role of inhibin B as a basal determinant of ovarian reserve, Gynecological Endocrinology, 17, 287-293, 2003	Study does not provide data on outcomes of interest.
Fleming,R., Deshpande,N., Traynor,I., Yates,R.W., Dynamics of FSH-induced follicular growth in subfertile women: relationship with age, insulin resistance, oocyte yield and anti-Mullerian hormone, Human Reproduction, 21, 1436-1441, 2006	Study does not provide data on outcomes of interest.
Foong,S.C., Abbott,D.H., Lesnick,T.G., Session,D.R., Walker,D.L., Dumesic,D.A., Diminished intrafollicular estradiol levels in in vitro fertilization cycles from women with reduced ovarian response to recombinant human follicle-stimulating hormone, Fertility and Sterility, 83, 1377-1383, 2005	Study does not provide data on outcomes of interest.
Foong,S.C., Fleetham,J.A., O'Keane,J.A., Scott,S.G., Tough,S.C., Greene,C.A., A prospective randomized trial of conventional in vitro fertilization versus intracytoplasmic sperm injection in unexplained infertility, Journal of Assisted Reproduction and Genetics, 23, 137-140, 2006	Study does not provide data on outcomes of interest.
Frattarelli,J.L., Gerber,M.D., Basal and cycle androgen levels correlate with in vitro fertilization stimulation parameters but do not predict pregnancy outcome, Fertility and Sterility, 86, 51-57, 2006	Study does not provide data on outcomes of interest.

Bibliographic information	Reason for exclusion
Freiesleben,N.L.C., Lossl,K., Bogstad,J., Bredkjaer,H.E., Toft,B., Loft,A., Bangsboll,S., Pinborg,A., Budtz-Jorgensen,E., Andersen,A.N., Predictors of ovarian response in intrauterine insemination patients and development of a dosage nomogram, Reproductive Biomedicine Online, 17, 632-641, 2008	Study provides insufficient data to calculate outcomes of interest.
Fried,G., Remaeus,K., Harlin,J., Krog,E., Csemiczky,G., Aanesen,A., Tally,M., Inhibin B predicts oocyte number and the ratio IGF-I/IGFBP-1 may indicate oocyte quality during ovarian hyperstimulation for in vitro fertilization, Journal of Assisted Reproduction and Genetics, 20, 167-176, 2003	Study does not provide data on outcomes of interest.
Friedler,S., Raziel,A., Strassburger,D., Schachter,M., Soffer,Y., Ron-El,R., Factors influencing the outcome of ICSI in patients with obstructive and non-obstructive azoospermia: A comparative study, Human Reproduction, 17, 3114-3121, 2002	Study does not provide any data on outcomes of interest. Study examines role of azoospermia in ICSI.
Galtier-Dereure,F., De,BouardV, Picot,M.C., Vergnes,C., Humeau,C., Bringer,J., Hedon,B., Ovarian reserve test with the gonadotrophin-releasing hormone agonist buserelin: Correlation with in-vitro fertilization outcome, Human Reproduction, 11, 1393-1398, 1996	Study does not provide data on outcomes of interest.
Ganesh,A., Goswami,S., Chattopadhyay,R., Chakraborty,C., Chaudhury,K., Chakravarty,B.N., Luteal phase estradiol level: a potential predictive marker for successful pregnancy in in vitro fertilization/intracytoplasmic sperm injection, Fertility and Sterility, 91, 1018-1022, 2009	Study does not provide data on outcomes of interest.
Garrido,N., Melo,M.A.B., Simon,C., Remohi,J., Pellicer,A., Meseguer,M., Ovarian stimulation length, number of follicles higher than 17.mm and estradiol on the day of human chorionic gonadotropin administration are risk factors for multiple pregnancy in intrauterine insemination, Reproductive Medicine and Biology, 6, -26, 2007	Study does not provide data on outcomes of interest.
Gibreel,Fathy Ahmed, Maheshwari,Abha, Bhattacharya,Siladitya, Clomiphene citrate for controlled ovarian stimulation in women undergoing in vitro fertilization, Cochrane Database of Systematic Reviews, -, 2010	Review
Gleicher,N., Weghofer,A., Barad,D.H., Anti-Mullerian hormone (AMH) defines, independent of age, low versus good live-birth chances in women with severely diminished ovarian reserve, Fertility and Sterility, 94, 2824-2827, 2010	Poor quality and does not present AUC information
Gleicher,N., Weghofer,A., Barad,D.H., Discordances between follicle stimulating hormone (FSH) and anti-Mullerian hormone (AMH) in female infertility, Reproductive Biology and Endocrinology, 8, 64-, 2010	Study does not provide data on outcomes of interest.
Gnoth,C., Schuring,A.N., Friol,K., Tigges,J., Mallmann,P., Godehardt,E., Relevance of anti-Mullerian hormone measurement in a routine IVF program, Human Reproduction, 23, 1359-1365, 2008	Inappropriate definition of low response
Gohar,A.O., El-Edwi,A.R., Abdallah,H.E.S.H., Ovulation prediction in spontaneous and induced cycles: The role of ovarian reserve markers, Middle East Fertility Society Journal, 9, 47-57, 2004	Study provides insufficient ndata to calculate outcomes of interest.
Gurgan,T., Urman,B., Yarali,H., Duran,H.E., Follicle-stimulating hormone levels on cycle day 3 to predict ovarian response in women undergoing controlled ovarian hyperstimulation for in vitro fertilization using a flare-up protocol, Fertility and Sterility, 68, 483-487, 1997	Reported data not useful

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Haadsma,M.L., Groen,H., Fidler,V., Bukman,A., Roeloffzen,E.M., Groenewoud,E.R., Broekmans,F.J., Heineman,M.J., Hoek,A., The predictive value of ovarian reserve tests for spontaneous pregnancy in subfertile ovulatory women, Human Reproduction, 23, 1800-1807, 2008	Study does not provide data on outcomes of interest.
Haadsma,M.L., Groen,H., Fidler,V., Seinen,L.H., Broekmans,F.J., Heineman,M.J., Hoek,A., The predictive value of ovarian reserve tests for miscarriage in a population of subfertile ovulatory women, Human Reproduction, 24, 546-552, 2009	Study does not provide data on outcomes of interest.
Hall,J.E., Welt,C.K., Cramer,D.W., Inhibin A and inhibin B reflect ovarian function in assisted reproduction but are less useful at predicting outcome, Human Reproduction, 14, 409-415, 1999	Study does not provide data on outcomes of interest.
Hansen,L.M., Batzer,F.R., Gutmann,J.N., Corson,S.L., Kelly,M.P., Gocial,B., Evaluating ovarian reserve: Follicle stimulating hormone and oestradiol variability during cycle days 2-5, Human Reproduction, 11, 486-489, 1996	Study doe snot provide any data on outcomes of interest. Study on intra- and inter-cycle variability of FSH on cycle days 2 - 5
Hazout,A., Bouchard,P., Seifer,D.B., Aussage,P., Junca,A.M., Cohen-Bacrie,P., Serum antimullerian hormone/mullerian-inhibiting substance appears to be a more discriminatory marker of assisted reproductive technology outcome than follicle-stimulating hormone, inhibin B, or estradiol, Fertility and Sterility, 82, 1323-1329, 2004	Study does not provide data on outcomes of interest.
Hendriks,D.J., Broekmans,F.J., Bancsi,L.F., Looman,C.W., de Jong,F.H., te Velde,E.R., Single and repeated GnRH agonist stimulation tests compared with basal markers of ovarian reserve in the prediction of outcome in IVF, Journal of Assisted Reproduction and Genetics, 22, 65-73, 2005	Retrospective study.
Hendriks,D.J., Mol,B.W., Bancsi,L.F., te Velde,E.R., Broekmans,F.J., Antral follicle count in the prediction of poor ovarian response and pregnancy after in vitro fertilization: a meta-analysis and comparison with basal follicle-stimulating hormone level, Fertility and Sterility, 83, 291-301, 2005	Old review. Individual studies included.
Hendriks,D.J., Mol,B.W., Bancsi,L.F., te Velde,E.R., Broekmans,F.J., The clomiphene citrate challenge test for the prediction of poor ovarian response and nonpregnancy in patients undergoing in vitro fertilization: a systematic review. [60 refs], Fertility and Sterility, 86, 807-818, 2006	Review
hghani-Firouzabadi,R., Tayebi,N., Asgharnia,M., Serum level of anti-mullerian hormone in early follicular phase as a predictor of ovarian reserve and pregnancy outcome in assisted reproductive technology cycles, Archives of Iranian Medicine, 11, 371-376, 2008	Study does not provide data on outcomes of interest.
Ho,H.Y., Lee,R.K., Lin,M.H., Hwu,Y.M., Estradiol level on day 9 as a predictor of risk for ovarian hyperresponse during controlled ovarian hyperstimulation, Journal of Assisted Reproduction and Genetics, 20, 222-226, 2003	Study does not provide data on outcomes of interest.
Hofmann,G.E., Khoury,J., Michener,C., Elevated serum progesterone-to-estradiol ratio during gonadotropin stimulation for intrauterine insemination or in vitro fertilization is not associated with diminished ovarian reserve, Fertility and Sterility, 78, 47-50, 2002	Study does not provide any data on outcomes of interest. Study used CCCT as reference standard and used P/E2 ratios to detect diminished ovarian response

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Holte,J., Brodin,T., Berglund,L., Hadziosmanovic,N., Olovsson,M., Bergh,T., Antral follicle counts are strongly associated with live-birth rates after assisted reproduction, with superior treatment outcome in women with polycystic ovaries, Fertility and Sterility, 96, 594-599, 2011	Did not provide information on diagnostic accuracy of tests.
Hsieh,Y.Y., Chang,C.C., Tsai,H.D., Antral follicle counting in predicting the retrieved oocyte number after ovarian hyperstimulation, Journal of Assisted Reproduction and Genetics, 18, 320-324, 2001	Study does not provide data on outcomes of interest
Hudecova,M., Holte,J., Olovsson,M., Sundstrom,PoromaaI, Long-term follow-up of patients with polycystic ovary syndrome: Reproductive outcome and ovarian reserve, Human Reproduction, 24, 1176-1183, 2009	Study does not provide data on outcomes of interest.
Imani,B., Eijkemans,M.J., te Velde,E.R., Habbema,J.D., Fauser,B.C., Predictors of patients remaining anovulatory during clomiphene citrate induction of ovulation in normogonadotropic oligoamenorrheic infertility, Journal of Clinical Endocrinology and Metabolism, 83, 2361-2365, 1998	Study did not provide data on outcomes of interest.
Ishikawa,H., Ohashi,M., Hata,M., Kaneko,S., Oda,T., Ejaculatory disturbance due to spinal injury-artificial insemination with cryopreserved sperm resulted in pregnancy / birth of a child, Molecular Andrology, 5, 247-250, 1993	Study has sample size less than 10
Iwase,A., Ando,H., Kuno,K., Mizutani,S., Use of follicle-stimulating hormone test to predict poor response in in vitro fertilization, Obstetrics & Gynecology, 105, 645-652, 2005	Study does not provide data on outcome of interest.
Jain,T., Soules,M.R., Collins,J.A., Comparison of basal follicle-stimulating hormone versus the clomiphene citrate challenge test for ovarian reserve screening, Fertility and Sterility, 82, 180-185, 2004	Narartive review
Jarvela,I.Y., Sladkevicius,P., Kelly,S., Ojha,K., Campbell,S., Nargund,G., Quantification of ovarian power Doppler signal with three-dimensional ultrasonography to predict response during in vitro fertilization, Obstetrics and Gynecology, 102, 816-822, 2003	Study does not provide data on outcomes of interest.
Jayaprakasan,K., Campbell,B., Hopkisson,J., Clewes,J., Johnson,I., Raine-Fenning,N., Establishing the intercycle variability of three-dimensional ultrasonographic predictors of ovarian reserve, Fertility and Sterility, 90, 2126-2132, 2008	Study does not provide data on oputcomes of interest. Study of intrecycle variability of US predictors of ovarian reserve.
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Jayaprakasan,K., Hopkisson,J.F., Campbell,B.K., Clewes,J., Johnson,I.R., Raine-Fenning,N.J., Quantification of the effect of pituitary down-regulation on 3D ultrasound predictors of ovarian response, Human Reproduction, 23, 1538-1544, 2008	Study population is potentially biased

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Jinno,M., Hoshiai,T., Nakamura,Y., Teruya,K., Tsunoda,T., A novel method for assessing assisted female fertility: bioelectric impedance, Journal of Clinical Endocrinology and Metabolism, 85, 471-474, 2000	Study does not provide data on outcomes of interest.
Johnson,N.P., Bagrie,E.M., Coomarasamy,A., Bhattacharya,S., Shelling,A.N., Jessop,S., Farquhar,C., Khan,K.S., Ovarian reserve tests for predicting fertility outcomes for assisted reproductive technology: the International Systematic Collaboration of Ovarian Reserve Evaluation protocol for a systematic review of ovarian reserve test accuracy. [56 refs], BJOG: An International Journal of Obstetrics and Gynaecology, 113, 1472-1480, 2006	Protocol for a systematic review of ovarian reserve test accuracy.
Joiner,L.L.R., Robinson,R.D., Bates,G.W., Propst,A.M., Establishing institutional critical values of follicle-stimulating hormone levels to predict in vitro fertilization success, Military Medicine, 172, -204, 2007	Retrospective study.
Jun,S.H., Choi,B., Shahine,L., Westphal,L.M., Behr,B., Reijo Pera,R.A., Wong,W.H., Yao,M.W., Defining human embryo phenotypes by cohort-specific prognostic factors, PLoS ONE [Electronic Resource], 3, e2562-, 2008	Study does not provide data on outcomes of interest.
Jurema,M.W., Bracero,N.J., Garcia,J.E., Fine tuning cycle day 3 hormonal assessment of ovarian reserve improves in vitro fertilization outcome in gonadotropin-releasing hormone antagonist cycles, Fertility and Sterility, 80, 1156-1161, 2003	Retrospective study.
Kahraman,S., Vicdan,K., Isik,A.Z., Ozgun,O.D., Alaybeyoglu,L., Polat,G., Biberoglu,K., Clomiphene citrate challenge test in the assessment of ovarian reserve before controlled ovarian hyperstimulation for intracytoplasmic sperm injection, European Journal of Obstetrics, Gynecology, and Reproductive Biology, 73, 177-182, 1997	Retrospective study.
Kandil,M., Selim,M., Hormonal and sonographic assessment of ovarian reserve before and after laparoscopic ovarian drilling in polycystic ovary syndrome, BJOG: An International Journal of Obstetrics and Gynaecology, 112, 1427-1430, 2005	Study does not provide data on outcomes of interest.
Keay,S.D., Liversedge,N.H., Akande,V.A., Mathur,R.S., Jenkins,J.M., Serum IGF-1 concentrations following pituitary desensitization do not predict the ovarian response to gonadotrophin stimulation prior to IVF, Human Reproduction, 18, 1797-1801, 2003	Study does not provide data on outcomes of interest.
Khalifa,E., Toner,J.P., Muasher,S.J., Acosta,A.A., Significance of basal follicle-stimulating hormone levels in women with one ovary in a program of in vitro fertilization.[Erratum appears in Fertil Steril 1992 Aug;58(2):458], Fertility and Sterility, 57, 835-839, 1992	Study does not provide data on outcomes of interest.
Khalil,M.R., Rasmussen,P.E., Erb,K., Laursen,S.B., Rex,S., Westergaard,L.G., Homologous intrauterine insemination. An evaluation of prognostic factors based on a review of 2473 cycles, Acta Obstetricia et Gynecologica Scandinavica, 80, 74-81, 2001	Study provides insufficient data on outcomes of interest.
Knauff,E.A., Eijkemans,M.J., Lambalk,C.B., ten Kate-Booij,M.J., Hoek,A., Beerendonk,C.C., Laven,J.S., Goverde,A.J., Broekmans,F.J., Themmen,A.P., de Jong,F.H., Fauser,B.C., Dutch Premature Ovarian Failure Consortium., Anti-Mullerian hormone, inhibin B, and antral follicle count in young women with ovarian failure, Journal of Clinical Endocrinology and Metabolism, 94, 786-792, 2009	Study does not provide data on outcomes of interest.

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Kokcu,A., Turhan,E., Cetinkaya,M.B., Yanik,F., Alper,T., Malatyalioglu,E., Inhibin B levels on cycle day 3 to predict the ovulatory response in women with PCOS undergoing ovulation induction via low dose step-up gonadotropin protocol, Archives of Gynecology and Obstetrics, 270, 255-259, 2004	Study does not provide data on outcomes of interest.
Kolibianakis,E.M., Albano,C., Kahn,J., Camus,M., Tournaye,H., Van Steirteghem,A.C., Devroey,P., Exposure to high levels of luteinizing hormone and estradiol in the early follicular phase of gonadotropin-releasing hormone antagonist cycles is associated with a reduced chance of pregnancy, Fertility and Sterility, 79, 873-880, 2003	Tests of ovarian reserve on women undergoing stimulation.
Kreiner,D., Muasher,S.J., Acosta,A.A., Jones,G.S., Liu,H.C., Rosenwaks,Z., Monitoring gonadotropin-stimulated cycles for in vitro fertilization and embryo transfer, Journal of in Vitro Fertilization and Embryo Transfer, 5, 230-233, 1988	Study does not provide data on outcomes of interest.
Kugu,K., Momoeda,M., Sharma,S.S., Osuga,Y., Fujiwara,T., Okagaki,R., Fukushima,H., Yano,T., Tsutsumi,O., Taketani,Y., Is an elevation in basal follicle-stimulating hormone levels in unexplained infertility predictive of fecundity regardless of age?, Endocrine Journal, 48, 711-715, 2001	Study does not provide data on outcomes of interest.
Kumbak,B., Oral,E., Kahraman,S., Karlikaya,G., Karagozoglu,H., Young patients with diminished ovarian reserve undergoing assisted reproductive treatments: a preliminary report, Reproductive Biomedicine Online, 11, 294-299, 2005	Study does not provide data on outcomes of interest.
Kupesic,S., Kurjak,A., Predictors of IVF outcome by three-dimensional ultrasound, Human Reproduction, 17, 950-955, 2002	Study does not provide data on outcomes of interest.
Kwee,J., Schats,R., McDonnell,J., Themmen,A., de,Jong F., Lambalk,C., Evaluation of anti-Mullerian hormone as a test for the prediction of ovarian reserve, Fertility and Sterility, 90, 737-743, 2008	Study population is potential biased
Kyrou,D., Popovic-Todorovic,B., Fatemi,H.M., Bourgain,C., Haentjens,P., Van,Landuyt L., Devroey,P., Does the estradiol level on the day of human chorionic gonadotrophin administration have an impact on pregnancy rates in patients treated with rec-FSH/GnRH antagonist?, Human Reproduction, 24, 2902-2909, 2009	Tests of ovarian reserve on women undergoing stimulation.
la,CourFreieslebenN, Rosendahl,M., Johannsen,T.H., Lossl,K., Loft,A., Bangsboll,S., Friis-Hansen,L., Pinborg,A., Nyboe,AndersenA, Prospective investigation of serum anti-Mullerian hormone concentration in ovulatory intrauterine insemination patients: A preliminary study, Reproductive Biomedicine Online, #20, 582-587, 2010	Study provides insufficient ndata to calculate outcomes of interest.
La,MarcaA, Sighinolfi,G., Radi,D., Argento,C., Baraldi,E., Artenisio,A.C., Stabile,G., Volpe,A., Anti-Mullerian hormone (AMH) as a predictive marker in assisted reproductive technology (ART), Human Reproduction Update, 16, 113-130, 2010	Review
Lashen,H., Afnan,M., Sharif,K., A controlled comparison of ovarian response to controlled stimulation in first generation Asian women compared with white Caucasians undergoing in vitro fertilisation, British Journal of Obstetrics and Gynaecology, 106, 407-409, 1999	Study does not provide data on outcomes of interest.

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Lass,A., Silye,R., Abrams,D.C., Krausz,T., Hovatta,O., Margara,R., Winston,R.M., Follicular density in ovarian biopsy of infertile women: a novel method to assess ovarian reserve, Human Reproduction, 12, 1028-1031, 1997	Study does not provide data on outcomes of interest.
Lass,A., Skull,J., McVeigh,E., Margara,R., Winston,R.M.L., Measurement of ovarian volume by transvaginal sonography before ovulation induction with human menopausal gonadotrophin for in-vitro fertilization can predict poor response, Human Reproduction, 12, 294-297, 1997	Study provides no data on outcome sof interest.
Lee,F.K., Lai,T.H., Lin,T.K., Horng,S.G., Chen,S.C., Relationship of progesterone/estradiol ratio on day of hCG administration and pregnancy outcomes in high responders undergoing in vitro fertilization, Fertility and Sterility, 92, 1284-1289, 2009	Retrospective study
Lee,T.H., Liu,C.H., Huang,C.C., Wu,Y.L., Shih,Y.T., Ho,H.N., Yang,Y.S., Lee,M.S., Serum anti-Mullerian hormone and estradiol levels as predictors of ovarian hyperstimulation syndrome in assisted reproduction technology cycles, Human Reproduction, 23, 160-167, 2008	Required sensitivity and specificity data not reported
Lekamge,D.N., Lane,M., Gilchrist,R.B., Tremellen,K.P., Increased gonadotrophin stimulation does not improve IVF outcomes in patients with predicted poor ovarian reserve, Journal of Assisted Reproduction and Genetics, 25, 515-521, 2008	Study does not provide data on outcomes of interest.
Lobo,R.A., Gysler,M., March,C.M., Goebelsmann,U., Mishell,D.R.,Jr., Clinical and laboratory predictors of clomiphene response, Fertility and Sterility, 37, 168-174, 1982	Study does not provide data on outcomes of interest.
Lockwood,G., The diagnostic value of inhibin in infertility evaluation. [67 refs], Seminars in Reproductive Medicine, 22, 195-208, 2004	Review
Lorusso,F., Vicino,M., Lamanna,G., Trerotoli,P., Serio,G., Depalo,R., Performance of different ovarian reserve markers for predicting the numbers of oocytes retrieved and mature oocytes, Maturitas, 56, 429-435, 2007	Retrospective study.
Loverro,G., Nappi,L., Mei,L., Giacomoantonio,L., Carriero,C., Tartagni,M., Evaluation of functional ovarian reserve in 60 patients, Reproductive Biomedicine Online, 7, 200-204, 2003	Study does not provide data on outcomes of interest.
Lutchman,SinghK, Muttukrishna,S., Stein,R.C., McGarrigle,H.H., Patel,A., Parikh,B., Groome,N.P., Davies,M.C., Chatterjee,R., Predictors of ovarian reserve in young women with breast cancer, British Journal of Cancer, 96, 1808-1816, 2007	Study does not provide any data on outcome sof interest. Study examines predictors of ovarian reserve in young women with breast cancer.
Magarelli,P.C., Pearlstone,A.C., Buyalos,R.P., Discrimination between chronological and ovarian age in infertile women aged 35 years and older: predicting pregnancy using basal follicle stimulating hormone, age and number of ovulation induction/intra-uterine insemination cycles, Human Reproduction, 11, 1214-1219, 1996	Study does not provide data on outcomes of interest.
Majumder,K., Gelbaya,T.A., Laing,I., Nardo,L.G., The use of anti-Mullerian hormone and antral follicle count to predict the potential of oocytes and embryos, European Journal of Obstetrics, Gynecology, and Reproductive Biology, 150, 166-170, 2010	Study population is potentially biased

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Maseelall,P.B., Hernandez-Rey,A.E., Oh,C., Maagdenberg,T., McCulloh,D.H., McGovern,P.G., Antral follicle count is a significant predictor of livebirth in in vitro fertilization cycles, Fertility and Sterility, 91, 1595-1597, 2009	Correspondence
Meo,F., Ranieri,D.M., Khadum,I., Serhal,P., Ovarian response and in vitro fertilization outcome in patients with reduced ovarian reserve who were stimulated with recombinant follicle-stimulating hormone or human menopausal gonadotropin, Fertility and Sterility, 77, 630-632, 2002	Correspondence.
Merce,L.T., Gomez,B., Engels,V., Bau,S., Bajo,J.M., Intraobserver and interobserver reproducibility of ovarian volume, antral follicle count, and vascularity indices obtained with transvaginal 3-dimensional ultrasonography, power Doppler angiography, and the virtual organ computer-aided analysis imaging program, Journal of Ultrasound in Medicine, 24, 1279-1287, 2005	Study does not provide any data on outcomes of interest. Study examined intra- /inter-observer reproducibility of 3D ultrasound scan.
Miao,M.F., Huang,H.F., Dynamic measurements of serum inhibin B and estradiol: a predictive evaluation of ovarian response to gonadotrophin stimulation in the early stage of IVF treatment, Journal of Zhejiang University, Science. B. 10, 35-45, 2009	Study does not provide data on outcomes of interest.
Mikkelsen,A.L., Andersson,A.M., Skakkebaek,N.E., Lindenberg,S., Basal concentrations of oestradiol may predict the outcome of in-vitro maturation in regularly menstruating women, Human Reproduction, 16, 862-867, 2001	Study does not provide data on outcoems of interest.
Mirkin,S., Gimeno,T.G., Bovea,C., Stadtmauer,L., Gibbons,W.E., Oehninger,S., Factors associated with an optimal pregnancy outcome in an oocyte donation program, Journal of Assisted Reproduction and Genetics, 20, 400-408, 2003	Retrospective study.
Moawad,A., Elmawgood,H.A., Shaeer,M., Early follicular anti-mullerian hormone as a predictor of ovarian response during ICSI cycles, Middle East Fertility Society Journal, 15, 281-287, 2010	Does not report on diagnostic accuracy on specified outcomes.
Moos,J., Rezabek,K., Filova,V., Moosova,M., Pavelkova,J., Peknicova,J., Comparison of follicular fluid and serum levels of Inhibin A and Inhibin B with calculated indices used as predictive markers of Ovarian Hyperstimulation Syndrome in IVF patients, Reproductive Biology and Endocrinology, 7, 86-, 2009	Study does not report any data on outcomes of interest. Study examines predictors of OHSS
Mukherjee,T., Copperman,A.B., Lapinski,R., Sandler,B., Bustillo,M., Grunfeld,L., An elevated day three follicle-stimulating hormone:luteinizing hormone ratio (FSH:LH) in the presence of a normal day 3 FSH predicts a poor response to controlled ovarian hyperstimulation, Fertility and Sterility, 65, 588-593, 1996	Study does not examine a test on interest.
Mulders,A.G.M.G., Laven,J.S.E., Eijkemans,M.J.C., Hughes,E.G., Fauser,B.C.J.M., Patient predictors for outcome of gonadotrophin ovulation induction in women with normogonadotrophic anovulatory infertility: A meta-analysis, Human Reproduction Update, 9, 429-449, 2003	Review
Muttukrishna,S., McGarrigle,H., Wakim,R., Khadum,I., Ranieri,D.M., Serhal,P., Antral follicle count, anti-mullerian hormone and inhibin B: predictors of ovarian response in assisted reproductive technology?, BJOG: An International Journal of Obstetrics and Gynaecology, 112, 1384-1390, 2005	Study provided no data on outcomes of interest.

Bibliographic information	Reason for exclusion
Muttukrishna,S., Suharjono,H., McGarrigle,H., Sathanandan,M., Inhibin B and anti-Mullerian hormone: markers of ovarian response in IVF/ICSI patients?, BJOG: An International Journal of Obstetrics and Gynaecology, 111, 1248-1253, 2004	Samples for assay were taken form stimulated women.
Nahum,R., Shifren,J.L., Chang,Y., Leykin,L., Isaacson,K., Toth,T.L., Antral follicle assessment as a tool for predicting outcome in IVF--is it a better predictor than age and FSH?, Journal of Assisted Reproduction and Genetics, 18, 151-155, 2001	Study does not provide data on outcomes of interest.
Nakhuda,G.S., The role of mullerian inhibiting substance in female reproduction, Current Opinion in Obstetrics & Gynecology, 20, 257-264, 2008	Review
Nardo,L.G., Gelbaya,T.A., Wilkinson,H., Roberts,S.A., Yates,A., Pemberton,P., Laing,I., Circulating basal anti-Mullerian hormone levels as predictor of ovarian response in women undergoing ovarian stimulation for in vitro fertilization, Fertility and Sterility, 92, 1586-1593, 2009	Test of ovarian reserve on women undergoing stimulation.
Navot,D., Rosenwaks,Z., Margalioth,E.J., Prognostic assessment of female fecundity, Lancet, 2, 645-647, 1987	AUC data for CCCT not available
Nelson,S.M., Yates,R.W., Lyall,H., Jamieson,M., Traynor,I., Gaudoin,M., Mitchell,P., Ambrose,P., Fleming,R., Anti-Mullerian hormone-based approach to controlled ovarian stimulation for assisted conception, Human Reproduction, 24, 867-875, 2009	Unclear of AMH levels were assessed before or after stimulation.
Ng,E.H., Tang,O.S., Ho,P.C., The significance of the number of antral follicles prior to stimulation in predicting ovarian responses in an IVF programme, Human Reproduction, 15, 1937-1942, 2000	Required sensitivity and specificity data not reported
Ng,E.H.Y., Tang,O.S., Ho,P.C., The significance of the number of antral follicles prior to stimulation in predicting ovarian responses in an IVF programme, Human Reproduction, 15, -1942, 2000	Study does not provide data on outcomes of interest.
Noci,I., Biagiotti,R., Maggi,M., Ricci,F., Cinotti,A., Scarselli,G., Low day 3 luteinizing hormone values are predictive of reduced response to ovarian stimulation, Human Reproduction, 13, 531-534, 1998	Retrospective study
Noci,I., Maggi,M., Biagiotti,R., D'Agata,A., Criscuoli,L., Marchionni,M., Serum CA-125 values on the day of oocyte retrieval are not predictive of subsequent pregnancy with in-vitro fertilization, Human Reproduction, 14, 1773-1776, 1999	Study did not use tests of interest: examined serum CA-125.
Oghoetuoma,J., Polson,D.W., Troup,S.A., Lieberman,B.A., Are follicle stimulating hormone measurements predictive of ovarian response to hyperstimulation with human menopausal gonadotrophin?, Journal of Obstetrics and Gynaecology, 17, 188-191, 1997	Retrospective study
Ohl,J., Partisani,M., Wittemer,C., Schmitt,M.P., Cranz,C., Stoll-Keller,F., Rongieres,C., Bettahar-Lebugle,K., Lang,J.M., Nisand,I., Assisted reproduction techniques for HIV serodiscordant couples: 18 months of experience, Human Reproduction, 18, 1244-1249, 2003	Retrospective study.
Opsahl,M.S., Blauer,K.L., Black,S.H., Lincoln,S.R., Thorsell,L., Sherins,R.J., The number of embryos available for transfer predicts successful pregnancy outcome in women over 39 years with normal ovarian hormonal reserve testing, Journal of Assisted Reproduction and Genetics, 18, 551-556, 2001	Retrospective study.

Bibliographic information	Reason for exclusion
Ozdegirmenci,O., Dilbaz,S., Cinar,O., Aydin,S., Beydilli,G., Cakir,L., Guven,E.S., Akyol,M., Haberal,A., Can serum oestradiol be a predictor of quality of oocytes and embryos, maturation of oocytes and pregnancy rate in ICSI cycles?, Gynecological Endocrinology, 27, 279-285, 2011	Study on women with normal ovarian reserve and no attempt to examine cutoffs for response.
Pal,L., Bevilacqua,K., Santoro,N.F., Chronic psychosocial stressors are detrimental to ovarian reserve: a study of infertile women, Journal of Psychosomatic Obstetrics and Gynecology, 31, 130-139, 2010	Study does not provide data on outcomes of interest.
Palomba,S., Falbo,A., Orio,F.,Jr., Tolino,A., Zullo,F., Efficacy predictors for metformin and clomiphene citrate treatment in anovulatory infertile patients with polycystic ovary syndrome, Fertility and Sterility, 91, 2557-2567, 2009	Study does not provide data on outcomes of interest.
Papanikolaou,E.G., Pozzobon,C., Kolibianakis,E.M., Camus,M., Tournaye,H., Fatemi,H.M., Van,Steirteghem A., Devroey,P., Incidence and prediction of ovarian hyperstimulation syndrome in women undergoing gonadotropin-releasing hormone antagonist in vitro fertilization cycles, Fertility and Sterility, 85, 112-120, 2006	Study does not provide any data on outcomes of interest. Study examines incidence and predictiors of OHSS.
Pellicer,A., Ardiles,G., Neuspiller,F., Remohi,J., Simon,C., Bonilla-Musoles,F., Evaluation of the ovarian reserve in young low responders with normal basal levels of follicle-stimulating hormone using three-dimensional ultrasonography, Fertility and Sterility, 70, 671-675, 1998	Study does not provide data on outcomes of interest.
Pena,J.E., Chang,P.L., Thornton,M.H., Sauer,M.V., Serum estradiol levels after 4 days of ovarian hyperstimulation in oocyte donors are predictive of embryo quality and clinical outcomes, Gynecologic and Obstetric Investigation, 54, 207-212, 2002	Retrospective study.
Penarrubia,J., Balasch,J., Fabregues,F., Carmona,F., Casamitjana,R., Moreno,V., Calafell,J.M., Vanrell,J.A., Day 5 inhibin B serum concentrations as predictors of assisted reproductive technology outcome in cycles stimulated with gonadotrophin-releasing hormone agonist-gonadotrophin treatment, Human Reproduction, 15, 1499-1504, 2000	Retrospective study
Penarrubia,J., Fabregues,F., Creus,M., Manau,D., Casamitjana,R., Guimera,M., Carmona,F., Vanrell,J.A., Balasch,J., LH serum levels during ovarian stimulation as predictors of ovarian response and assisted reproduction outcome in down-regulated women stimulated with recombinant FSH, Human Reproduction, 18, 2689-2697, 2003	Study did not use tests of interest: examined LH
Penarrubia,J., Fabregues,F., Manau,D., Creus,M., Casals,G., Casamitjana,R., Carmona,F., Vanrell,J.A., Balasch,J., Basal and stimulation day 5 anti-Mullerian hormone serum concentrations as predictors of ovarian response and pregnancy in assisted reproductive technology cycles stimulated with gonadotropin-releasing hormone agonist--gonadotropin treatment, Human Reproduction, 20, 915-922, 2005	Retrospective study.
Phophong,P., Ranieri,D.M., Khadum,I., Meo,F., Serhal,P., Basal 17beta-estradiol did not correlate with ovarian response and in vitro fertilization treatment outcome, Fertility and Sterility, 74, 1133-1136, 2000	Retrospective study.

Bibliographic information	Reason for exclusion
Pittrof,R.U., Shaker,A., Dean,N., Bekir,J.S., Campbell,S., Tan,S.L., Success of intrauterine insemination using cryopreserved donor sperm is related to the age of the woman and the number of preovulatory follicles, Journal of Assisted Reproduction and Genetics, 13, 310-314, 1996	Study does not provide data on outcomes of interest.
Popovic-Todorovic,B., Loft,A., Bredkjaeer,H.E., Bangsboll,S., Nielsen,I.K., Andersen,A.N., A prospective randomized clinical trial comparing an individual dose of recombinant FSH based on predictive factors versus a 'standard' dose of 150 IU/day in 'standard' patients undergoing IVF/ICSI treatment, Human Reproduction, 18, 2275-2282, 2003	Study does not provide data on outcomes of interest.
Riggs,R.M., Duran,E.H., Baker,M.W., Kimble,T.D., Hobeika,E., Yin,L., Matos-Bodden,L., Leader,B., Stadtmauer,L., Assessment of ovarian reserve with anti-Mullerian hormone: a comparison of the predictive value of anti-Mullerian hormone, follicle-stimulating hormone, inhibin B, and age, American Journal of Obstetrics and Gynecology, 199, 202-208, 2008	Study provides insufficient data to calculate outcomes of interest.
Rosen,M.P., Johnstone,E., ddauan-Andersen,C., Cedars,M.I., A lower antral follicle count is associated with infertility, Fertility and Sterility, 95, -1954e1, 2011	Figures do not allow for calculation of AUC
Rosen,M.P., Zamah,A.M., Shen,S., Dobson,A.T., McCulloch,C.E., Rinaudo,P.F., Lamb,J.D., Cedars,M.I., The effect of follicular fluid hormones on oocyte recovery after ovarian stimulation: FSH level predicts oocyte recovery, Reproductive Biology and Endocrinology, 7, 35-, 2009	Study does not provide data on outcomes of interest.
Scott,R.T., Leonardi,M.R., Hofmann,G.E., Illions,E.H., Neal,G.S., Navot,D., A prospective evaluation of clomiphene citrate challenge test screening of the general infertility population, Obstetrics and Gynecology,Obstet.Gynecol., 82, 539-544, 1993	AUC data not reported
Seibel,M.M., Kearnan,M., Kiessling,A., Parameters that predict success for natural cycle in vitro fertilization-embryo transfer, Fertility and Sterility, 63, 1251-1254, 1995	Study provides insufficient data on outcomes of interest.
Seibel,M.M., Oskowitz,S., Kamrava,M., Taymor,M.L., Bromocriptine response in normoprolactinemic patients with polycystic ovary disease: A preliminary report, Obstetrics and Gynecology, 64, 213-219, 1984	Study does not provide data on outcomes of interest.
Seifer,D.B., Charland,C., Berlinsky,D., Penzias,A.S., Haning,R.V.,Jr., Naftolin,F., Barker,B.E., Proliferative index of human luteinized granulosa cells varies as a function of ovarian reserve, American Journal of Obstetrics and Gynecology, 169, 1531-1535, 1993	Study does not provide any data on outcomes of interest. Study examinesthe proliferative index of human luteinized granulosa cells as a predictor of ovarian reserve.
Seifer,D.B., MacLaughlin,D.T., Christian,B.P., Feng,B., Shelden,R.M., Early follicular serum mullerian-inhibiting substance levels are associated with ovarian response during assisted reproductive technology cycles, Fertility and Sterility, 77, 468-471, 2002	Study does not provide data on outcomes of interest.
Senoz,S., Gulekli,B., Turhan,N.O., Ozaksit,G., Odabasi,A.R., Oral,H., Ozcan,U., Gokmen,O., Do the suppression criteria in GnRH-a cycles predict in vitro fertilization outcome?, Gynecological Endocrinology, 9, 91-96, 1995	Study does not provide data on outcomes of interest.

Bibliographic information	Reason for exclusion
Sharara,F.I., Beatse,S.N., Leonardi,M.R., Navot,D., Scott,R.T.,Jr., Cigarette smoking accelerates the development of diminished ovarian reserve as evidenced by the clomiphene citrate challenge test, Fertility and Sterility, 62, 257-262, 1994	Retrospective study.
Sharara,F.I., McClamrock,H.D., Ratio of oestradiol concentration on the day of human chorionic gonadotrophin administration to mid-luteal oestradiol concentration is predictive of in-vitro fertilization outcome, Human Reproduction, 14, 2777-2782, 1999	Retrospective study.
Shrim,A., Elizur,S.E., Seidman,D.S., Rabinovici,J., Wiser,A., Dor,J., Elevated day 3 FSH/LH ratio due to low LH concentrations predicts reduced ovarian response, Reproductive Biomedicine Online, 12, 418-422, 2006	Retrospective study. Study does not provide data on outcomes of interest.
Singer,T., Barad,D.H., Weghofer,A., Gleicher,N., Correlation of antimullerian hormone and baseline follicle-stimulating hormone levels, Fertility and Sterility, 91, 2616-2619, 2009	Retrospective study. Study does not provide data on outcomes of interest.
Smotrich,D.B., Widra,E.A., Gindoff,P.R., Levy,M.J., Hall,J.L., Stillman,R.J., Prognostic value of day 3 estradiol on in vitro fertilization outcome, Fertility and Sterility, 64, 1136-1140, 1995	Study does not provide data on outcomes of interest.
Srouji,S.S., Mark,A., Levine,Z., Betensky,R.A., Hornstein,M.D., Ginsburg,E.S., Predicting in vitro fertilization live birth using stimulation day 6 estradiol, age, and follicle-stimulating hormone, Fertility and Sterility, 84, 795-797, 2005	Correspondence
Steiner,A.Z., Herring,A.H., Kesner,J.S., Meadows,J.W., Stanczyk,F.Z., Hoberman,S., Baird,D.D., Antimullerian hormone as a predictor of natural fecundability in women aged 30-42 years, Obstetrics and Gynecology, 117, 798-804, 2011	Study does not report diagnostic accuracy of tests.
Stern,J.E., Goldman,M.B., Hatasaka,H., MacKenzie,T.A., Surrey,E.S., Racowsky,C., Society for Assisted Reproductive Technology Writing Group., Optimizing the number of cleavage stage embryos to transfer on day 3 in women 38 years of age and older: a Society for Assisted Reproductive Technology database study, Fertility and Sterility, 91, 767-776, 2009	Study does not provide data on outcomes of interest. Study to determine the optimal number of embryo transfer
Tanbo,T., Dale,P.O., Lunde,O., Norman,N., Abyholm,T., Prediction of response to controlled ovarian hyperstimulation: a comparison of basal and clomiphene citrate-stimulated follicle-stimulating hormone levels, Fertility and Sterility, 57, 819-824, 1992	AUC data not reported.
Tehraninejad,E.S., Amirchaghmaghi,E., Owj,M., Rashidi,B.H., Jalilian,N., Sadeghi,M., The role of inhibin B in prediction of in vitro fertilization or intracytoplasmic sperm injection cycles' outcome, Saudi Medical Journal, 28, 1028-1033, 2007	Women were already undergoing stimulation when tested.
Tinkanen,H., Blauer,M., Laippala,P., Tuohimaa,P., Kujansuu,E., Prognostic factors in controlled ovarian hyperstimulation, Fertility and Sterility, 72, 932-936, 1999	Retrospective study. Study does not provide data on outcomes of interest.
Traub,M.L., Van,Arsdale A., Pal,L., Jindal,S., Santoro,N., Endometrial thickness, Caucasian ethnicity, and age predict clinical pregnancy following fresh blastocyst embryo transfer: a retrospective cohort, Reproductive Biology and Endocrinology, 7, 33-, 2009	Study does not provide data on outcomes of interest.

Bibliographic information	Reason for exclusion
Tsafrir,A., Simon,A., Revel,A., Reubinoff,B., Lewin,A., Laufer,N., Retrospective analysis of 1217 IVF cycles in women aged 40 years and older, Reproductive Biomedicine Online, 14, 348-355, 2007	Retrospective study.
Urbancsek,J., Fedorcsak,P., Klinga,K., Devenyi,N., Papp,Z., Rabe,T., Strowitzki,T., Impact of obesity and leptin levels on the secretion of estradiol, inhibin A and inhibin B during ovarian stimulation with gonadotropins, Gynecological Endocrinology, 16, 285-292, 2002	Study does not provide data on outcomes of interest.
Van der Meer,M., Hompes,P.G., de Boer,J.A., Schats,R., Schoemaker,J., Cohort size rather than follicle-stimulating hormone threshold level determines ovarian sensitivity in polycystic ovary syndrome, Journal of Clinical Endocrinology and Metabolism, 83, 423-426, 1998	Study does not provide data on outcomes of interest.
van,Disseldorp J., Eijkemans,M.J., Klinkert,E.R., te Velde,E.R., Fauser,B.C., Broekmans,F.J., Cumulative live birth rates following IVF in 41- to 43-year-old women presenting with favourable ovarian reserve characteristics, Reproductive Biomedicine Online, 14, 455-463, 2007	Retrospective study. Study does not provide data on outcomes of interest.
van,RooijI, Broekmans,F.J.M., Hunault,C.C., Scheffer,G.J., Eijkemans,M.J.C., de,JongF, Themmen,A.P.N., te,VeldeE, Use of ovarian reserve tests for the prediction of ongoing pregnancy in couples with unexplained or mild male infertility, Reproductive Biomedicine Online, 12, 182-190, 2006	Study does not provide data on outcomes of interest.
van,WeertJ, Repping,S., Van,DerSteegJ, Steures,P., van,derVeenF, Mol,B.W., A prediction model for ongoing pregnancy after in vitro fertilization in couples with male subfertility, Journal of Reproductive Medicine for the Obstetrician and Gynecologist, 53, 250-256, 2008	Study does not provide any data on outcomes of interest. Study examines predictors of pregnancy in male sub-fertility.
Verberg,M.F.G., Eijkemans,M.J.C., Macklon,N.S., Heijnen,E.M.E.W., Fauser,B.C.J.M., Broekmans,F.J., Predictors of ongoing pregnancy after single-embryo transfer following mild ovarian stimulation for IVF, Fertility and Sterility, 89, 1159-1165, 2008	Study does not provide any data on outcomes of interest. Study examines predictive modelling for pregnancy.
Verit,F.F., Erel,O., Kocyigit,A., Association of increased total antioxidant capacity and anovulation in nonobese infertile patients with clomiphene citrate-resistant polycystic ovary syndrome, Fertility and Sterility, 88, 418-424, 2007	Study does not provide data on outcomes of interest.
Vitale,A., Lancuba,S., Ballerini,M.G., Groome,N., Campo,S., Tesone,M., Inhibin A and B levels in follicular fluid of patients undergoing assisted reproduction: Correlation with hormone levels and pregnancy, Fertility and Sterility, 75, 221-222, 2001	Correspondence
Vladimirov,I.K., Tacheva,D.M., Kalinov,K.B., Ivanova,A.V., Blagoeva,V.D., Prognostic value of some ovarian reserve tests in poor responders, Archives of Gynecology and Obstetrics, 272, 74-79, 2005	Study population is potentially biased
Vladimirov,I.K., Tacheva,D.M., Kalinov,K.B., Mean ovarian diameter (MOD) as a predictor of poor ovarian response, Journal of Assisted Reproduction and Genetics, 21, 73-77, 2004	Study does not use a test on interest: examines mean ovarian diameter.
von,Wolff M., Thaler,C.J., Frambach,T., Zeeb,C., Lawrenz,B., Popovici,R.M., Strowitzki,T., Ovarian stimulation to cryopreserve fertilized oocytes in cancer patients can be started in the luteal phase, Fertility and Sterility, 92, 1360-1365, 2009	Study provides insufficient data on outcomes of interest.

Bibliographic information	Reason for exclusion
Warne,D.W., Tredway,D., Schertz,J.C., Schnieper-Samec,S., Alam,V., Eshkol,A., Midluteal serum progesterone levels and pregnancy following ovulation induction with human follicle-stimulating hormone: results of a combined-data analysis, Journal of Reproductive Medicine, 56, 31-38, 2011	Does not address study question
Weghofer,A., Margreiter,M., Fauster,Y., Schaetz,T., Brandstetter,A., Boehm,D., Feichtinger,W., Age-specific FSH levels as a tool for appropriate patient counselling in assisted reproduction, Human Reproduction, 20, 2448-2452, 2005	Retrospective study. Study does not provide data on outcomes of interest.
Woldringh,G.H., Frunt,M.H., Kremer,J.A., Spaanderman,M.E., Decreased ovarian reserve relates to pre-eclampsia in IVF/ICSI pregnancies, Human Reproduction, 21, 2948-2954, 2006	Study does not provide data on outcomes of interest: examines ovarian eserve and pre-eclampsia.
Wu,C.H., Chen,Y.C., Wu,H.H., Yang,J.G., Chang,Y.J., Tsai,H.D., Serum anti-Mullerian hormone predicts ovarian response and cycle outcome in IVF patients, Journal of Assisted Reproduction and Genetics, 26, 383-389, 2009	Study does not provide data on outcomes of interest.
Wunder,D.M., Guibourdenche,J., Birkhauser,M.H., Bersinger,N.A., Anti-Mullerian hormone and inhibin B as predictors of pregnancy after treatment by in vitro fertilization/intracytoplasmic sperm injection, Fertility and Sterility, 90, 2203-2210, 2008	Study does not provide data on outcomes of interest.
Yang,J.H., Chen,H.F., Lien,Y.R., Chen,S.U., Ho,H.N., Yang,Y.S., Elevated E2: oocyte ratio in women undergoing IVF and tubal ET. Correlation with a decrease in the implantation rate, Journal of Reproductive Medicine, 46, 434-438, 2001	Retrospective study. Study does not provide data on outcomes of interest.
Yding,AndersenC, Bungum,L., Nyboe,AndersenA, Humaidan,P., Preovulatory progesterone concentration associates significantly to follicle number and LH concentration but not to pregnancy rate, Reproductive Biomedicine Online, 23, 187-195, 2011	Does not present diagnostic accuracy data
Yong,P.Y.K., Baird,D.T., JooThong,K., McNeilly,A.S., Anderson,R.A., Prospective analysis of the relationships between the ovarian follicle cohort and basal FSH concentration, the inhibin response to exogenous FSH and ovarian follicle number at different stages of the normal menstrual cycle and after pituitary down-regulation, Human Reproduction, 18, 35-44, 2003	Study provides no data on outcomes of interest.
Younis,J.S., Haddad,S., Matilsky,M., Radin,O., Ben-Ami,M., Undetectable basal ovarian stromal blood flow in infertile women is related to low ovarian reserve, Gynecological Endocrinology, 23, 284-289, 2007	Study does not provide sufficient data to calculate outcomes of interest.
Younis,J.S., Matilsky,M., Radin,O., Ben-Ami,M., Increased progesterone/estradiol ratio in the late follicular phase could be related to low ovarian reserve in in vitro fertilization-embryo transfer cycles with a long gonadotropin-releasing hormone agonist, Fertility and Sterility, 76, 294-299, 2001	Study does not provide data on outcomes of interest.
Zitzmann,M., Nordhoff,V., von,Schonfeld,V, Nordsiek-Mengede,A., Kliesch,S., Schuring,A.N., Luetjens,C.M., Kamischke,A., Cooper,T., Simoni,M., Nieschlag,E., Elevated follicle-stimulating hormone levels and the chances for azoospermic men to become fathers after retrieval of elongated spermatids from cryopreserved testicular tissue, Fertility and Sterility, 86, 339-347, 2006	Study of male factor infertility only.

Sperm washing and viral transmission

Table G.2 What is the effectiveness and safety of sperm washing to reduce the risk of viral transmission?

Bibliographic information	Reason for exclusion
Barreto,MeloM, Meseguer,M., Bellver,J., Remohi,J., Pellicer,A., Garrido,N., Human immunodeficiency type-1 virus (HIV-1) infection in serodiscordant couples (SDCs) does not have an impact on embryo quality or intracytoplasmic sperm injection (ICSI) outcome, Fertility and Sterility, 89, 141-150, 2008	Does not report on outcomes that are relevant to the review question. Seroconversions and post-pregnancy outcomes were not reported
Bujan,L., Daudin,M., Moinard,N., Plante,P., Parinaud,J., Pasquier,C., Azoospermic HIV-1 infected patients wishing to have children: Proposed strategy to reduce HIV-1 transmission risk during sperm retrieval and intracytoplasmic sperm injection: Case report, Human Reproduction, 22, 2377-2381, 2007	Case report. Studies with more participants are available
Frodsham,L.C., Smith,J.R., Gilling-Smith,C., Assessment of welfare of the child in HIV positive couples, Human Reproduction, 19, 2420-2423, 2004	Does not look at couples post treatment, only their suitability for treatment. Included couples where men were HIV negative and women were HIV positive (ie sperm washing not relevant)
Garrido,N., Gil-Salom,M., Martinez-Jabaloyas,J.M., Meseguer,M., First report of the absence of viral load in testicular sperm samples obtained from men with hepatitis C and HIV after washing and their subsequent use, Fertility and Sterility, 92, 1012-1015, 2009	This is a case series of only three participants. Studies with more participants are available
Kato,S., Hanabusa,H., Kaneko,S., Takakuwa,K., Suzuki,M., Kuji,N., Jinno,M., Tanaka,R., Kojima,K., Iwashita,M., Yoshimura,Y., Tanaka,K., Complete removal of HIV-1 RNA and proviral DNA from semen by the swim-up method: assisted reproduction technique using spermatozoa free from HIV-1, AIDS, 20, 967-973, 2006	The study does not report the number of cycles started
Nicopoullos,J.D., Almeida,P.A., Ramsay,J.W., Gilling-Smith,C., The effect of human immunodeficiency virus on sperm parameters and the outcome of intrauterine insemination following sperm washing, Human Reproduction, 19, 2289-2297, 2004	Does not report outcomes of interest. There is no data on pregnancy outcomes
Nicopoullos,J.D., Almeida,P., Vourliotis,M., Goulding,R., Gilling-Smith,C., A decade of sperm washing: clinical correlates of successful insemination outcome, Human Reproduction, 25, 1869-1876, 2010	Same study population as Nicopoullos (2010), which is included in this review and compares the data in a way that is more relevant to the review question
Nicopoullos,J.D.M., Almeida,P., Vourliotis,M., Goulding,R., Gilling-Smith,C., A decade of sperm washing: Clinical correlates of successful insemination outcome, Human Reproduction, 25, 1869-1876, 2010	Does not address review question
Nicopoullos,J.D., Frodsham,L.C., Ramsay,J.W., Almeida,P.A., Rozis,G., Gilling-Smith,C., Synchronous sperm retrieval and sperm washing in an intracytoplasmic sperm injection cycle in an azoospermic man who was positive for human immunodeficiency virus, Fertility and Sterility, 81, 670-674, 2004	Case report. Studies with more participants are available

Bibliographic information	Reason for exclusion
Sunderam,S., Hollander,L., Macaluso,M., Vucetich,A., Jamieson,D.J., Osimo,F., Duerr,A., Semprini,A.E., Safe Conception for HIV Discordant Couples through Sperm-Washing: Experience and Perceptions of Patients in Milan, Italy, Reproductive Health Matters, 16, 211-219, 2008	Patient satisfaction was reported for ART as a whole and not specifically for sperm washing

Table G.3 Transmission with low viral load studies and PrEP studies

Study	Reason for exclusion
Apondi,R., Bunnell,R., Ekwaru,J.P., Moore,D., Bechange,S., Khana,K., King,R., Campbell,J., Tappero,J., Mermin,J., Sexual behavior and HIV transmission risk of Ugandan adults taking antiretroviral therapy: 3 year follow-up, AIDS, 25, 1317-1327, 2011	Seroconversion rates were not specifically reported for couples with male index cases
Attia,S., Egger,M., Muller,M., Zwahlen,M., Low,N., Sexual transmission of HIV according to viral load and antiretroviral therapy: systematic review and meta-analysis. [39 refs], AIDS, 23, 1397-1404, 2009	Relevant studies were included
Barreiro,P., Castilla,J.A., Labarga,P., Soriano,V., Is natural conception a valid option for HIV-serodiscordant couples?, Human Reproduction, 22, 2353-2358, 2007	Review
Barreiro,P., Duerr,A., Beckerman,K., Soriano,V., Reproductive options for HIV-serodiscordant couples. [82 refs], AIDS Reviews, 8, 158-170, 2006	Review
Gray,R.H., Wawer,M.J., Brookmeyer,R., Sewankambo,N.K., Serwadda,D., Wabwire-Mangen,F., Lutalo,T., Li,X., VanCott,T., Quinn,T.C., Probability of HIV-1 transmission per coital act in monogamous, heterosexual, HIV-1-discordant couples in Rakai, Uganda, Lancet, 357, 1149-1153, 2001	Seroconversion rates were not reported for specific viral loads or use of HAART in male index cases.
Huong,D.T., Bannister,W., Phong,P.T., Kirk,O., Peters,L., Factors associated with HIV-1 virological failure in an outpatient clinic for HIV-infected people in Haiphong, Vietnam, International Journal of STD and AIDS, 22, 659-664, 2011	The study does not involve serodiscordant couples
Kalichman,S.C., Rompa,D., Luke,W., Austin,J., HIV transmission risk behaviours among HIV-positive persons in serodiscordant relationships, International Journal of STD and AIDS, 13, 677-682, 2002	Results were derived from a mathematical model
Kebba,A., Kaleebu,P., Serwanga,J., Rowland,S., Yirrell,D., Downing,R., Gilmour,J., Imami,N., Gotch,F., Whitworth,J., HIV Type 1 Antigen-Responsive $CD4^+$ T-Lymphocytes in Exposed Yet HIV Type 1 Seronegative Ugandans, AIDS Research and Human Retroviruses, 20, 67-75, 2004	Non-relevant outcome
Lampe,M.A., Smith,D.K., Anderson,G.J., Edwards,A.E., Nesheim,S.R., Achieving safe conception in HIV-discordant couples: the potential role of oral preexposure prophylaxis (PrEP) in the United States, American Journal of Obstetrics and Gynecology, 204, 488-488, 2011	Report
Mandelbrot,L., Heard,I., Henrion-Gant,E., Henrion,R., Natural conception in HIV-negative women with HIV-infected partners, The Lancet, 349, 850-851, 1997	Non-comparative study design

Study	Reason for exclusion
Marks,G., Crepaz,N., Janssen,R.S., Estimating sexual transmission of HIV from persons aware and unaware that they are infected with the virus in the USA, AIDS, 20, 1447-1450, 2006	Results derived from a mathematical model
Merino,A., Malhotra,R., Morton,M., Mulenga,J., Allen,S., Hunter,E., Tang,J., Kaslow,R.A., Impact of a functional KIR2DS4 allele on heterosexual HIV-1 transmission among discordant Zambian couples, Journal of Infectious Diseases, 203, 487-495, 2011	Seroconversion rates in couples with male index cases were not specifically reported for different viral loads
Nisbet,S.M., Reeve,A.M., Ellis-Pegler,R.B., Woodhouse,A.F., Ingram,R.J., Roberts,S.A., McAllister,S.M., Thomas,M.G., Good outcome in HIV-infected refugees after resettlement in New Zealand: population study, Internal Medicine Journal, 37, 290-294, 2007	Study population is not relevant
Okwundu,Charles I., Okoromah,Christy AN, Antiretroviral pre-exposure prophylaxis (PrEP) for preventing HIV in high-risk individuals, Cochrane Database of Systematic Reviews, -, 2009	Relevant study from the review has been included
Pedraza,M.A., Del,RomeroJ, Roldan,F., Garcia,S., Ayerbe,M.C., Noriega,A.R., Alcami,J., Heterosexual transmission of HIV-1 is associated with high plasma viral load levels and a positive viral isolation in the infected partner, Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology, 21, 120-125, 1999	Non-comparative study design
Pirrone,V., Thakkar,N., Jacobson,J.M., Wigdahl,B., Krebs,F.C., Combinatorial approaches to the prevention and treatment of HIV-1 infection, Antimicrobial Agents and Chemotherapy, 55, 1831-1842, 2011	Review
Tamburrini,E., Ravizza,M., Floridia,M., Tibaldi,C., Alberico,S., Anzidei,G., Maccabruni,A., Meloni,A., Antoni,A.D., Mori,F., Dalzero,S., Conservan,V., Pinnetti,C., Ferrazzi,E., Italian Group on Surveillance on Antiretroviral Treatment in Pregnancy., HIV RNA viral load and CD4+ T-cell counts in HIV-infected pregnant women with and without treatment discontinuation in early pregnancy, Antiviral Therapy, 13, 519-527, 2008	Non-relevant study population
Vandermaelen,A., Englert,Y., Human immunodeficiency virus serodiscordant couples on highly active antiretroviral therapies with undetectable viral load: conception by unprotected sexual intercourse or by assisted reproduction techniques?, Human Reproduction, 25, 374-379, 2010	Review
Wandera,B., Kamya,M.R., Castelnuovo,B., Kiragga,A., Kambugu,A., Wanyama,J.N., Easterbrook,P., Sethi,A.K., Sexual behaviors over a 3-year period among individuals with advanced HIV/AIDS receiving antiretroviral therapy in an urban HIV clinic in Kampala, Uganda, Journal of Acquired Immune Deficiency Syndromes: JAIDS, 57, 62-68, 2011	Non-relevant outcome
Wawer,M.J., Gray,R.H., Sewankambo,N.K., Serwadda,D., Li,X., Laeyendecker,O., Kiwanuka,N., Kigozi,G., Kiddugavu,M., Lutalo,T., Nalugoda,F., Wabwire-Mangen,F., Meehan,M.P., Quinn,T.C., Rates of HIV-1 transmission per coital act, by stage of HIV-1 infection, in Rakai, Uganda, Journal of Infectious Diseases, 191, 1403-1409, 2005	Seroconversion rates were not specifically reported for couples with male index cases

Chapter 8. Ovulation Disorders

Group I WHO women

Table G.4 What is the effectiveness and safety of ovulation induction strategies in women with WHO Group I ovulation disorders?

Bibliographic information	Reason for exclusion
Abdrabbo,M.S., Khalil,M.H., Elsedeek,M.S.E., Elagawany,A., The use of clomiphene citrates for ovulation induction in women with functional ovarian cysts, Middle East Fertility Society Journal, 16, 200-203, 2011	Not a population of interest
Balen,A.H., Braat,D.D., West,C., Patel,A., Jacobs,H.S., Cumulative conception and live birth rates after the treatment of anovulatory infertility: safety and efficacy of ovulation induction in 200 patients, Hum Reprod, 9, 1563-1570, 1994	Retrospective cohort
Bass,S., Pearce,G., Young,N., Seeman,E., Bone mass during growth: the effects of exercise. Exercise and mineral accrual, Acta Universitatis Carolinae - Medica, 40, 3-6, 1994	Commentary
Braat,D.D., Ayalon,D., Blunt,S.M., Bogchelman,D., Coelingh Bennink,H.J., Handelsman,D.J., Heineman,M.J., Lappohn,R.E., Lorijn,R.H., Rolland,R., Pregnancy outcome in luteinizing hormone-releasing hormone induced cycles: a multicentre study, Gynecological Endocrinology, 3, 35-44, 1989	Retrospective study
Braat,D.D., Schoemaker,J., Endocrinology of gonadotropin-releasing hormone induced cycles in hypothalamic amenorrhea: the role of the pulse dose, Fertility and Sterility, 56, 1054-1059, 1991	Relevant outcomes were not reported. No control group was included
Burgus S, Spanish Collaborative Group on Female Hypogonadotrophic Hypogonadism., The effectiveness and safety of recombinant human LH to support follicular development induced by recombinant human FSH in WHO group I anovulation: evidence from a multicentre study in Spain, Human Reproduction, 16, 2525-2532, 2001	Prospective study, not a comparative study
Centre for Reviews and Dissemination., GnRH agonist for triggering final oocyte maturation in the GnRH antagonist ovarian hyperstimulation protocol: a systematic review and meta-analysis (Provisional abstract), Database of Abstracts of Reviews of Effects, -, 2011	Structured abstract full study not yet published
Centre for Reviews and Dissemination., Premature ovarian failure: a systematic review on therapeutic interventions to restore ovarian function and achieve pregnancy (Structured abstract), Database of Abstracts of Reviews of Effects, -, 2011	Review of interventions for a different population group than the one this question addresses
Centre for Reviews and Dissemination., Recombinant versus urinary gonadotrophins for triggering ovulation in assisted conception (Brief record), Database of Abstracts of Reviews of Effects, -, 2011	Brief record based on a Cochrane Protocol or Review
Cotreatment with growth hormone and gonadotropin for ovulation induction in hypogonadotropic patients: a prospective, randomized, placebo-controlled, dose-response study. European and Australian Multicenter Study, Fertility and Sterility, 64, 917-923, 1995	Not a relevant intervention
D'Angelo,D.V., Whitehead,N., Helms,K., Barfield,W., Ahluwalia,I.B., Birth outcomes of intended pregnancies among women who used assisted reproductive technology, ovulation stimulation, or no treatment, Fertility and Sterility, 96, 314-320, 2011	Compares women who received ART, ovulation induction medication, and no treatment

Bibliographic information	Reason for exclusion
Feigenbaum,S.L., Miller,P., Kaufmann,R., Elkind-Hirsch,K., Fein,S.H., Marshall,D.C., A new highly purified human-derived FSH, Bravelle, is as effective and well tolerated as recombinant follitropin beta in ovulation induction in infertile women with ovulatory dysfunction, Today's Therapeutic Trends, 19, 297-313, 2001	Not a comparison of interest
Filicori,M., Flamigni,C., Dellai,P., Cognigni,G., Michelacci,L., Arnone,R., Sambataro,M., Falbo,A., Treatment of anovulation with pulsatile gonadotropin-releasing hormone: Prognostic factors and clinical results in 600 cycles, Journal of Clinical Endocrinology and Metabolism, 79, 1215-1220, 1994	Not a comparative study. Some patients received an intervention other than treatment of anovulation
Fluker,M.R., Urman,B., Mackinnon,M., Barrow,S.R., Pride,S.M., Yuen,B.H., Exogenous gonadotropin therapy in world health organization groups I and II ovulatory disorders, Obstetrics and Gynecology, 83, 189-196, 1994	Retrospective review
Fox,R., Ekeroma,A., Wardle,P., Ovarian response to purified FSH in infertile women with long-standing hypogonadotrophic hypogonadism, Aust N Z J Obstet Gynaecol, 37, 92-94, 1997	Cross-over trial where data for each arm could not be separated
George,K., Nair,R., Tharyan,P., Ovulation triggers in anovulatory women undergoing ovulation induction, Cochrane Database of Systematic Reviews, #2008. Article Number, -, 2008	Does not report on outcomes of interest
Jaramillo,C.J., Charro-Salgado,A., Infante,V., del Campo,G.L., Botella,Llusi, Coy,D.H., Schally,A.V., Clinical studies with d-Trp 6-luteinizing hormone-releasing hormone in anovulatory women, Fertility and Sterility, 29, 418-423, 1978	Selection criteria of participants - does not describe anovulation disorder compatible with WHO Group I
Kaufmann,R., Dunn,R., Vaughn,T., Hughes,G., O'Brien,F., Hemsey,G., Thomson,B., St.,L.O'DeaL., Recombinant human luteinizing hormone, lutropin alfa, for the induction of follicular development and pregnancy in profoundly gonadotrophin-deficient women, Clinical Endocrinology, 67, 563-569, 2007	No indication how many women received IUI and there is no subgroup analysis
Letterie,G.S., Coddington,C.C., Collins,R.L., Merriam,G.R., Ovulation induction using s.c. pulsatile gonadotrophin-releasing hormone: effectiveness of different pulse frequencies, Human Reproduction, 11, 19-22, 1996	Small sample size
Loumaye,E., Engrand,P., Shoham,Z., Hillier,S.G., Baird,D.T., Clinical evidence for an LH 'ceiling' effect induced by administration of recombinant human LH during the late follicular phase of stimulated cycles in World Health Organization type I and type II anovulation, Human Reproduction, 18, 314-322, 2003	No outcomes of interest
Loumaye,E., Piazzi,A., Warne,D., Kalubi,M., Cox,P., Lancaster,S., Rotem,S., Sauvage,M., Ursicino,G., Baird,D., Cittadini,E., Palermo,R., Homburg,R., Shoham,Z., Insler,V., Flamigni,C., Porcu,E., Schaison,G., Bouchard,P., Franks,S., Hull,M., Jacobs,H., Recombinant human luteinizing hormone (LH) to support recombinant human follicle-stimulating hormone (FSH)-induced follicular development in LH- and FSH-deficient anovulatory women: A dose-finding study, Journal of Clinical Endocrinology and Metabolism, 83, 1507-1514, 1998	Does not report outcomes of interest
Malo,J.W., Bezdicek,B., Campbell,E., Pavelka,D.A., Covato,T., Ovulation induction with pulsatile intravenous GnRH, Journal of Reproductive Medicine, 30, 902-906, 1985	Heterogeneous population

Bibliographic information	Reason for exclusion
Martin,K.A., Hall,J.E., Adams,J.M., Crowley,Jr, Comparison of exogenous gonadotropins and pulsatile gonadotropin-releasing hormone for induction of ovulation in hypogonadotropic amenorrhea, Journal of Clinical Endocrinology and Metabolism, 77, 125-129, 1993	Retrospective study design
Martinez,NunezJ, Altagracia,MartinezM, Rios,C., Kravzov,JinichJ, Hinojosa,CruzJ, Vital,ReyesV, Cost-effectiveness study of clomiphene citrate versus anastrozole for inducing ovulation in infertile adult patients in a public hospital, La Raza in Mexico City, Journal of Pharmaceutical Health Services Research, 2, 35-40, 2011	No new relevant data. Not clear if women were randomised to treatment. One group consisted of only 5 women.
Mendes,M.C., Ferriani,R.A., Sala,M.M., Moura,M.D., De,S., Induction of ovulation with clomiphene citrate in combination with metoclopramide in patients with amenorrhea of hypothalamic origin, Gynecological Endocrinology, 13, 149-154, 1999	The study does not report outcomes of interest
O'Dea,L., O'Brien,F., Currie,K., Hemsey,G., Follicular development induced by recombinant luteinizing hormone (LH) and follicle-stimulating hormone (FSH) in anovulatory women with LH and FSH deficiency: evidence of a threshold effect, Current Medical Research and Opinion, 24, 2785-2793, 2008	Women could use barrier contraception and so pregnancy outcomes could not be obtained for these women. Only 34 women wanted to conceive, and it was not reported how which intervention group/s these women were in
O'Dea,L., O'Brien,F., Hemsey,G., Dunn,R.C., Kaufmann,R., Vaughn,T., Flexible dosing of recombinant human follitropin alfa (r-hFSH) optimizes pregnancy rates for profoundly luteinizing hormone (LH)-deficient hypogonadotropic hypogonadal patients treated with recombinant human lutropin alfa (r-hLH), Fertility and Sterility, 82, S307-, 2004	Conference abstract
Oelsner,G., Serr,D.M., Mashiach,S., Blankstein,J., Snyder,M., Lunenfeld,B., The study of induction of ovulation with menotropins: analysis of results of 1897 treatment cycles, Fertility and Sterility, 30, 538-544, 1978	Heterogeneous population (includes women with galactorrhea)
Shoham,Z., Balen,A., Patel,A., Jacobs,H.S., Results of ovulation induction using human menopausal gonadotropin or purified follicle-stimulating hormone in hypogonadotropic hypogonadism patients, Fertility and Sterility, 56, 1048-1053, 1991	Does not report outcomes of interest
Shoham,Z., Howles,C.M., Zalel,Y., Weissman,A., Insler,V., Induction of follicular growth and production of a normal hormonal milieu in spite of using a constant low dose of luteinizing hormone in women with hypogonadotrophic hypogonadism, Human Reproduction, 9, 431-436, 1994	Case study
Skarin,G., Ahlgren,M., Pulsatile gonadotropin releasing hormone (GnRH) - Treatment for hypothalamic amenorrhoea causing infertility, Acta Obstetricia et Gynecologica Scandinavica, 73, 482-485, 1994	Not the population of interest
Suginami,H., Kitagawa,H., Nakahashi,N., Yano,K., Matsubara,K., A clomiphene citrate and tamoxifen citrate combination therapy: A novel therapy for ovulation induction, Fertility and Sterility, 59, 976-979, 1993	Not restricted to WHO Group I women

Bibliographic information	Reason for exclusion
Taketani,Y., Kelly,E., Yoshimura,Y., Hoshiai,H., Irahara,M., Mizunuma,H., Saito,H., Andoh,K., Bebia,Z., Yanaihara,T., Recombinant follicle-stimulating hormone (follitropin alfa) for ovulation induction in Japanese patients with anti-estrogen-ineffective oligo-or anovulatory infertility: Results of a phase II dose-response study, Reproductive Medicine and Biology, 9, 91-97, 2010	PCOS women
Ulug,U., Ben-Shlomo,I., Tosun,S., Erden,H.F., Akman,M.A., Bahceci,M., The reproductive performance of women with hypogonadotropic hypogonadism in an in vitro fertilization and embryo transfer program, Journal of Assisted Reproduction and Genetics, 22, 167-171, 2005	Retrospective study
Vegetti,W., Riccaboni,A., Columbo,M., Baroni,E., Diaferia,D., Ragni,G., Crosignani,P.G., Randomized study of induction of ovulation by two different molecules with antioestrogenic effects, in patients with chronic anovulation disorders, Fertility and Sterility, 72, S234-S235, 1999	Not the population of interest
Webster,J., Piscitelli,G., Polli,A., Ferrari,C.I., Ismail,I., Scanlon,M.F., A comparison of cabergoline and bromocriptine in the treatment of hyperprolactinemic amenorrhea. Cabergoline Comparative Study Group, New England Journal of Medicine, 331, 904-909, 1994	Not a comparison of interest

Group II WHO women

Table G.5 What is the effectiveness and safety of ovulation induction strategies in women with WHO Group II ovulation disorders?

Bibliographic information	Reason for exclusion
Abdrabbo,M.S., Khalil,M.H., Elsedeek,M.S.E., Elagawany,A., The use of clomiphene citrates for ovulation induction in women with functional ovarian cysts, Middle East Fertility Society Journal, 16, 200-203, 2011	Not a population of interest
Aboulghar,M.A., Mansour,R.T., Serour,G.I., Rizk,P., Riad,R., Improvement of spontaneous pregnancy rate after stopping gonadotropin therapy for anovulatory infertility, Fertility and Sterility, 55, 722-725, 1991	Non-randomised study. PCOS not clearly defined
Abu,Hashim H., El-Shafei,M., Badawy,A., Wafa,A., Zaglol,H., Does laparoscopic ovarian diathermy change clomiphene-resistant PCOS into clomiphene-sensitive?, Archives of Gynecology and Obstetrics, 284, 503-507, 2011	Not a comparative study
Abu,Hashim H., Foda,O., Ghayaty,E., Elawa,A., Laparoscopic ovarian diathermy after clomiphene failure in polycystic ovary syndrome: is it worthwhile? A randomized controlled trial, Archives of Gynecology and Obstetrics, 284, 1303-1309, 2011	Not a population of interest - women had previously responded to clomifene citrate but then experienced six cycles of clomifene failure
Abu,Hashim H., Mashaly,A.M., Badawy,A., Letrozole versus laparoscopic ovarian diathermy for ovulation induction in clomiphene-resistant women with polycystic ovary syndrome: a randomized controlled trial, Archives of Gynecology and Obstetrics, 282, 567-571, 2010	Not a comparison of interest

Bibliographic information	Reason for exclusion
Amer,S.A., Li,T.C., Metwally,M., Emarh,M., Ledger,W.L., Randomized controlled trial comparing laparoscopic ovarian diathermy with clomiphene citrate as a first-line method of ovulation induction in women with polycystic ovary syndrome, Human Reproduction, 24, 219-225, 2009	69% of women in surgery group received clomiphene citrate and 34% of those in the clomiphene citrate group received surgery
Arce,J.C., Smitz,J., Exogenous hCG activity, but not endogenous LH activity, is positively associated with live birth rates in anovulatory infertility, Human Fertility, 14, 192-199, 2011	Retrospective study
Badawy,A., Gibreal,A., Clomiphene citrate versus tamoxifen for ovulation induction in women with PCOS: a prospective randomized trial, European Journal of Obstetrics, Gynecology, and Reproductive Biology, 159, 151-154, 2011	Not a comparison of interest
Badawy,A., Mosbah,A., Shady,M., Anastrozole or letrozole for ovulation induction in clomiphene-resistant women with polycystic ovarian syndrome: a prospective randomized trial, Fertility and Sterility, 89, 1209-1212, 2008	Comparison of different aromatase inhibitors
Balen,A., Platteau,P., Andersen,A.N., Devroey,P., Helmgaard,L., Arce,J.C., for the Bravelle Ovulation Induction (BOI) Study Group., Highly purified FSH is as efficacious as recombinant FSH for ovulation induction in women with WHO Group II anovulatory infertility: a randomized controlled non-inferiority trial, Human Reproduction, 22, 1816-1823, 2007	Comparison of two gonadotrophin interventions
Baran,S., Api,M., Goksedef,B.P., Cetin,A., Comparison of metformin and clomiphene citrate therapy for induction of ovulation in the polycystic ovary syndrome, Archives of Gynecology and Obstetrics, 282, 439-443, 2010	Non-randomised prospective trial
Baruah,J., Roy,K.K., Rahman,S.M., Kumar,S., Sharma,J.B., Karmakar,D., Endometrial effects of letrozole and clomiphene citrate in women with polycystic ovary syndrome using spiral artery Doppler, Archives of Gynecology and Obstetrics, 279, 311-314, 2009	Outcomes reported per cycle
Bayram,N., van,Wely M., van,der,V, Bossuyt,P.M., Nieuwkerk,P., Treatment preferences and trade-offs for ovulation induction in clomiphene citrate-resistant patients with polycystic ovary syndrome.[Erratum appears in Fertil Steril. 2005 Nov;84(5):1557 Note: Nieuwkerk, Pythia [added]], Fertility and Sterility, 84, 420-425, 2005	Measures preference for treatment before and after an intervention based on hypothetical pregnancy rates
Bayram,N., Van,WelyM, Van,DerVeenF, Pulsatile gonadotrophin releasing hormone for ovulation induction in subfertility associated with polycystic ovary syndrome, Cochrane database of systematic reviews (Online), #2004. Date of Publication, CD000412-, 2004	Only one relevant trial was included in the analysis. The trial was therefore considered separately for the review
Bayram,Neriman, van Wely,Madelon, Van der Veen,Fulco, Recombinant FSH versus urinary gonadotrophins or recombinant FSH for ovulation induction in subfertility associated with polycystic ovary syndrome, Cochrane Database of Systematic Reviews, -, 2009	Study included in Ferility guideline 2004 Comparison of different doses of FSH and different types of FSH
Beck,J.I., Boothroyd,C., Proctor,M., Farquhar,C., Hughes,E., Oral anti-oestrogens and medical adjuncts for subfertility associated with anovulation. [69 refs][Update in Cochrane Database Syst Rev. 2009;(4):CD002249; PMID: 19821295], Cochrane Database of Systematic Reviews, CD002249-, 2005	Does not report comparisons of interest

Bibliographic information	Reason for exclusion
Boomsma,C.M., Eijkemans,M.J.C., Hughes,E.G., Visser,G.H.A., Fauser,B.C.J.M., Macklon,N.S., A meta-analysis of pregnancy outcomes in women with polycystic ovary syndrome, Human Reproduction Update, 12, 673-683, 2006	Does not report relevant outcomes
Boostanfar,R., Jain,J.K., Mishell,D.R.,Jr., Paulson,R.J., A prospective randomized trial comparing clomiphene citrate with tamoxifen citrate for ovulation induction, Fertility and Sterility, 75, 1024-1026, 2001	Not a comparison of interest
Brown,Julie, Farquhar,Cindy, Beck,James, Boothroyd,Clare, Hughes,Edward, Clomiphene and anti-oestrogens for ovulation induction in PCOS, Cochrane Database of Systematic Reviews, -, 2010	Does not look at comparisons of interest
Christin-Maitre,S., Hugues,J.N., Recombinant FSH Study Group., A comparative randomized multicentric study comparing the step-up versus step-down protocol in polycystic ovary syndrome, Human Reproduction, 18, 1626-1631, 2003	Not a comparison of interest
Clomiphene or metformin for PCOS infertility?, Journal of Family Practice, 56, 349-, 2007	Summary of study considered separately for inclusion in the review (Legro, 2007)
Creanga,A.A., Bradley,H.M., McCormick,C., Witkop,C.T., Use of metformin in polycystic ovary syndrome: a meta-analysis, Obstetrics and Gynecology, 111, 959-968, 2008	Not clear whether included studies used ART or not
Cudmore,D.W., Tupper,W.R., Induction of ovulation with clomiphene citrate. A double-blind study, Fertility and Sterility, 17, 363-373, 1966	Not a randomised trial. Cross-over design.
D'Angelo,D.V., Whitehead,N., Helms,K., Barfield,W., Ahluwalia,I.B., Birth outcomes of intended pregnancies among women who used assisted reproductive technology, ovulation stimulation, or no treatment, Fertility and Sterility, 96, 314-320, 2011	Compares women who received ART, ovulation induction medication, and no treatment
De,PaulaGuedesNetoE, Savaris,R.F., Von,EyeCorletaH, De,MoraesG, Do,AmaralCristovamR, Lessey,B.A., Prospective, randomized comparison between raloxifene and clomiphene citrate for ovulation induction in polycystic ovary syndrome, Fertility and Sterility, 96, 769-773, 2011	Compared raloxifene and clomifene citrate - not a comparison of interest
Dhaliwal,L.K., Suri,V., Gupta,K.R., Sahdev,S., Tamoxifen: An alternative to clomiphene in women with polycystic ovary syndrome, Journal of Human Reproductive Sciences, 4, 76-79, 2011	Not a comparison of interest - different doses of tamoxifen
Eckmann,K.R., Kockler,D.R., Aromatase inhibitors for ovulation and pregnancy in polycystic ovary syndrome. [33 refs], Annals of Pharmacotherapy, 43, 1338-1346, 2009	Narrative review
El Bigawy,A.F., Fouda,U.M.F., Wahab,H.A.E., A randomized trial of letrazole versus clomiphene citrate in induction of ovulation in patients with polycystic ovary syndrome (PCOS), Middle East Fertility Society Journal, 13, 52-56, 2008	Alternate allocation used
El-Berry,S., Razik,M.A., Nitric oxide donors increases pregnancy rate in clomiphene citrate treated polycystic ovary infertile patients, Middle East Fertility Society Journal, 15, 106-109, 2010	Compares clomiphene citrate with clomiphene citrate + isosobid mononitrate
El-Biely,M.M., Habba,M., The use of metformin to augment the induction of ovulation in obese infertile patients with polycystic ovary syndrome, Middle East Fertility Society Journal, 6, 43-49, 2001	No outcomes of interest reported

Bibliographic information	Reason for exclusion
Elmashad,A.I., Impact of laparoscopic ovarian drilling on anti-Mullerian hormone levels and ovarian stromal blood flow using three-dimensional power Doppler in women with anovulatory polycystic ovary syndrome, Fertility and Sterility, 95, 2342-2346, 2011	Compares PCOS and non-PCOS women. Not a randomised controlled trial
Elnashar,A., Abdelmageed,E., Fayed,M., Sharaf,M., Clomiphene citrate and dexamethazone in treatment of clomiphene citrate-resistant polycystic ovary syndrome: a prospective placebo-controlled study, Human Reproduction, 21, 1805-1808, 2006	Compares clomiphene citrate + dexamethasone with clomiphene citrate alone
Ergr AR, Yergk YZ, Ertekin,A., K, ngen,E., L., Clomiphene citrate-resistant polycystic ovary syndrome. Preventing multifollicular development, Journal of Reproductive Medicine, 43, 185-190, 1998	Compares hMG + GnRH agonist with hMG
Ertunc,D., Tok,E.C., Savas,A., Ozturk,I., Dilek,S., Gonadotropin-releasing hormone antagonist use in controlled ovarian stimulation and intrauterine insemination cycles in women with polycystic ovary syndrome, Fertility and Sterility, 93, 1179-1184, 2010	Compares rFSH with rFSH + GnRH antagonist
Esmaeilzadeh,S., Amiri,M.G., Basirat,Z., Shirazi,M., Does adding dexamethasone to clomiphene citrate improve ovulation in PCOS patients? A triple - blind randomized clinical trial study, International Journal of Fertility and Sterility, 5, 9-12, 2011	Compares clomifene citrate + dexamethasone to clomifene citrate alone - not a comparison of interest
Farhi,J., Homburg,R., Lerner,A., Ben-Rafael,Z., The choice of treatment for anovulation associated with polycystic ovary syndrome following failure to conceive with clomiphene, Human Reproduction, 8, 1367-1371, 1993	Compares pFSH with hMG with GnRH analogue + hMG
Farquhar,C.M., An economic evaluation of laparoscopic ovarian diathermy versus gonadotrophin therapy for women with clomiphene citrate-resistant polycystic ovarian syndrome. [53 refs], Current Opinion in Obstetrics and Gynecology, 17, 347-353, 2005	Economic evaluation based on Farquahar 2002, which was considered separately for inclusion in the review
Farquhar,C.M., Williamson,K., Brown,P.M., Garland,J., An economic evaluation of laparoscopic ovarian diathermy versus gonadotrophin therapy for women with clomiphene citrate resistant polycystic ovary syndrome, Human Reproduction, 19, 1110-1115, 2004	Economic evaluation based on Farquahar 2002, which was considered separately for inclusion in the review
Farquhar,Cindy, Lilford,Richard, Marjoribanks,Jane, Vanderkerchove,Patrick, Laparoscopic 'drilling' by diathermy or laser for ovulation induction in anovulatory polycystic ovary syndrome, Cochrane Database of Systematic Reviews, -, 2009	Study included in Ferility guideline 2004 One study used IUI. One study was a crossover trial and it was not clear if only phase one data was used. One study was an interim report from eleven years prior to the review being published with no updated trial available. Trials included in this meta analysis were therefore considered separately for this review
Farzadi,L., Salman,ZadehS, Metformin-therapy effects in 50 clomiphene citrate resistant PCOS patients, Journal of Medical Sciences, 6, 765-771, 2006	Compares metformin and placebo
Fernandez,H., Morin-Surruca,M., Torre,A., Faivre,E., Deffieux,X., Gervaise,A., Ovarian drilling for surgical treatment of polycystic ovarian syndrome: a comprehensive review, Reproductive Biomedicine Online, 22, 556-568, 2011	Review with no comparisons of interest

Bibliographic information	Reason for exclusion
Flyckt,R.L., Goldberg,J.M., Laparoscopic ovarian drilling for clomiphene-resistant polycystic ovary syndrome, Seminars in Reproductive Medicine, 29, 138-146, 2011	Narrative review
Gadir,A.A., Alnaser,H.M., Mowafi,R.S., Shaw,R.W., The response of patients with polycystic ovarian disease to human menopausal gonadotropin therapy after ovarian electrocautery or a luteinizing hormone-releasing hormone agonist, Fertility and Sterility, 57, 309-313, 1992	Compares surgery + hMG with LH agonist + hMG
Garcia,C.R., Freeman,E.W., Rickels,K., Wu,C., Scholl,G., Galle,P.C., Boxer,A.S., Behavioral and emotional factors and treatment responses in a study of anovulatory infertile women, Fertility and Sterility, 44, 478-483, 1985	Not a comparison of interest
George,K., Nair,R., Tharyan,P., Ovulation triggers in anovulatory women undergoing ovulation induction. [23 refs], Cochrane Database of Systematic Reviews, CD006900-, 2008	Population is not just WHO Group II and no subgroup analysis was done
Gerhard,I., Matthes,J., Runnebaum,B., The induction of ovulation with pulsatile gonadotrophin-releasing hormone (GnRH) administration in hyperandrogenic women after down-regulation with buserelin or suppression with an oral contraceptive, Human Reproduction, 8, 2033-2038, 1993	Not a comparison of interest
Ghazeeri,G., Kutteh,W.H., Bryer-Ash,M., Haas,D., Ke,R.W., Effect of rosiglitazone on spontaneous and clomiphene citrate-induced ovulation in women with polycystic ovary syndrome, Fertility and Sterility, 79, 562-566, 2003	The MHRA has recommended that Rosiglitazone be withdrawn from use due to an association with increased risks of cardiovascular disorders
Hamed,H.O., Hasan,A.F., Ahmed,O.G., Ahmed,M.A., Metformin versus laparoscopic ovarian drilling in clomiphene- and insulin-resistant women with polycystic ovary syndrome, International Journal of Gynecology and Obstetrics, 108, 143-147, 2010	Compares diagnostic surgery + metformin with surgery
Hashim,H.A., Anwar,K., El-Fatah,R.A., N-acetyl cysteine plus clomiphene citrate versus metformin and clomiphene citrate in treatment of clomiphene-resistant polycystic ovary syndrome: a randomized controlled trial, Journal of Women's Health, 19, 2043-2048, 2010	Compares N-acetylcysteine + clomiphene citrate with metformin + clomiphene citrate
He,D., Jiang,F., Meta-analysis of letrozole versus clomiphene citrate in polycystic ovary syndrome, Reproductive Biomedicine Online, 23, 91-96, 2011	Six studies were included - current review already includes 4, 1 used IUI and the other was a foreign language paper. The foreign language papers was not reported with not enough details for quality to be assessed, and included only 5 women in each arm.
Hedon,B., Hugues,J.N., Emperaire,J.C., Chabaud,J.J., Barbereau,D., Boujenah,A., Howles,C.M., Truong,F., A comparative prospective study of a chronic low dose versus a conventional ovulation stimulation regimen using recombinant human follicle stimulating hormone in anovulatory infertile women, Human Reproduction, 13, 2688-2692, 1998	Not a comparison of interest

Bibliographic information	Reason for exclusion
Hoeger,K.M., Guzick,D.S., Review: metformin used alone or combined with clomifene may improve ovulation rates in the polycystic ovary syndrome, Evidence-Based Medicine, 9, 85-85, 2004	Included studies not reported. It is not clear what denominator was used in calculating the clinical pregnancy rate and no raw data is provided. The paper is based on a Cochrane review which is considered separately for this review
Homburg,R., Hendriks,M.L., Konig,T., Anderson,R.A., Balen,A., Brincat,M., Child,T., Davis,M., D'Hooghe,T., Martinez,A., Rajkhowa,M., Rueda-Saenz,R., Lambalk,C.B., Clomifene or low-dose FSH for the first-line treatment of anovulatory PCOS: a prospective randomised multinational study (COFFI), Human Reproduction.European Society of Human Reproduction and Embryology, ESHRE 25th Annual meeting Amsterdam 28th June to 1st July, 2009. Vol.24 Suppl 1, pp.i22 O-058 Oral, 2009., -058, 2009	Conference abstract
Hosseini,M.A., Aleyasin,A., Saeedi,H., Mahdavi,A., Comparison of gonadotropin-releasing hormone agonists and antagonists in assisted reproduction cycles of polycystic ovarian syndrome patients, Journal of Obstetrics and Gynaecology Research, 36, 605-610, 2010	Compares GnRH agonist + follitrophin alpha + hMG with follitrophin alpha + GnRH antagonist + hMG
Hugues,J.N., drin-Durnerin,I., Howles,C.M., FSH OI Study Group, Amram,M., Angelini,A., Balen,A., Barbereau,D., Birkhauser,M., Boujenah,A., De,Leo,V, De,Placido G., Dessole,S., Favrin,S., Ferrazi,E., Gay,C., Germond,M., Hedon,B., Hocke,C., Jolly,C., Lamarca-Roth,E., Lanzone,A., Marchand,F., Marcolin,G., Mascaretti,G., Moreau,L., Massobrio,M., Nappi,C., Pardi,G., Pennehouat,G., Porcu,E., Seibert,M., Selvaggi,L., Thiers,D., Venturini,P., The use of a decremental dose regimen in patients treated with a chronic low-dose step-up protocol for WHO Group II anovulation: a prospective randomized multicentre study, Human Reproduction, 21, 2817-2822, 2006	Not a comparison of interest
Infertility treatment in PCOS, ACOG Clinical Review, 12, 9-9, 2007	Commentary
Johnson,J.E.,Jr., Cohen,M.R., Goldfarb,A.F., Rakoff,A.E., Kistner,R.W., Plotz,E.J., Vorys,N., The efficacy of clomiphene citrate for induction of ovulation. A controlled study, International Journal of Fertility, 11, 265-270, 1966	Not a comparison of interest
Johnson,N., Metformin is a reasonable first-line treatment option for non-obese women with infertility related to anovulatory polycystic ovary syndrome--a meta-analysis of randomised trials, Australian and New Zealand Journal of Obstetrics and Gynaecology, 51, 125-129, 2011	Three included studies have already been review for the current review - this meta-analysis does not add anything further
Johnson,N.P., PCOSMIC polycystic ovarian syndrome, metformin for infertility with clomiphene: a multi-centre double-blind randomised controlled trial, Human Reproduction.European Society of Human Reproduction and Embryology, ESHRE 25th Annual meeting Amsterdam 28th June to 1st July, 2009. Vol.24 Suppl 1, pp.i24 O-061 Oral, 2009., -061, 2009	Conference abstract
Karimzadeh,M.A., Eftekhar,M., Taheripanah,R., Tayebi,N., Sakhavat,L., Zare,F., The effect of administration of metformin on lipid profile changes and insulin resistance in patients with polycystic ovary syndrome, Middle East Fertility Society Journal, 12, 174-178, 2007	Compares metformin with placebo

Bibliographic information	Reason for exclusion
Kashyap,S., Wells,G.A., Rosenwaks,Z., Insulin-sensitizing agents as primary therapy for patients with polycystic ovarian syndrome, Human Reproduction, 19, 2474-2483, 2004	Pregnancy was determined by urinary or serum beta-hCG rather than ultrasound. No other relevant outcomes were reported
Kaya,H., Sezik,M., Ozkaya,O., Evaluation of a new surgical approach for the treatment of clomiphene citrate-resistant infertility in polycystic ovary syndrome: laparoscopic ovarian multi-needle intervention, Journal of Minimally Invasive Gynecology, 12, 355-358, 2005	One of the groups received IUI
Khorram,O., Helliwell,J.P., Katz,S., Bonpane,C.M., Jaramillo,L., Two weeks of metformin improves clomiphene citrate-induced ovulation and metabolic profiles in women with polycystic ovary syndrome, Fertility and Sterility, 85, 1448-1451, 2006	Does not report outcomes of interest
Kjotrod,S.B., Carlsen,S.M., Rasmussen,P.E., Holst-Larsen,T., Mellembakken,J., Thurin-Kjellberg,A., Haapaniemikouru,K., Morin-Papunen,L., Humaidan,P., Sunde,A., von,During,V, Use of metformin before and during assisted reproductive technology in non-obese young infertile women with polycystic ovary syndrome: a prospective, randomized, double-blind, multi-centre study, Human Reproduction, 26, 2045-2053, 2011	Not a relevant comparison
Kocak,I., Ustn C., Effects of metformin on insulin resistance, androgen concentration, ovulation and pregnancy rates in women with polycystic ovary syndrome following laparoscopic ovarian drilling, Journal of Obstetrics and Gynaecology Research, 32, 292-298, 2006	Compares surgery with surgery + metformin
Kocak,M., Caliskan,E., Simsir,C., Haberal,A., Metformin therapy improves ovulatory rates, cervical scores, and pregnancy rates in clomiphene citrate-resistant women with polycystic ovary syndrome, Fertility and Sterility, 77, 101-106, 2002	Alternate allocation used
Krzysiek,J., Klimek,M., Milewicz,T., The pulsatile gonadotropin releasing hormone administration and ovarian electrocautery in infertile hyperandrogenic women, Italian Journal of Gynaecology and Obstetrics, 12, 96-103, 2000	Compares GnRH with surgery
Kupferminc,M.J., Lessing,J.B., Peyser,M.R., Ovulation induction with gonadotropins in women with polycystic ovary disease, Journal of Reproductive Medicine, 36, 61-64, 1991	Not a comparative study
Legro,R.S., Metformin as adjuvant therapy to IVF in women with PCOS: when is intention-to-treat unintentional?, Human Reproduction, 26, 2043-2044, 2011	Women received IVF
Li,X.J., Yu,Y.X., Liu,C.Q., Zhang,W., Zhang,H.J., Yan,B., Wang,L.Y., Yang,S.Y., Zhang,S.H., Metformin vs thiazolidinediones for treatment of clinical, hormonal and metabolic characteristics of polycystic ovary syndrome: a meta-analysis, Clinical Endocrinology, 74, 332-339, 2011	Not a comparison of interest. Eight of the ten included studies compared metformin with rosiglitazone, which the MHRA has recommended by withdrawn from clinical use
Lord,J.M., Flight,I.H., Norman,R.J., Metformin in polycystic ovary syndrome: systematic review and meta-analysis. [26 refs], BMJ, 327, 951-953, 2003	Individual studies considered separately for current review
Malkawi,H.Y., Qublan,H.S., Hamaideh,A.H., Medical vs. surgical treatment for clomiphene citrate-resistant women with polycystic ovary syndrome, Journal of Obstetrics and Gynaecology, 23, 289-293, 2003	Compares metformin with surgery

Bibliographic information	Reason for exclusion
Martinez,NunezJ, Altagracia,MartinezM, Rios,C., Kravzov,JinichJ, Hinojosa,CruzJ, Vital,ReyesV, Cost-effectiveness study of clomiphene citrate versus anastrozole for inducing ovulation in infertile adult patients in a public hospital, La Raza in Mexico City, Journal of Pharmaceutical Health Services Research, 2, 35-40, 2011	No new relevant data. Not clear if women were randomised to treatment. One group consisted of only 5 women.
McFaul,P.B., Traub,A.I., Sheridan,B., Leslie,H., Daily or alternate-day FSH therapy in patients with polycystic ovarian disease resistant to clomiphene citrate treatment, International Journal of Fertility, 34, 194-198, 1989	Comparison of daily and alternate day administration of FSH
Moll,E., Korevaar,J.C., Bossuyt,P.M., van,der,V, Does adding metformin to clomifene citrate lead to higher pregnancy rates in a subset of women with polycystic ovary syndrome?, Human Reproduction, 23, 1830-1834, 2008	Study reports subgroup analysis of the study Moll et al, 2006
Moll,E., van,der,V, van,Wely M., The role of metformin in polycystic ovary syndrome: a systematic review. [75 refs], Human Reproduction Update, 13, 527-537, 2007	The focus of this review is metformin rather than clomiphene citrate or tamoxifen. Relevant studies from the paper have been considered separately for this review
Montville,C.P., Khabbaz,M., Aubuchon,M., Williams,D.B., Thomas,M.A., Luteal support with intravaginal progesterone increases clinical pregnancy rates in women with polycystic ovary syndrome using letrozole for ovulation induction, Fertility and Sterility, 94, 678-683, 2010	Retrospective chart review
Moran,L.J., Hutchison,S.K., Norman,R.J., Teede,H.J., Lifestyle changes in women with polycystic ovary syndrome, Cochrane Database of Systematic Reviews, 7, CD007506-, 2011	Only 2 women in one of the included studies were trying to conceive. The other reported outcomes were not pregnancy related
Moran,L.J., Hutchison,S.K., Norman,R.J., Teede,H.J., Lifestyle changes in women with polycystic ovary syndrome. [Update of Cochrane Database Syst Rev. 2011;(2):CD007506; PMID: 21328294], Cochrane Database of Systematic Reviews, CD007506-, 2011	None of the included studies reported relevant outcomes
Moran,L.J., Noakes,M., Clifton,P.M., Tomlinson,L., Galletly,C., Norman,R.J., Dietary composition in restoring reproductive and metabolic physiology in overweight women with polycystic ovary syndrome, Journal of Clinical Endocrinology and Metabolism, 88, 812-819, 2003	Eight of the 28 women were not trying to conceive
Moran,Lisa J., Hutchison,Samantha K., Norman,Robert J., Teede,Helena J., Lifestyle changes in overweight women with Polycystic Ovary Syndrome, Cochrane Database of Systematic Reviews, -, 2009	Protocol - full review is available (Moran, 2011)
Muenstermann,U., Kleinstein,J., Long-term GnRH analogue treatment is equivalent to laparoscopic laser diathermy in polycystic ovarian syndrome patients with severe ovarian dysfunction, Human Reproduction, 15, 2526-2530, 2000	Uses alternate allocation rather than randomisation
Nahuis,M., Van,DerVeenF, Oosterhuis,J., Mol,B.W., Hompes,P., Van,WelyM, Review of the safety, efficacy, costs and patient acceptability of recombinant follicle-stimulating hormone for injection in assisting ovulation induction in infertile women, International Journal of Women's Health, 1, -211, 2009	Not a comparison of interest

Bibliographic information	Reason for exclusion
Nahuis,M.J., Kose,N., Bayram,N., van Dessel,H.J., Braat,D.D., Hamilton,C.J., Hompes,P.G., Bossuyt,P.M., Mol,B.W., van,der,V, van,Wely M., Long-term outcomes in women with polycystic ovary syndrome initially randomized to receive laparoscopic electrocautery of the ovaries or ovulation induction with gonadotrophins, Human Reproduction, 26, 1899-1904, 2011	Original study already included in the review (Bayram, 2004) - this study does not provide any additional relevant outcomes
Nahuis,M.J., Kose,N., Bayram,N., Van,DesselH, Braat,D.D.M., Hamilton,C.J.C.M., Hompes,P.G.A., Bossuyt,P.M., Mol,B.W.J., Van,DerVeenF, Van,WelyM, Long-term outcomes in women with polycystic ovary syndrome initially randomized to receive laparoscopic electrocautery of the ovaries or ovulation induction with gonadotrophins, Human Reproduction, 26, 1899-1904, 2011	Long-term data from Bayram (2004). Relevant outcomes are already included from the original study
Nardo,L.G., Management of anovulatory infertility associated with polycystic ovary syndrome: Tamoxifen citrate an effective alternative compound to clomiphene citrate, Gynecological Endocrinology, #19, 235-238, 2004	Observational study
Neveu,N., Granger,L., St-Michel,P., Lavoie,H.B., Comparison of clomiphene citrate, metformin, or the combination of both for first-line ovulation induction and achievement of pregnancy in 154 women with polycystic ovary syndrome, Fertility and Sterility, 87, 113-120, 2007	Not a randomised controlled trial
Ng,E.H., Wat,N.M., Ho,P.C., Effects of metformin on ovulation rate, hormonal and metabolic profiles in women with clomiphene-resistant polycystic ovaries: a randomized, double-blinded placebo-controlled trial, Human Reproduction, 16, 1625-1631, 2001	Not a comparison of interest
Ovulation induction in polycystic ovary syndrome, ACOG Clinical Review, 11, 7-7, 2006	Commentary
Palomba,S., Falbo,A., Battista,L., Russo,T., Venturella,R., Tolino,A., Orio,F., Zullo,F., Laparoscopic ovarian diathermy vs clomiphene citrate plus metformin as second-line strategy for infertile anovulatory patients with polycystic ovary syndrome: a randomized controlled trial, American Journal of Obstetrics and Gynecology, 202, 577-578, 2010	Does not report outcomes of interest
Palomba,S., Falbo,A., Giallauria,F., Russo,T., Rocca,M., Tolino,A., Zullo,F., Orio,F., Six weeks of structured exercise training and hypocaloric diet increases the probability of ovulation after clomiphene citrate in overweight and obese patients with polycystic ovary syndrome: a randomized controlled trial, Human Reproduction, 25, 2783-2791, 2010	Pregnancy rates in the three groups are not clearly reported, and it is the only relevant outcome in the study
Palomba,S., Falbo,A., Orio,F.,Jr., Manguso,F., Russo,T., Tolino,A., Annamaria,C., Dale,B., Zullo,F., A randomized controlled trial evaluating metformin pre-treatment and co-administration in non-obese insulin-resistant women with polycystic ovary syndrome treated with controlled ovarian stimulation plus timed intercourse or intrauterine insemination, Human Reproduction, 20, 2879-2886, 2005	Included women who received IUI with no subgroup analysis
Palomba,S., Falbo,A., Orio,F.,Jr., Tolino,A., Zullo,F., Efficacy predictors for metformin and clomiphene citrate treatment in anovulatory infertile patients with polycystic ovary syndrome, Fertility and Sterility, 91, 2557-2567, 2009	Non randomised study
Palomba,S., Falbo,A., Orio,Jr, Zullo,F., Effect of preconceptional metformin on abortion risk in polycystic ovary syndrome: a systematic review and meta-analysis of randomized controlled trials, Fertility and Sterility, 92, 1646-1658, 2009	Only looked at abortion rates - included comparisons with FSH, clomiphene citrate and placebo with no subgroup analysis

Bibliographic information	Reason for exclusion
Palomba,S., Giallauria,F., Falbo,A., Russo,T., Oppedisano,R., Tolino,A., Colao,A., Vigorito,C., Zullo,F., Orio,F., Structured exercise training programme versus hypocaloric hyperproteic diet in obese polycystic ovary syndrome patients with anovulatory infertility: a 24-week pilot study, Human Reproduction, 23, 642-650, 2008	Women were not randomised
Palomba,S., Orio,F.,Jr., Falbo,A., Russo,T., Caterina,G., Manguso,F., Tolino,A., Colao,A., Zullo,F., Metformin administration and laparoscopic ovarian drilling improve ovarian response to clomiphene citrate (CC) in oligo-anovulatory CC-resistant women with polycystic ovary syndrome, Clinical Endocrinology, 63, 631-635, 2005	Compares surgery + metformin + clomiphene citrate with surgery + placebo + clomiphene citrate
Palomba,S., Orio,F.,Jr., Falbo,A., Russo,T., Tolino,A., Zullo,F., Clomiphene citrate versus metformin as first-line approach for the treatment of anovulation in infertile patients with polycystic ovary syndrome, Journal of Clinical Endocrinology and Metabolism, 92, 3498-3503, 2007	Non-randomised study
Palomba,S., Orio,F.,Jr., Nardo,L.G., Falbo,A., Russo,T., Corea,D., Doldo,P., Lombardi,G., Tolino,A., Colao,A., Zullo,F., Metformin administration versus laparoscopic ovarian diathermy in clomiphene citrate-resistant women with polycystic ovary syndrome: a prospective parallel randomized double-blind placebo-controlled trial.[Erratum appears in J Clin Endocrinol Metab. 2005 Jul;90(7):3945], Journal of Clinical Endocrinology and Metabolism, 89, 4801-4809, 2004	Copmares surgery + metformin with surgery + placebo
Palomba,S., Pasquali,R., Orio,F.,Jr., Nestler,J.E., Clomiphene citrate, metformin or both as first-step approach in treating anovulatory infertility in patients with polycystic ovary syndrome (PCOS): a systematic review of head-to-head randomized controlled studies and meta-analysis. [55 refs], Clinical Endocrinology, 70, 311-321, 2009	It is not clear whether women received IUI or IVF or nothing in the individual studies - the individual studies were therefore reviewed separately
Parsanezhad,M.E., Alborzi,S., Jahromi,B.N., A prospective, double-blind, randomized, placebo-controlled clinical trial of bromocriptine in clomiphene-resistant patients with polycystic ovary syndrome and normal prolactin level, International Journal of Fertility and Womens Medicine, 47, 272-277, 2002	Alternate allocation used
Parsanezhad,M.E., Alborzi,S., Motazedian,S., Omrani,G., Use of dexamethasone and clomiphene citrate in the treatment of clomiphene citrate-resistant patients with polycystic ovary syndrome and normal dehydroepiandrosterone sulfate levels: a prospective, double-blind, placebo-controlled trial, Fertility and Sterility, 78, 1001-1004, 2002	Compares clomiphene citrate + dexamethasone with clomiphene citrate + placebo
Parsanezhad,M.E., Alborzi,S., Namavar,Jahromi B., A prospective, double-blind, randomized, placebo-controlled clinical trial of bromocriptin in clomiphene-resistant patients with polycystic ovary syndrome and normal prolactin level, Archives of Gynecology and Obstetrics, 269, 125-129, 2004	Non-randomised study
Parsanezhad,M.E., Motazedian,S., Alborzi,S., Omrani,G., Effect of high dose, short course dexamethasone in clomiphene citrate resistant women with polycystic ovary syndrome, Middle East Fertility Society Journal, 7, 93-97, 2002	Not a comparison of interest
Parsanezhad,M.E., Zarei,A., Sayadi,M., Jaafarzadeh,A., Rajaeefard,A., Frank,V., Schmidt,E.H., Surgical ovulation induction in women with polycystic ovary syndrome: A systematic review, Iranian Journal of Medical Sciences, 35, 225-241, 2010	This is a narrative review with no meta-analysis data

Bibliographic information	Reason for exclusion
Pirwany,I., Tulandi,T., Laparoscopic treatment of polycystic ovaries: is it time to relinquish the procedure?. [135 refs], Fertility and Sterility, 80, 241-251, 2003	Does not include any randomised trials
Platteau,P., Andersen,A.N., Balen,A., Devroey,P., Sorensen,P., Helmgaard,L., Arce,J.C., Menopur Ovulation Induction (MOI) Study Group., Similar ovulation rates, but different follicular development with highly purified menotrophin compared with recombinant FSH in WHO Group II anovulatory infertility: a randomized controlled study, Human Reproduction, 21, 1798-1804, 2006	Not a comparison of interest
Polyzos,N.P., Tsappi,M., Mauri,D., Atay,V., Cortinovis,I., Casazza,G., Aromatase inhibitors for infertility in polycystic ovary syndrome. The beginning or the end of a new era?, Fertility and Sterility, 89, 278-280, 2008	Does not report outcomes of interest
Raffone,E., Rizzo,P., Benedetto,V., Insulin sensitiser agents alone and in co-treatment with r-FSH for ovulation induction in PCOS women, Gynecological Endocrinology, 26, 275-280, 2010	Compares metformin + rFSH with myoinositol + rFSH
Raja,A., Hashmi,S.N., Sultana,N., Rashid,H., Presentation of polycystic ovary syndrome and its management with clomiphene alone and in combination with metformin, Journal of Ayub Medical College, Abbottabad: JAMC, 17, 50-53, 2005	Presentation - not a published study
Ramzy,A.M., El-Kateb,S., Al-Inany,H., Badie,M.A., Aboulmaaty,Z., The use of metformin in overweight and lean infertile patients with polycystic ovarian syndrome: A randomized controlled trial, Middle East Fertility Society Journal, 8, 143-149, 2003	Not a truly randomised trial (alternate allocation)
Rashidi,B., Haghollahi,F., Shariat,M., Zayerii,F., The effects of calcium-vitamin D and metformin on polycystic ovary syndrome: a pilot study, Taiwanese Journal of Obstetrics and Gynecology, 48, 142-147, 2009	Compares calcium + vitamin D with calcium + vitamin D + metformin with metformin alone
Remorgida,V., Venturini,P.L., Anserini,P., Salerno,E., de,Cecco L., Use of combined exogenous gonadotropins and pulsatile gonadotropin-releasing hormone in patients with polycystic ovarian disease.[Erratum appears in Fertil Steril 1991 Jun;55(6):1213], Fertility and Sterility, 55, 61-65, 1991	Definition of PCOS is not clear
Morgan,T., Urman,B., Aksu,T., Yarali,H., Develioglu,O., Kisnisci,H.A., The effect of short-interval laparoscopic lysis of adhesions on pregnancy rates following Nd-YAG laser photocoagulation of polycystic ovaries, Obstetrics and Gynecology, 80, 45-47, 1992	PCOS criteria not defined
Rizk,A.Y., Bedaiwy,M.A., Al-Inany,H.G., N-acetyl-cysteine is a novel adjuvant to clomiphene citrate in clomiphene citrate-resistant patients with polycystic ovary syndrome, Fertility and Sterility, 83, 367-370, 2005	Compares N-acetylcysteine + clomiphene citrate and clomiphene citrate + placebo
Rouzi,A.A., Ardawi,M.S., A randomized controlled trial of the efficacy of rosiglitazone and clomiphene citrate versus metformin and clomiphene citrate in women with clomiphene citrate-resistant polycystic ovary syndrome, Fertility and Sterility, 85, 428-435, 2006	The MHRA has recommended that Rosiglitazone be withdrawn from use due to an association with increased risks of cardiovascular disorders
Roy,K.K., Baruah,J., Sharma,A., Sharma,J.B., Kumar,S., Kachava,G., Karmakar,D., A prospective randomized trial comparing the clinical and endocrinological outcome with rosiglitazone versus laparoscopic ovarian drilling in patients with polycystic ovarian disease resistant to ovulation induction with clomiphene citrate, Archives of Gynecology and Obstetrics, 281, 939-944, 2010	The MHRA has recommended that Rosiglitazone be withdrawn from use due to an association with increased risks of cardiovascular disorders

Bibliographic information	Reason for exclusion
Saleh,A.M., Khalil,H.S., Review of nonsurgical and surgical treatment and the role of insulin-sensitizing agents in the management of infertile women with polycystic ovary syndrome. [85 refs], Acta Obstetricia et Gynecologica Scandinavica, 83, 614-621, 2004	Included studies were not reported in enough detail to determine their relevance to the current review. Included studies were considered separately for inclusion
Schachter,M., Raziel,A., Strassburger,D., Rotem,C., Ron-El,R., Friedler,S., Prospective, randomized trial of metformin and vitamins for the reduction of plasma homocysteine in insulin-resistant polycystic ovary syndrome, Fertility and Sterility, 88, 227-230, 2007	Compares rFSH alone with rFSH + metformin with rFSH + vitamin B with rFSH + metformin + vitamin B
Scheele,F., Hompes,P.G., van der,Meer M., Schoute,E., Schoemaker,J., Pulsatile gonadotrophin releasing hormone stimulation after medium-term pituitary suppression in polycystic ovary syndrome, Human Reproduction, 8 Suppl 2, 197-199, 1993	Definition of PCOS is not in line with WHO Group II definition
Sherwal,V., Malik,S., Bhatia,V., Effect of bromocriptine on the severity of ovarian hyperstimulation syndrome and outcome in high responders undergoing assisted reproduction, Journal of Human Reproductive Sciences, 3, 85-90, 2010	Women received IVF treatment. Population was not limited to those with PCOS. Not a comparison of interest.
Siebert,T.I., Kruger,T.F., Steyn,D.W., Nosarka,S., Is the addition of metformin efficacious in the treatment of clomiphene citrate-resistant patients with polycystic ovary syndrome? A structured literature review, Fertility and Sterility, 86, 1432-1437, 2006	No outcomes of interest are reported
Siristatidis,C.S., Maheshwari,A., Bhattacharya,S., In vitro maturation in sub fertile women with polycystic ovarian syndrome undergoing assisted reproduction, Cochrane Database of Systematic Reviews, #2009. Article Number, -, 2009	Systematic review with no included studies
Stadtmauer,L.A., Sarhan,A., Duran,E.H., Beydoun,H., Bocca,S., Pultz,B., Oehninger,S., The impact of a gonadotropin-releasing hormone antagonist on gonadotropin ovulation induction cycles in women with polycystic ovary syndrome: a prospective randomized study, Fertility and Sterility, 95, 216-220, 2011	Not drug comparison of interest
Sturrock,N.D., Lannon,B., Fay,T.N., Metformin does not enhance ovulation induction in clomiphene resistant polycystic ovary syndrome in clinical practice, British Journal of Clinical Pharmacology, 53, 469-473, 2002	Cross over trial where data from each phase could not separated
Swanton,A., Lighten,A., Granne,I., McVeigh,E., Lavery,S., Trew,G., Talmor,A., Raine-Fenning,N., Jayaprakasan,K., Child,T., Do women with ovaries of polycystic morphology without any other features of PCOS benefit from short-term metformin co-treatment during IVF? A double-blind, placebo-controlled, randomized trial, Human Reproduction, 26, 2178-2184, 2011	Not a relevant comparison
Szilagyi,A., Bartfai,G., Manfai,A., Koloszar,S., Pal,A., Szabo,I., Low-dose ovulation induction with urinary gonadotropins or recombinant follicle stimulating hormone in patients with polycystic ovary syndrome, Gynecological Endocrinology, 18, 17-22, 2004	Not a comparison of interest
Tang,T., Glanville,J., Hayden,C.J., White,D., Barth,J.H., Balen,A.H., Combined lifestyle modification and metformin in obese patients with polycystic ovary syndrome. A randomized, placebo-controlled, double-blind multicentre study, Human Reproduction, 21, 80-89, 2006	Not a comparison of interest

Bibliographic information	Reason for exclusion
Tang,Thomas, Lord,Jonathan M., Norman,Robert J., Yasmin,Ephia, Balen,Adam H., Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subfertility, Cochrane Database of Systematic Reviews, -, 2010	The clomiphene citrate vs metformin analysis included a study that may have used IUI. The metformin vs placebo analysis included some studies that also gave women clomiphene citrate, rFSH or lifestyle modification without a subgroup analysis
Thomson,R.L., Buckley,J.D., Noakes,M., Clifton,P.M., Norman,R.J., Brinkworth,G.D., The effect of a hypocaloric diet with and without exercise training on body composition, cardiometabolic risk profile, and reproductive function in overweight and obese women with polycystic ovary syndrome, Journal of Clinical Endocrinology and Metabolism, 93, 3373-3380, 2008	Not all women wished to become pregnant
Tredway,D., Schertz,J.C., Bock,D., Hemsey,G., Diamond,M.P., Anastrozole single-dose protocol in women with oligo- or anovulatory infertility: results of a randomized phase II dose-response study, Fertility and Sterility, 95, 1725-1729, 2011	Some women received IUI. Their results were not reported separately.
Tredway,D., Schertz,J.C., Bock,D., Hemsey,G., Diamond,M.P., Anastrozole vs. clomiphene citrate in infertile women with ovulatory dysfunction: a phase II, randomized, dose-finding study, Fertility and Sterility, 95, 1720-1724, 2011	Some women received IUI. Their results were not reported separately.
Trolle,B., Lauszus,F.F., Frystyk,J., Flyvbjerg,A., Adiponectin levels in women with polycystic ovary syndrome: impact of metformin treatment in a randomized controlled study, Fertility and Sterility, 94, 2234-2238, 2010	No relevant outcomes reported. Cross-over trial with data not reported separately by phase
Tso,L.O., Costello,M.F., Albuquerque,L.E., Andriolo,R.B., Freitas,V., Metformin treatment before and during IVF or ICSI in women with polycystic ovary syndrome, Cochrane Database of Systematic Reviews, #2009. Article Number, -, 2009	Women received IVF or ICSI
van,Wely M., Bayram,N., Bossuyt,P.M., van,der,V, Laparoscopic electrocautery of the ovaries versus recombinant FSH in clomiphene citrate-resistant polycystic ovary syndrome. Impact on women's health-related quality of life, Human Reproduction, 19, 2244-2250, 2004	Mixed intervention
van,Wely M., Bayram,N., van,der,V, Bossuyt,P.M., An economic comparison of a laparoscopic electrocautery strategy and ovulation induction with recombinant FSH in women with clomiphene citrate-resistant polycystic ovary syndrome, Human Reproduction, 19, 1741-1745, 2004	
Vause,T.D., Cheung,A.P., Sierra,S., Claman,P., Graham,J., Guillemin,J.A., Lapensee,L., Steward,S., Wong,B.C., Society of Obstetricians and Gynaecologists of Canada., Ovulation induction in polycystic ovary syndrome: No. 242, May 2010, International Journal of Gynaecology and Obstetrics, 111, 95-100, 2010	Narrative review
Vause,T.D., Cheung,A.P., Sierra,S., Claman,P., Graham,J., Guillemin,J.A., Lapensee,L., Steward,S., Wong,B.C., Society of Obstetricians and Gynecologists of Canada., Ovulation induction in polycystic ovary syndrome, Journal of Obstetrics and Gynaecology Canada: JOGC, 32, 495-502, 2010	Narrative review

Bibliographic information	Reason for exclusion
Vause,T.D.R., Cheung,A.P., Sierra,S., Claman,P., Graham,J., Guillemin,J.A., Lapensee,L., Steward,S., Wong,B.C.-M., Ovulation induction in polycystic ovary syndrome: No. 242, may 2010, International Journal of Gynecology and Obstetrics, 111, 95-100, 2010	Narrative review
Vegetti,W., Ragni,G., Baroni,E., Testa,G., Marsico,S., Laparoscopic ovarian drilling versus low-dose pure FSH in anovulatory clomiphene-resistant patients with polycystic ovarian syndrome: randomized prospective study, Human Reproduction, Vol.13, pp.120, 1998., -, -32676	Conference abstract
Xue,T., Li,S.W., Wang,Y., Effectiveness of bromocriptine monotherapy or combination treatment with clomiphene for infertility in women with galactorrhea and normal prolactin: A systematic review and meta-analysis, Current Therapeutic Research - Clinical and Experimental, 71, 199-210, 2010	Not a relevant comparison
Yarali,H., Yildiz,B.O., Demirol,A., lu,H.B., it,N., lmez,O., Koray,Z., Co-administration of metformin during rFSH treatment in patients with clomiphene citrate-resistant polycystic ovarian syndrome: a prospective randomized trial, Human Reproduction, 17, 289-294, 2002	Compares metformin and placebo
Zheng,J., Cao,Z., Zong,L., Effect of rosiglitazone and metformin on clomiphene citrate resistance in women with polycystic ovary syndrome, Academic Journal of Xi'an Jiaotong University, 17, 62-65+71, 2005	The MHRA has recommended that Rosiglitazone be withdrawn from use due to an association with increased risks of cardiovascular disorders

Chapter 11. Unexplained infertility

Table G.6 What is the effectiveness and safety of ovarian stimulation strategies in women with unexplained infertility?

Bibliographic information	Reason for exclusion
Al-Fozan,H., Al-Khadouri,M., Tan,S.L., Tulandi,T., A randomized trial of letrozole versus clomiphene citrate in women undergoing superovulation, Fertility and Sterility, 82, 1561-1563, 2004	Women received IUI
Annapurna,V., Dhaliwal,L.K., Gopalan,S., Effect of two anti-estrogens, clomiphene citrate and tamoxifen, on cervical mucus and sperm-cervical mucus interaction, International Journal of Fertility and Womens Medicine, 42, 215-218, 1997	Does not report on relevant outcomes
Arcaini,L., Bianchi,S., Baglioni,A., Marchini,M., Tozzi,L., Fedele,L., Superovulation and intrauterine insemination vs. superovulation alone in the treatment of unexplained infertility. A randomized study, Journal of Reproductive Medicine, 41, 614-618, 1996	Comparator not relevant
Athaullah,Nat, Proctor,Michelle, Johnson,Neil, Oral versus injectable ovulation induction agents for unexplained subfertility, Cochrane Database of Systematic Reviews, -, 2009	Some women received IUI. Included studies considered separately for current review
Badawy,A., Baker El,Nashar A., El,Totongy M., Clomiphene citrate plus N-acetyl cysteine versus clomiphene citrate for augmenting ovulation in the management of unexplained infertility: a randomized double-blind controlled trial, Fertility and Sterility, 86, 647-650, 2006	Comparator not relevant
Badawy,A., Elnashar,A., Totongy,M., Clomiphene citrate or aromatase inhibitors combined with gonadotropins for superovulation in women undergoing intrauterine insemination: a prospective randomised trial, Journal of Obstetrics and Gynaecology, 30, 617-621, 2010	30 to 35% of couples had male factor infertility and no subgroup analysis was done for those with unexplained infertility
Badawy,A., Elnashar,A., Totongy,M., Clomiphene citrate or aromatase inhibitors for superovulation in women with unexplained infertility undergoing intrauterine insemination: a prospective randomized trial, Fertility and Sterility, 92, 1355-1359, 2009	Women received IUI
Balasch,J., Balles, JL, Pimentel,C., Creus,M., bregues,F., Vanrell,J.A., Late low-dose pure follicle stimulating hormone for ovarian stimulation in intra-uterine insemination cycles, Human Reproduction, 9, 1863-1866, 1994	Women received IUI
Barroso,G., Menocal,G., Felix,H., Rojas-Ruiz,J.C., Arslan,M., Oehninger,S., Comparison of the efficacy of the aromatase inhibitor letrozole and clomiphene citrate as adjuvants to recombinant follicle-stimulating hormone in controlled ovarian hyperstimulation: a prospective, randomized, blinded clinical trial, Fertility and Sterility, 86, 1428-1431, 2006	Women received IUI
Bedaiwy,M.A., Forman,R., Mousa,N.A., Al Inany,H.G., Casper,R.F., Cost-effectiveness of aromatase inhibitor co-treatment for controlled ovarian stimulation, Human Reproduction, 21, 2838-2844, 2006	Only 40 to 42% of the study group had unexplained infertility and no subgroup analysis was done
Biljan,M.M., Mahutte,N.G., Tulandi,T., Tan,S.L., Prospective randomized double-blind trial of the correlation between time of administration and antiestrogenic effects of clomiphene citrate on reproductive end organs, Fertility and Sterility, 71, 633-638, 1999	Women received IUI. Cross-over trial

Bibliographic information	Reason for exclusion
Centre for Reviews and Dissemination., Treatment of unexplained infertility with aromatase inhibitors or clomiphene citrate: a systematic review and meta-analysis (Structured abstract), Database of Abstracts of Reviews of Effects, -, 2010	Structured abstract - full text retrieved
D'Angelo,D.V., Whitehead,N., Helms,K., Barfield,W., Ahluwalia,I.B., Birth outcomes of intended pregnancies among women who used assisted reproductive technology, ovulation stimulation, or no treatment, Fertility and Sterility, 96, 314-320, 2011	Compares women who received ART, ovulation induction medication, and no treatment
DeVane,G.W., Guzick,D.S., Bromocriptine therapy in normoprolactinemic women with unexplained infertility and galactorrhea, Fertility and Sterility, 46, 1026-1031, 1986	Does not include relevant comparators
Exercise for dysmenorrhoea, Obstetrics and Gynecology, 116, 186-187, 2010	Commentary
Fisch,P., Casper,R.F., Brown,S.E., Wrixon,W., Collins,J.A., Reid,R.L., Simpson,C., Unexplained infertility: evaluation of treatment with clomiphene citrate and human chorionic gonadotropin, Fertility and Sterility, 51, 828-833, 1989	At least 17/155 (11%) of the couples had explained or male factor infertility
Fujii,S., Fukui,A., Fukushi,Y., Kagiya,A., Sato,S., Saito,Y., The effects of clomiphene citrate on normally ovulatory women, Fertility and Sterility, 68, 997-999, 1997	Alternate allocation used. Some women in each group received IUI
Glazener,C.M., Coulson,C., Lambert,P.A., Watt,E.M., Hinton,R.A., Kelly,N.G., Hull,M.G., Clomiphene treatment for women with unexplained infertility: placebo-controlled study of hormonal responses and conception rates, Gynecological Endocrinology, 4, 75-83, 1990	Cross-over trial - unable to separate data for first arm of crossover
Hughes,E., Brown,J., Collins,J.J., Vanderkerchove,P., Clomiphene citrate for unexplained subfertility in women. [22 refs][Update of Cochrane Database Syst Rev. 2000;(3):CD000057; PMID: 10908459], Cochrane Database of Systematic Reviews, CD000057-, 2010	Women received IUI in some of the included studies. Four of the six included studies were cross over trials. The remaining eligible trials were considered separately for the current review
Karlstrom,P.O., Berkurezion,M., Bergh,T., Lundkvist,O., An extended prospective randomized trial of artificial insemination versus intercourse in cycles stimulated with human menopausal gonadotrophins (hMG) or clomiphene citrate (CC), Fertility and Sterility, 70, S420-, 1998	Conference abstract
Martinez,NunezJ, Altagracia,MartinezM, Rios,C., Kravzov,JinichJ, Hinojosa,CruzJ, Vital,ReyesV, Cost-effectiveness study of clomiphene citrate versus anastrozole for inducing ovulation in infertile adult patients in a public hospital, La Raza in Mexico City, Journal of Pharmaceutical Health Services Research, 2, 35-40, 2011	No new relevant data. Not clear if women were randomised to treatment. One group consisted of only 5 women.
Mitwally,M.F., Casper,R.F., Aromatase inhibition reduces gonadotrophin dose required for controlled ovarian stimulation in women with unexplained infertility, Human Reproduction, 18, 1588-1597, 2003	Women received IUI
Mukherjee,S., Sharma,S., Chakravarty,B.N., Comparative evaluation of pregnancy outcome in gonadotrophin-clomiphene combination vs clomiphene alone in polycystic ovarian syndrome and unexplained infertility-A prospective clinical trial, Journal of Human Reproductive Sciences, 3, 80-84, 2010	Both groups received clomifene citrate - not a comparison of interest

Bibliographic information	Reason for exclusion
Nakajima,A.K., Smith,L.L., Wong,B., Scott,J.Z., Cumming,D.C., Tataryn,I.V., Sagle,M.A., McAra,D., Nordstrom,L., A randomized trial of clomiphene citrate plus intrauterine insemination versus recombinant follicle stimulating hormone plus intrauterine insemination for the treatment of unexplained infertility, Fertility and Sterility, 72, S208, 1999-, 1999	Women received IUI
Polyzos,N.P., Tzioras,S., Badawy,A.M., Valachis,A., Dritsas,C., Mauri,D., Aromatase inhibitors for female infertility: a systematic review of the literature. [59 refs], Reproductive Biomedicine Online, 19, 456-471, 2009	Of the ten papers comparing the use of clomiphene citrate, five did not report the number of cycles, two were not randomised controlled trials and one did not report any relevant outcomes. The remaining two studies were considered separately for inclusion in the current review
Polyzos,N.P., Tzioras,S., Mauri,D., Tsappi,M., Cortinovis,I., Tsali,L., Casazza,G., Treatment of unexplained infertility with aromatase inhibitors or clomiphene citrate: a systematic review and meta-analysis. [31 refs], Obstetrical and Gynecological Survey, 63, 472-479, 2008	A more recent review of the same studies was retrieved (Polyzos, 2009)
Reindollar,R.H., Regan,M.M., Neumann,P.J., Levine,B.S., Thornton,K.L., Alper,M.M., Goldman,M.B., A randomized clinical trial to evaluate optimal treatment for unexplained infertility: the fast track and standard treatment (FASTT) trial, Fertility and Sterility, 94, 888-899, 2010	Women received IUI and IVF
Revelli,A., Poso,F., Gennarelli,G., Moffa,F., Grassi,G., Massobrio,M., Recombinant versus highly-purified, urinary follicle-stimulating hormone (r-FSH vs. HP-uFSH) in ovulation induction: a prospective, randomized study with cost-minimization analysis, Reproductive Biology and Endocrinology, 4, 38-, 2006	30% of the included women had polycystic ovary syndrome listed as the cause of their infertility and no subgroup analysis was done for those with unexplained fertility
Sh Tehrani,Nejad E., Abediasl,Z., Rashidi,B.H., Azimi,Nekoo E., Shariat,M., Amirchaghmaghi,E., Comparison of the efficacy of the aromatase inhibitor letrozole and clomiphen citrate gonadotropins in controlled ovarian hyperstimulation: a prospective, simply randomized, clinical trial, Journal of Assisted Reproduction and Genetics, 25, 187-190, 2008	The number of cycles was not reported and so relevant outcomes could not be calculated
Shokeir,T.A., Tamoxifen citrate for women with unexplained infertility, Archives of Gynecology and Obstetrics, 274, 279-283, 2006	Does not include relevant comparators

Chapter 12. Intrauterine insemination

Table G.7 What is the effectiveness of intrauterine insemination (IUI)?

Bibliographic information	Reason for exclusion
Abu,Hashim H., Ombar,O., Abd,Elaal,I, Intrauterine insemination versus timed intercourse with clomiphene citrate in polycystic ovary syndrome: a randomized controlled trial, Acta Obstetricia et Gynecologica Scandinavica, 90, 344-350, 2011	Both had stimulated cycles
Agarwal,S., Mittal,S., A randomised prospective trial of intrauterine insemination versus timed intercourse in superovulated cycles with clomiphene, Indian Journal of Medical Research, 120, 519-522, 2004	Both arms of the study received ovarian stimulation
Arici,A., Byrd,W., Bradshaw,K., Kutteh,W.H., Marshburn,P., Carr,B.R., Evaluation of clomiphene citrate and human chorionic gonadotropin treatment: a prospective, randomized, crossover study during intrauterine insemination cycles, Fertility and Sterility, 61, 314-318, 1994	Cross-over design
Bagis,T., Haydardedeoglu,B., Kilicdag,E.B., Cok,T., Simsek,E., Parlakgumus,A.H., Single versus double intrauterine insemination in multi-follicular ovarian hyperstimulation cycles: A randomized trial, Human Reproduction, 25, 1684-1690, 2010	Not review question
Berard,A., Sheehy,O., Fraser,W., Bissonnette,F., Tan,S.L., Trasler,J., Monnier,P., Use of ovulation stimulation (OS) alone, intrauterine insemination (IUI) and assisted reproductive techniques (ART) and the risk of multiplicity - The TWINPREG Study, Journal of Population Therapeutics and Clinical Pharmacology, 18, e211-e212, 2011	Conference abstract
Bhattacharya,S., Harrild,K., Harold,A., Lyall,H., McQueen,D., Tay,C., A randomised trial of expectant management, clomifene and intrauterine insemination (IUI) in the treatment of infertility, Fertility Sterility Abstract Book, Vol.Q102, pp.S43, 2006., S43, 2006	Conference abstract
Buvat,J., Buvat-Herbaut,M., Marcolin,G., Guittard,C., Herbaut,J.C., Louvet,A.L., Couplet,G., Verbecq,Ph, Dehaene,J.L., Renouard,O., Male subfertility: Randomized comparison of intra-uterine insemination versus timed intercourse after superovulation in the female. 18, 435-438, 1990	Male subfertility
Cantineau,EP Astrid, Cohlen,Ben J., Ovarian stimulation protocols (anti-oestrogens, gonadotrophins with and without GnRH agonists/antagonists) for intrauterine insemination (IUI) in women with subfertility, Cochrane Database of Systematic Reviews, -, 2010	Review - data from individual studies wss included in review.
Centre for Reviews and Dissemination., Comparison of intrauterine insemination with timed intercourse in superovulated cycles with gonadotropins: a meta-analysis (Structured abstract), Database of Abstracts of Reviews of Effects, -, 2010	All patients received COH
Centre for Reviews and Dissemination., Intrauterine insemination versus timed intercourse for cervical hostility in subfertile couples (Brief record), Database of Abstracts of Reviews of Effects, -, 2010	Cervical hostility not included in scope
Centre for Reviews and Dissemination., What is the most valid comparison treatment in trials of intrauterine insemination, timed or uninfluenced intercourse? A systematic review and meta-analysis of indirect evidence (Structured abstract), Database of Abstracts of Reviews of Effects, -, 2010	2 studies in this review were included (Steures et al, 2006; Bhattacharya et al, 2008)

Bibliographic information	Reason for exclusion
Check,J.H., Spirito,P., Higher pregnancy rates following treatment of cervical factor with intrauterine insemination without superovulation versus intercourse: the importance of a well-timed postcoital test for infertility, Archives of Andrology, 35, 71-77, 1995	Mixed intervention: most women in the comparison group received ovarian stimulation
Cohlen,B.J., Vandekerckhove,P., te Velde,E.R., Habbema,J.D., Timed intercourse versus intra-uterine insemination with or without ovarian hyperstimulation for subfertility in men. [17 refs][Update in Cochrane Database Syst Rev. 2007;(3):CD000360; PMID: 17636632], Cochrane Database of Systematic Reviews, CD000360-, 2000	This review has been updated by Cochrane
Comhaire,F.H., El,Garem Y., Mahmoud,A., Eertmans,F., Schoonjans,F., Combined conventional/antioxidant "Astaxanthin" treatment for male infertility: a double blind, randomized trial, Asian Journal of Andrology, 7, 257-262, 2005	Not all patients received IUI
Deaton,J.L., Gibson,M., Blackmer,K.M., Nakajima,S.T., Badger,G.J., Brumsted,J.R., A randomized, controlled trial of clomiphene citrate and intrauterine insemination in couples with unexplained infertility or surgically corrected endometriosis, Fertility and Sterility, 54, 1083-1088, 1990	Not omparisons of interest
Gezginc,K., Gorkemli,H., Celik,C., Karatayli,R., Cicek,M.N., Olakoglu,M.C., Comparison of single versus double intrauterine insemination, Taiwanese Journal of Obstetrics and Gynecology, 47, 57-61, 2008	Question not being reviewed
Glazener,C.M., Coulson,C., Lambert,P.A., Watt,E.M., Hinton,R.A., Kelly,N.J., Hull,M.G., The value of artificial insemination with husband's semen in infertility due to failure of postcoital sperm-mucus penetration--controlled trial of treatment, British Journal of Obstetrics and Gynaecology, 94, 774-778, 1987	Male factor subfertility. Included in Cochrane Review (Helmerhorst, 2010)
Gregoriou,O., Vitoratos,N., Papadias,C., Konidaris,S., Gargaropoulos,A., Louridas,C., Controlled ovarian hyperstimulation with or without intrauterine insemination for the treatment of unexplained infertility, International Journal of Gynaecology and Obstetrics, 48, 55-59, 1995	All patients received ovarian stimulation. Included in Cochrane review Veltman-Verhulst 2010
Gregoriou,O., Vitoratos,N., Papadias,C., Konidaris,S., Gargaropoulos,A., Rizos,D., Pregnancy rates in gonadotrophin stimulated cycles with timed intercourse or intrauterine insemination for the treatment of male subfertility, European Journal of Obstetrics, Gynecology, and Reproductive Biology, 64, 213-216, 1996	Male factor infertility
Helmerhorst,F.M., van Vliet,H.A., Gornas,T., Finken,M.J., Grimes,D.A., Intrauterine insemination versus timed intercourse for cervical hostility in subfertile couples. [44 refs], Obstetrical and Gynecological Survey, 61, 402-414, 2006	Cervical hostility not included in scope
Helmerhorst,Frans M., Van Vliet,AAM Huib, Gornas,Twina, Finken,M.J., Grimes,David A., Intra-uterine insemination versus timed intercourse or expectant management for cervical hostility in subfertile couples, Cochrane Database of Systematic Reviews, -, 2010	Not within scope of guideline
Hughes,E.G., The effectiveness of ovulation induction and intrauterine insemination in the treatment of persistent infertility: a meta-analysis, Human Reproduction, 12, 1865-1872, 1997	only trials with ovarian stimulation included

Bibliographic information	Reason for exclusion
Karlstrom,P.O., Bergh,T., Lundkvist,O., A prospective randomized trial of artificial insemination versus intercourse in cycles stimulated with human menopausal gonadotropin or clomiphene citrate, Fertility and Sterility, 59, 554-559, 1993	All patients received ovulation stimulating agents.
Kosmas,I.P., Tatsioni,A., Fatemi,H.M., Kolibianakis,E.M., Tournaye,H., Devroey,P., Human chorionic gonadotropin administration vs. luteinizing monitoring for intrauterine insemination timing, after administration of clomiphene citrate: a meta-analysis, Fertility and Sterility, 87, 607-612, 2007	Review of timing for IUI
Lewis,V., Queenan,J., Hoeger,K., Stevens,J., Guzick,D.S., Clomiphene citrate monitoring for intrauterine insemination timing: a randomized trial, Fertility and Sterility, 85, 401-406, 2006	All women received clomiphene citrate.
Liu,W., Gong,F., Luo,K., Lu,G., Comparing the pregnancy rates of one versus two intrauterine inseminations (IUIs) in male factor and idiopathic infertility, Journal of Assisted Reproduction and Genetics, 23, 75-79, 2006	Question not being reviewed
Martinez,A.R., Bernardus,R.E., Voorhorst,F.J., Vermeiden,J.P., Schoemaker,J., Intrauterine insemination does and clomiphene citrate does not improve fecundity in couples with infertility due to male or idiopathic factors: a prospective, randomized, controlled study, Fertility and Sterility, 53, 847-853, 1990	Cross over design
Melis,G.B., Paoletti,A.M., Ajossa,S., Guerriero,S., Depau,G.F., Mais,V., Ovulation induction with gonadotropins as sole treatment in infertile couples with open tubes: a randomized prospective comparison between intrauterine insemination and timed vaginal intercourse, Fertility and Sterility, 64, 1088-1093, 1995	Both groups received COH Included in Cochrane review Veltman-Verhulst 2010
Moslemizadeh,N., Moghadam,T.G., Peyvandi,S., Evaluation of vaginal misoprostol effect on pregnancy rate after intrauterine insemination, Pakistan Journal of Biological Sciences, 12, 64-68, 2009	Study does not examine an ovulation stimulating agent of interest
Murdoch,A.P., Harris,M., Mahroo,M., Williams,M., Dunlop,W., Gamete intrafallopian transfer (GIFT) compared with intrauterine insemination in the treatment of unexplained infertility, British Journal of Obstetrics and Gynaecology, 98, 1107-1111, 1991	Not a comparator of interest
Nulsen,J.C., Walsh,S., Dumez,S., Metzger,D.A., A randomized and longitudinal study of human menopausal gonadotropin with intrauterine insemination in the treatment of infertility, Obstetrics and Gynecology, 82, 780-786, 1993	Study is not an RCT - used alternation to allocate to treatment
Ovarian stimulation plus IUI in subfertile couples, ACOG Clinical Review, 12, 4-5, 2007	Review and commentary on an excluded study
Polyzos,N.P., Tzioras,S., Mauri,D., Tatsioni,A., Double versus single intrauterine insemination for unexplained infertility: a meta-analysis of randomized trials, Fertility and Sterility, 94, 1261-1266, 2010	Question not being reviewed
Rahman,S.M., Malhotra,N., Kumar,S., Roy,K.K., Agarwal,A., A randomized controlled trial comparing the effectiveness of single versus double intrauterine insemination in unexplained infertility, Fertility and Sterility, 94, 2913-2915, 2010	Question not being reviewed

Bibliographic information	Reason for exclusion
Snick,H.K., Collins,J.A., Evers,J.L., What is the most valid comparison treatment in trials of intrauterine insemination, timed or uninfluenced intercourse? A systematic review and meta-analysis of indirect evidence. [52 refs], Human Reproduction, 23, 2239-2245, 2008	Not a comparison of interest
Steures,P., Custers,I.M., Rumste,M.M.E., van der Steeg,J.W., Hompes,P.G.A., Renckens,C.N.M., Broekmans,F.J.M., Eijkemans,M.J.C., van,der,V, Mol,B.W.J., Pregnancy chances in couples with unexplained subfertility after initial treatment with IUI or expectant management: a follow up study of 3 years, Human Reproduction.European Society of Human Reproduction and Embryology ESHRE 24th Annual Meeting Barcelona, 6-9 July, 2008 Vol.23 Suppl 1, pp.i25 Abstract No: O-059 Oral, 2008., O-059, 2008	Conference abstract
Steures,P., van der Steeg,J.W., Hompes,P.G., Bossuyt,P.M., Habbema,J.D., Eijkemans,M.J., Schols,W.A., Burggraaff,J.M., van,der,V, Mol,B.W., CECERM (Collaborative Effort for Clinical Evaluation in Reproductive Medicine), Effectiveness of intrauterine insemination in subfertile couples with an isolated cervical factor: a randomized clinical trial, Fertility and Sterility, 88, 1692-1696, 2007	Correspondence
Stewart,J.A., Stimulated intra-uterine insemination is not a natural choice for the treatment of unexplained subfertility, Human Reproduction, 18, 903-907, 2003	Commentary
te Velde,E.R., van Kooy,R.J., Waterreus,J.J., Intrauterine insemination of washed husband's spermatozoa: a controlled study, Fertility and Sterility, 51, 182-185, 1989	Patient group was not unexplained infertility. Included in Cochrane Review (Helmerhorst, 2010)
Tonguc,E., Var,T., Onalan,G., Altinbas,S., Tokmak,A., Karakas,N., Gulerman,C., Comparison of the effectiveness of single versus double intrauterine insemination with three different timing regimens, Fertility and Sterility, 94, 1267-1270, 2010	Question not being reviewed
van Rumste,M.M., Custers,I.M., van,der,V, van,Wely M., Evers,J.L., Mol,B.W., The influence of the number of follicles on pregnancy rates in intrauterine insemination with ovarian stimulation: a meta-analysis. [57 refs], Human Reproduction Update, 14, 563-570, 2008	Review of the influence on follicle number on pregnancy rates in IUI
Verhulst,S.M., Cohlen,B.J., Hughes,E., Te,VeldeE, Heineman,M.J., Intra-uterine insemination for unexplained subfertility, Cochrane Database of Systematic Reviews, #2006. Article Number, -, 2006	Review has been revised with new data in 2010
Wordsworth,S., Buchanan,J., Mollison,J., Harrild,K., Robertson,L., Tay,C., Harrold,A., McQueen,D., Lyall,H., Johnston,L., Burrage,J., Grossett,S., Walton,H., Lynch,J., Johnstone,A., Kini,S., Raja,A., Templeton,A., Bhattacharya,S., Clomifene citrate and intrauterine insemination as first-line treatments for unexplained infertility: Are they cost-effective?, Human Reproduction, 26, 369-375, 2011	Health economics paper
Zeyneloglu,H.B., Arici,A., Olive,D.L., Duleba,A.J., Comparison of intrauterine insemination with timed intercourse in superovulated cycles with gonadotropins: a meta-analysis, Fertility and Sterility, 69, 486-491, 1998	All patients received COH
Zikopoulos,K., West,C.P., Wen,ThongP, Kacser,E.M., Morrison,J., Wu,F.C.W., Homologous intra-uterine insemination has no advantage over timed natural intercourse when used in combination with ovulation induction for the treatment of unexplained infertility, Human Reproduction, 8, 563-567, 1993	Not all patients received IUI

Chapter 14. Access criteria for IVF

Table G.8 How accurate are clinical scoring systems in predicting the outcome of IVF treatment?

Bibliographic information	Reason for exclusion
Bancsi,L.F., Huijs,A.M., den Ouden,C.T., Broekmans,F.J., Looman,C.W., Blankenstein,M.A., te Velde,E.R., Basal follicle-stimulating hormone levels are of limited value in predicting ongoing pregnancy rates after in vitro fertilization, Fertility and Sterility, 73, 552-557, 2000	Included in the systematic review
Banerjee,P., Choi,B., Shahine,L.K., Jun,S.H., O'Leary,K., Lathi,R.B., Westphal,L.M., Wong,W.H., Yao,M.W.M., Deep phenotyping to predict live birth outcomes in in vitro fertilization, Proceedings of the National Academy of Sciences of the United States of America, 107, 13570-13575, 2010	Incorrect patient population as it was predicting the probability of live birth from IVF in women having previous IVF treatment failure
Bouckaert,A., Psalti,I., Loumaye,E., De,Cooman S., Thomas,K., The probability of a successful treatment of infertility by in-vitro fertilization, Human Reproduction, 9, 448-455, 1994	Included as part of the systematic review
Carrera-Rotllan,J., Estrada-Garcia,L., Sarquella-Ventura,J., Prediction of pregnancy in IVF cycles on the fourth day of ovarian stimulation, Journal of Assisted Reproduction and Genetics, 24, 387-394, 2007	Included as part of the systematic review
Coppus,S.F., van,der,V, Opmeer,B.C., Mol,B.W., Bossuyt,P.M., Evaluating prediction models in reproductive medicine, Human Reproduction, 24, 1774-1778, 2009	A discussion paper on the evaluation of prediction models in predictive medicine
Gabbanini,M., Privitera,L., Monzo,A., Higueras,G., Fuster,S., Garrido,N., Bosch,E., Pellicer,A., The use of prediction models of spontaneous pregnancy in in vitro fertilization units reveals differences between the expected results of public and private clinics in Spain, Fertility and Sterility, 94, 2376-2378, 2010	External validation of pre-existing model
Griffiths,A., Dyer,S.M., Lord,S.J., Pardy,C., Fraser,I.S., Eckermann,S., A cost-effectiveness analysis of in-vitro fertilization by maternal age and number of treatment attempts, Human Reproduction, 25, 924-931, 2010	This was an economic evaluation which used a local database to estimate treatment effect by maternal age and number of treatment cycles but it wasn't a prediction model per se
Haan,G., Bernardus,R.E., Hollanders,J.M., Leerentveld,R.A., Prak,F.M., Naaktgeboren,N., Results of IVF from a prospective multicentre study, Human Reproduction, 6, 805-810, 1991	Included as part of the systematic review
Hauzman,E., Fedorcsak,P., Klinga,K., Papp,Z., Rabe,T., Strowitzki,T., Urbancsek,J., Use of serum inhibin A and human chorionic gonadotropin measurements to predict the outcome of in vitro fertilization pregnancies, Fertility and Sterility, 81, 66-72, 2004	Incorrect papulation as this study is looking at predictors after treatment has been given
Holte,J., Berglund,L., Hadziosmanovic,N., Tilly,J., Pettersson,H., Bergh,T., The construction and validation of a prediction model to minimize twin rates at preserved live birth rates in ART, Human Reproduction, 26, i62-, 2011	Conference abstract
Hughes,E.G., King,C., Wood,E.C., A prospective study of prognostic factors in in vitro fertilization and embryo transfer, Fertility and Sterility, 51, 838-844, 1989	Included in the systematic review

Bibliographic information	Reason for exclusion
Hunault,C.C., Eijkemans,M.J., Pieters,M.H., Te Velde,E.R., Habbema,J.D., Fauser,B.C., Macklon,N.S., A prediction model for selecting patients undergoing in vitro fertilization for elective single embryo transfer, Fertility and Sterility, 77, 725-732, 2002	Included as part of the Leushuis systematic review
Hunault,C.C., te Velde,E.R., Weima,S.M., Macklon,N.S., Eijkemans,M.J., Klinkert,E.R., Habbema,J.D., A case study of the applicability of a prediction model for the selection of patients undergoing in vitro fertilization for single embryo transfer in another center, Fertility and Sterility, 87, 1314-1321, 2007	This was the evaluation of a pre-existing prediction model, the results of which are presented in an included systematic review
Lintsen,A.M., Eijkemans,M.J., Hunault,C.C., Bouwmans,C.A., Hakkaart,L., Habbema,J.D., Braat,D.D., Predicting ongoing pregnancy chances after IVF and ICSI: a national prospective study, Human Reproduction, 22, 2455-2462, 2007	Included as part of the systematic review
Maugey-Laulom,B., Commenges-Ducos,M., Jullien,V., Papaxanthos-Roche,A., Scotet,V., Commenges,D., Endometrial vascularity and ongoing pregnancy after IVF, European Journal of Obstetrics, Gynecology, and Reproductive Biology, 104, 137-143, 2002	Women aged 38 and FSH>10 UI/ml were excluded and it was in a population where the decision to treat had been made
Minaretzis,D., Harris,D., Alper,M.M., Mortola,J.F., Berger,M.J., Power,D., Multivariate analysis of factors predictive of successful live births in in vitro fertilization (IVF) suggests strategies to improve IVF outcome, Journal of Assisted Reproduction and Genetics, 15, 365-371, 1998	Included as part of systemetic review
Nayudu,P.L., Gook,D.A., Hepworth,G., Lopata,A., Johnston,W.I., Prediction of outcome in human in vitro fertilization based on follicular and stimulation response variables, Fertility and Sterility,Fertil Steril, 51, 117-125, 1989	Included as part of the systematic review
Ottosen,L.D., Kesmodel,U., Hindkjaer,J., Ingerslev,H.J., Pregnancy prediction models and eSET criteria for IVF patients--do we need more information?, Journal of Assisted Reproduction and Genetics, 24, 29-36, 2007	Included as part of the systematic review
Rausch,Mary E., Legro,Richard S., Barnhart,Huiman X., Schlaff,William D., Carr,Bruce R., Diamond,Michael P., Carson,Sandra A., Steinkampf,Michael P., McGovern,Peter G., Cataldo,Nicholas A., Gosman,Gabriella G., Nestler,John E., Giudice,Linda C., Leppert,Phyllis C., Myers,Evan R., Coutifaris,Christos, for the Reproductive Medicine Network,, Predictors of Pregnancy in Women with Polycystic Ovary Syndrome, Journal of Clinical Endocrinology Metabolism,J Clin Endocrinol Metab, 94, 3458-3466, 2009	Population is too restrictive
Roberts,S.A., Fitzgerald,C.T., Brison,D.R., Modelling the impact of single embryo transfer in a national health service IVF programme, Human Reproduction, 24, 122-131, 2009	This analysis is based on a prediction model previously published in HTA report
Roberts,S.A., McGowan,L., Mark,Hirst W., Vail,A., Rutherford,A., Lieberman,B.A., Brison,D.R., towardSET,Collaboration, Reducing the incidence of twins from IVF treatments: predictive modelling from a retrospective cohort, Human Reproduction, 26, 569-575, 2011	This analysis is based on a prediction model previously published in HTA report
Smeenk,J.M., Stolwijk,A.M., Kremer,J.A., Braat,D.D., External validation of the templeton model for predicting success after IVF, Human Reproduction, 15, 1065-1068, 2000	External validation of a pre-existing model included in the systematic review

Bibliographic information	Reason for exclusion
Stolwijk,A.M., Straatman,H., Zielhuis,G.A., Jansen,C.A., Braat,D.D., van Dop,P.A., Verbeek,A.L., External validation of prognostic models for ongoing pregnancy after in-vitro fertilization, Human Reproduction, 13, 3542-3549, 1998	External validation of existing model included in the systematic review
Stolwijk,A.M., Wetzels,A.M., Braat,D.D., Cumulative probability of achieving an ongoing pregnancy after in-vitro fertilization and intracytoplasmic sperm injection according to a woman's age, subfertility diagnosis and primary or secondary subfertility, Human Reproduction, 15, 203-209, 2000	Included in the systematic review
Stolwijk,A.M., Zielhuis,G.A., Hamilton,C.J., Straatman,H., Hollanders,J.M., Goverde,H.J., van Dop,P.A., Verbeek,A.L., Prognostic models for the probability of achieving an ongoing pregnancy after in-vitro fertilization and the importance of testing their predictive value, Human Reproduction, 11, 2298-2303, 1996	Included as part of the systematic review
Stolwijk,A.M., Zielhuis,G.A., Sauer,M.V., Hamilton,C.J., Paulson,R.J., The impact of the woman's age on the success of standard and donor in vitro fertilization, Fertility and Sterility,Fertil Steril, 67, 702-710, 1997	Study only thought to address the impact of age
Strandell,A., Bergh,C., Lundin,K., Selection of patients suitable for one-embryo transfer may reduce the rate of multiple births by half without impairment of overall birth rates, Human Reproduction, 15, 2520-2525, 2000	Women excluded over 40 years of age
Sunkara,S.K., Rittenberg,V., Raine-Fenning,N., Bhattacharya,S., Zamora,J., Coomarasamy,A., Association between the number of eggs and live birth in IVF treatment: an analysis of 400 135 treatment cycles, Human Reproduction, 26, 1768-1774, 2011	Not a full prediction model. Based on same data as IVFpredict and HTA reports.
Sunkara,S.K., Rittenberg,V., Raine-Fenning,N., Bhattacharya,S., Zamora,J., Coomarasamy,A., Nomogram for predicting live birth from egg number: An analysis of 400,135 IVF cycles, Human Reproduction, 26, i34-, 2011	Conference abstract
van Loendersloot,L.L., van,Wely M., Repping,S., van,der,V, Bossuyt,P.M., Templeton prediction model underestimates IVF success in an external validation, Reproductive Biomedicine Online, 22, 597-602, 2011	Templeton model already included
van Weert,J.M., Repping,S., van der Steeg,J.W., Steures,P., van,der,V, Mol,B.W., A prediction model for ongoing pregnancy after in vitro fertilization in couples with male subfertility, Journal of Reproductive Medicine, 53, 250-256, 2008	Included in the systematic review
van,derSteegJ, Steures,P., Eijkemans,M.J.C., Habbema,J.D.F., Bossuyt,P.M.M., Hompes,P.G.A., van,derVeenF, Mol,B.W.J., Do clinical prediction models improve concordance of treatment decisions in reproductive medicine?, BJOG: An International Journal of Obstetrics and Gynaecology, 113, 825-831, 2006	This is a study to see whether prediction models can improve concordance in decision making
Verberg,M.F., Eijkemans,M.J., Macklon,N.S., Heijnen,E.M., Fauser,B.C., Broekmans,F.J., Predictors of ongoing pregnancy after single-embryo transfer following mild ovarian stimulation for IVF, Fertility and Sterility, 89, 1159-1165, 2008	Study was restricted to women aged under 38 years of age
Wang,Y.A., Healy,D., Black,D., Sullivan,E.A., Age-specific success rate for women undertaking their first assisted reproduction technology treatment using their own oocytes in Australia, 2002-2005, Human Reproduction, 23, 1633-1638, 2008	This study assesses the success rate of ART with increasing maternal age but is not a prediction model

Chapter 15. Procedures used during in vitro fertilisation treatment

IVF pre-treatment

Table G.9 What is the effectiveness of pre-treatment as part of an ovarian stimulation strategy for women undergoing IVF or ICSI treatment?

Bibliographic information	Reason for exclusion
Agostini,F., Monti,F., De,PascalisL, Paterlini,M., La,SalaG, Blickstein,I., Psychosocial support for infertile couples during assisted reproductive technology treatment, Fertility and Sterility, 95, 707-710, 2011	Compared men's and women's perceived psychosocial support during IVF - not a comparison of interest
Biljan,M.M., Mahutte,N.G., Dean,N., Hemmings,R., Bissonnette,F., Tan,S.L., Effects of pretreatment with an oral contraceptive on the time required to achieve pituitary suppression with gonadotropin-releasing hormone analogues and on subsequent implantation and pregnancy rates, Fertility and Sterility, 70, 1063-1069, 1998	Clinical pregnancy only reported per cycle. No other outcomes of interest reported
Blockeel,C., Riva,A., De,Vos M., Haentjens,P., Devroey,P., Administration of a gonadotropin-releasing hormone antagonist during the 3 days before the initiation of the in vitro fertilization/intracytoplasmic sperm injection treatment cycle: impact on ovarian stimulation. A pilot study, Fertility and Sterility, 95, 1714-1719, 2011	It is not clear which drugs each group received.
Cedrin-Durnerin,I., Bstandig,B., Parneix,I., Bied-Damon,V., Avril,C., Decanter,C., Hugues,J.N., Effects of oral contraceptive, synthetic progestogen or natural estrogen pre-treatments on the hormonal profile and the antral follicle cohort before GnRH antagonist protocol, Human Reproduction, 22, 109-116, 2007	Included in Smulders (2010) Cochrane review
Cedrin-Durnerin,I., Bulwa,S., Herv,F., Martin-Pont,B., Uzan,M., Hugues,J.N., The hormonal flare-up following gonadotrophin-releasing hormone agonist administration is influenced by a progestogen pretreatment, Human Reproduction, 11, 1859-1863, 1996	21 women received treatment in both groups and it was not possible to separate the data by first treatment (partial cross over trial)
Cedrin-Durnerin,I., Guivarch,A., Hugues,J.N., Bstandig,B., Parneix,I., Vasseur,C., Dubourdieu,S., Colombel,A., Pretreatment with estrogen does not affect in vitro fertilization cycle outcomes in gonadotropin releasing hormone antagonist protocols, Human Reproduction, 26, i47-, 2011	Conference abstract
Centre for Reviews and Dissemination., Oral contraceptive pretreatment significantly reduces ongoing pregnancy likelihood in gonadotropin-releasing hormone antagonist cycles: an updated meta-analysis (Provisional abstract), Database of Abstracts of Reviews of Effects, -, 2011	Abstract
Dirckx,K., Cabri,P., Merien,A., Galajdova,L., Gerris,J., Dhont,M., De,SutterP, Does low-dose aspirin improve pregnancy rate in IVF/ICSI? A randomized double-blind placebo controlled trial, Human Reproduction, 24, 856-860, 2009	Both groups received pre-treatment with an oral contraceptive
Ditkoff,E.C., Sauer,M.V., A combination of norethindrone acetate and leuprolide acetate blocks the gonadotrophin-releasing hormone agonistic response and minimizes cyst formation during ovarian stimulation, Human Reproduction, 11, 1035-1037, 1996	Included in Smulders (2010) Cochrane review

Bibliographic information	Reason for exclusion
Duvan,C.I., Ozmen,B., Satiroglu,H., Atabekoglu,C.S., Berker,B., Does addition of low-dose aspirin and/or steroid as a standard treatment in nonselected intracytoplasmic sperm injection cycles improve in vitro fertilization success? A randomized, prospective, placebo-controlled study, Journal of Assisted Reproduction and Genetics, 23, 15-21, 2006	No pre-treatment was used in this study
Engmann,L., Maconochie,N., Bekir,J., Tan,S.L., Progestogen therapy during pituitary desensitization with gonadotropin-releasing hormone agonist prevents functional ovarian cyst formation: a prospective, randomized study3086, American Journal of Obstetrics and Gynecology, 181, 576-582, 1999	Included in Smulders (2010) Cochrane review
Fanchin,R., Salomon,L., Castelo-Branco,A., Olivennes,F., Frydman,N., Frydman,R., Luteal estradiol pre-treatment coordinates follicular growth during controlled ovarian hyperstimulation with GnRH antagonists, Human Reproduction, 18, 2698-2703, 2003	Included in Smulders (2010) Cochrane review
Fedorcsak P., Dale,P.O., Storeng,R., Abyholm,T., Tanbo,T., The effect of metformin on ovarian stimulation and in vitro fertilization in insulin-resistant women with polycystic ovary syndrome: an open-label randomized cross-over trial, Gynecological Endocrinology, 17, 207-214, 2003	Not a relevant intervention
Franco Jr,J.G., Baruffi,R.L.R., Petersen,C.G., Mauri,A.L., Felipe,V., Contart,P., Comparison of Ovarian Stimulation with Recombinant FSH After 2 nd Phase Protocols with GnRH Analogs (I - estradiol + Ganirelix Versus II - Nafarelin)7482, Jornal Brasileiro de Reproducao Assistida, 7, 26-32, 2003	Included in Smulders (2010) Cochrane review
Garcia-Velasco,J.A., Bermejo,A., Ruiz-Flores,F., Martinez-Salazar,J., Requena,A., Pellicer,A., Fertility and Sterility, Fertility and Sterility, #2010 Denver, CO United States. Conference Start, S28-, 2010	Conference abstract
Griesinger,G., Venetis,C.A., Marx,T., Diedrich,K., Tarlatzis,B.C., Kolibianakis,E.M., Oral contraceptive pill pretreatment in ovarian stimulation with GnRH antagonists for IVF: a systematic review and meta-analysis, Fertility and Sterility, 90, 1055-1063, 2008	All studies included in the systematic review are included in a more recent Cochrane review (Smulders, 2010)
Guivarch,LevequeA, Homer,L., Broux,P.L., Moy,L., Priou,G., Vialard,J., Colleu,D., Arvis,P., Dewailly,D., Programming IVF retrievals during working days after a GnRH antagonist protocol with estrogen pre-treatment: Does the length of exposure to estradiol impact on COH outcomes?, Human Reproduction, 26, i316-, 2011	Conference abstract
Guivarc'h-Leveque,A., Homer,L., Arvis,P., Broux,P.L., Moy,L., Priou,G., Vialard,J., Colleu,D., Dewailly,D., Programming in vitro fertilization retrievals during working days after a gonadotropin-releasing hormone antagonist protocol with estrogen pretreatment: does the length of exposure to estradiol impact on controlled ovarian hyperstimulation outcomes?, Fertility and Sterility, 96, 872-876, 2011	Compared duration of pre-treatment - not a comparison of interest
Guivarc'h-Leveque,A., Homer,L., Arvis,P., Broux,P.L., Moy,L., Priou,G., Vialard,J., Colleu,D., Dewailly,D., Programming in vitro fertilization retrievals during working days after a gonadotropin-releasing hormone antagonist protocol with estrogen pretreatment: does the length of exposure to estradiol impact on controlled ovarian hyperstimulation outcomes?, Fertility and Sterility, 96, 872-876, 2011	Women were not randomised into treatment groups

Bibliographic information	Reason for exclusion
Hirohama,J., Jinno,M., Watanabe,A., Eguchi,N., Hatakeyama,N., Human Reproduction, Human Reproduction, 26th Annual Meeting of the European Society of Human Reproduction and Embryology, ESHRE Rome Italy. Conference Start, i291-, 2010	Conference abstract
Homburg,R., Levy,T., Ben-Rafael,Z., A comparative prospective study of conventional regimen with chronic low- dose administration of follicle-stimulating hormone for anovulation associated with polycystic ovary syndrome, Fertility and Sterility, 63, 729-733, 1995	Women were not randomised to treatment groups
Huirne,J.A., Hugues,J.N., Pirard,C., Fischl,F., Sage,J.C., Pouly,J.L., Obruca,A., Braat,D.M., van Loenen,A.C., Lambalk,C.B., Cetrorelix in an oral contraceptive-pretreated stimulation cycle compared with buserelin in IVF/ICSI patients treated with r-hFSH: a randomized, multicentre, phase IIIb study, Human Reproduction, 21, 1408-1415, 2006	Included in Smulders (2010) Cochrane review
Huirne,J.A., van Loenen,A.C., Donnez,J., Pirard,C., Homburg,R., Schats,R., McDonnell,J., Lambalk,C.B., Effect of an oral contraceptive pill on follicular development in IVF/ICSI patients receiving a GnRH antagonist: a randomized study, Reproductive Biomedicine Online, 13, 235-245, 2006	Included in Smulders (2010) Cochrane review
Hwang,J.L., Seow,K.M., Lin,Y.H., Huang,L.W., Hsieh,B.C., Tsai,Y.L., Wu,G.J., Huang,S.C., Chen,C.Y., Chen,P.H., Tzeng,C.R., Ovarian stimulation by concomitant administration of cetrorelix acetate and HMG following Diane-35 pre-treatment for patients with polycystic ovary syndrome: a prospective randomized study, Human Reproduction, 19, 1993-2000, 2004	Included in Smulders (2010) Cochrane review
Jung,H., Roh,H.K., The effects of E2 supplementation from the early proliferative phase to the late secretory phase of the endometrium in hMG-stimulated IVF-ET, Journal of Assisted Reproduction and Genetics, 17, 28-33, 2000	Not a pre-treatment study
Kim,C.H., Howles,C.M., Lee,H.A., The effect of transdermal testosterone gel pretreatment on controlled ovarian stimulation and IVF outcome in low responders, Fertility and Sterility, 95, 679-683, 2011	All women received estrogen and progesterone
Kjotrod,S.B., von,During,V, Carlsen,S.M., Metformin treatment before IVF/ICSI in women with polycystic ovary syndrome; a prospective, randomized, double blind study, Human Reproduction, 19, 1315-1322, 2004	Both groups received progesterone pre-treatment
Liu,K.E., Alhajri,M., Greenblatt,E., A randomized controlled trial of NuvaRing versus combined oral contraceptive pills for pretreatment in in vitro fertilization cycles, Fertility and Sterility, 96, 605-608, 2011	Not a comparison of interest
Mashiach,S., Dor,J., Goldenberg,M., Shalev,J., Blankstein,J., Rudak,E., Shoam,Z., Finelt,Z., Nebel,L., Goldman,B., Protocols for induction of ovulation. The concept of programmed cycles, Annals of the New York Academy of Sciences, 541, 37-45, 1988	Unclear how many women were included in the denominator. Unclear how randomisation was performed. Unclear how the control group was chosen. Unclear how many women received GnRH analogue
Meldrum,D.R., Patient preparation and standard stimulation regimens using gonadotropin-releasing hormone agonists, Clinical Obstetrics and Gynecology, 49, 4-11, 2006	Narrative review

Bibliographic information	Reason for exclusion
Moini,A., Zafarani,F., Haddadian,S., Ahmadi,J., Honar,H., Riazi,K., Effect of low-dose aspirin therapy on implantation rate in women undergoing in-vitro fertilization cycles, Saudi Medical Journal, 28, 732-736, 2007	Not a relevant intervention
Muriana,A., Bucolo,A., Scollo,P., Prevention of premature LH surge during ovulation induction in polycystic ovarian syndrome: A randomized, comparative study between oral contraceptive/short term GnRH-analogue and depot GnRH-analogue protocols, Italian Journal of Gynaecology and Obstetrics, 11, 52-56, 1999	Not clear if women received IVF or ICSI. Method of randomisation was not reported
Myers,E.R., McCrory,D.C., Mills,A.A., Price,T.M., Swamy,G.K., Tantibhedhyangkul,J., Wu,J.M., Matchar,D.B., Effectiveness of assisted reproductive technology (ART), Evidence report/technology assessment, 1-195),;#2008. Date of Publication, -195, 2008	Review with no meta-analysis
Orvieto,R., Meltcer,S., Liberty,G., Rabinson,J., Anteby,E.Y., Nahum,R., A combined approach to patients with repeated IVF failures, Fertility and Sterility, 94, 2462-2464, 2010	Not clear if the study was randomised. Not clear if both groups received pre-treatment. Not clear if this is a cross-over trial
Pakkila,M., Rasanen,J., Heinonen,S., Tinkanen,H., Tuomivaara,L., Makikallio,K., Hippelainen,M., Tapanainen,J.S., Martikainen,H., Low-dose aspirin does not improve ovarian responsiveness or pregnancy rate in IVF and ICSI patients: a randomized, placebo-controlled double-blind study, Human Reproduction, 20, 2211-2214, 2005	Aspirin or placebo given on the first day of gonadotrophin stimulation (ie not a pre-treatment)
Porrati,L., Vilela,M., Viglierchio,M.I., Valcarcel,A., Lombardi,E., Marconi,G., Oral contraceptive pretreatment achieves better pregnancy rates in IVF antagonists GnRH flexible protocols: A prospective randomized study, Human Reproduction, 25 suppl 1, i102-i259, 2010	Abstract
Raoofi,Z., Aflatoonian,A., Ovarian cysts formation during depot formulation of GnRH-a therapy and the effect of pretreatment with oral contraceptive pills on subsequent implantation and pregnancy rate in ART cycles9700, Iranian Journal of Pharmaceutical Research, 7, 109-113, 2008	Included in Smulders (2010) Cochrane review
Rombauts,L., Healy,D., Norman,R.J., Orgalutran Scheduling Study Group., A comparative randomized trial to assess the impact of oral contraceptive pretreatment on follicular growth and hormone profiles in GnRH antagonist-treated patients.[Erratum appears in Hum Reprod. 2006 Nov;21(11):3032], Human Reproduction, 21, 95-103, 2006	Included in Smulders (2010) Cochrane review
Shaker,A.G., Pittrof,R., Zaidi,J., Bekir,J., Kyei-Mensah,A., Tan,S.L., Administration of progestogens to hasten pituitary desensitization after the use of gonadotropin-releasing hormone agonist in in vitro fertilization--a prospective randomized study, Fertility and Sterility, 64, 791-795, 1995	Included in Smulders (2010) Cochrane review
Tartagni,M., Damiani,G.R., Di,Naro E., Persiani,P., Crescini,C., Loverro,G., Pregnancy in a woman with premature ovarian insufficiency undergoing intracytoplasmic sperm injection after pretreatment with estrogens followed by therapy with estrogens associated with ovarian stimulation with gonadotropins: remarks about oocyte and embryo quality, Menopause, 18, 932-934, 2011	Not a comparative study. Case report.

Bibliographic information	Reason for exclusion
van,Loenen A., Huirne,J., Schats,R., Donnez,J., Lambalk,C., An open-label multicentre, randomized, parallel, controlled phase II study to assess the feasibility of a new programming regimen using an oral contraceptive prior to the administration of recombinant FSH and a GnRH-antagonist in patients undergoing ART (IVF-ICSI) treatment, Human Reproduction, 17, 144-145, 2001	Conference abstract. Included in Smulders (2010) Cochrane review

IVF down regulation

Table G.10 What is the effectiveness of down regulation as part of an ovarian stimulation strategy for women undergoing IVF or ICSI treatment?

Bibliographic information	Reason for exclusion
Acharya,U., Irvine,S., Hamilton,M., Templeton,A., Prospective study of short and ultrashort regimens of gonadotropin-releasing hormone agonist in an in vitro fertilization program, Fertility and Sterility, 58, 1169-1173, 1992	Included in Maheshwari Cochrane review
Agostini,F., Monti,F., De,PascalisL, Paterlini,M., La,SalaG, Blickstein,I., Psychosocial support for infertile couples during assisted reproductive technology treatment, Fertility and Sterility, 95, 707-710, 2011	Compared men's and women's perceived psychosocial support during IVF - not a comparison of interest
Albano,C., Felberbaum,R.E., Smitz,J., ller-Winzen,H., Engel,J., Diedrich,K., Devroey,P., Ovarian stimulation with HMG: results of a prospective randomized phase III European study comparing the luteinizing hormone-releasing hormone (LHRH)-antagonist cetrorelix and the LHRH-agonist buserelin. European Cetrorelix Study Group, Human Reproduction, 15, 526-531, 2000	Included in Al-Inany (2011) Cochrane review
Aletebi,F., Comparing gonadotrophin-releasing hormone agonists or gonadotrophin - releasing hormone antagonists in poor responder in IVF, Middle East Fertility Society Journal, 12, 123-127, 2007	Not a randomised study
Al-Inany,H., Aboulghar,M., GnRH antagonist in assisted reproduction: A Cochrane review, Human Reproduction, 17, 874-885, 2002	A more recent Cochrane review is available (Al-Inany, 2011)
Al-Inany,H.G., bou-Setta,A.M., Aboulghar,M., Gonadotrophin-releasing hormone antagonists for assisted conception: A Cochrane review, Reproductive Biomedicine Online, 14, -, 2007	More recent Cochrane review available (Al-Inany, 2011)
Al-Inany,H.G., Youssef,M.A.F.M., Aboulghar,M., Broekmans,F., Sterrenburg,M., Smit,J., bou-Setta,A.M., GnRH antagonists are safer than agonists: An update of a Cochrane review, Human Reproduction Update, 17, 435-August, 2011	Summary of a Cochrane review that is already included (Al-Inany, 2011)
Al-Inany,Hesham G., bou-Setta,Ahmed M., Aboulghar,Mohamed, Gonadotrophin-releasing hormone antagonists for assisted conception, Cochrane Database of Systematic Reviews, -, 2009	More recent Cochrane review available (Al-Inany, 2011)
Baart,E.B., Martini,E., Eijkemans,M.J., Van,Opstal D., Beckers,N.G., Verhoeff,A., Macklon,N.S., Fauser,B.C., Milder ovarian stimulation for in-vitro fertilization reduces aneuploidy in the human preimplantation embryo: a randomized controlled trial, Human Reproduction, 22, 980-988, 2007	Included in Al-Inany (2011) Cochrane review

Bibliographic information	Reason for exclusion
Barmat,L.I., Chantilis,S.J., Hurst,B.S., Dickey,R.P., A randomized prospective trial comparing gonadotropin-releasing hormone (GnRH) antagonist/recombinant follicle-stimulating hormone (rFSH) versus GnRH-agonist/rFSH in women pretreated with oral contraceptives before in vitro fertilization, Fertility and Sterility, 83, 321-330, 2005	Included in Al-Inany (2011) Cochrane review
Beckers,N.G., Laven,J.S., Eijkemans,M.J., Fauser,B.C., Follicular and luteal phase characteristics following early cessation of gonadotrophin-releasing hormone agonist during ovarian stimulation for in-vitro fertilization, Human Reproduction, 15, 43-49, 2000	No outcomes of interest reported (only reported pregnancy was biochemical pregnancy)
Bloch,M., Azem,F., Aharonov,I., Ben,Avi,I, Yagil,Y., Schreiber,S., Amit,A., Weizman,A., GnRH-agonist induced depressive and anxiety symptoms during in vitro fertilization-embryo transfer cycles, Fertility and Sterility, 95, 307-309, 2011	Uneven groups. Poor reporting of methodology used. Inappropriate length of follow up for reported outcomes. Comparisons are mostly irrelevant (comparing depression at different stages of the IVF process). Not clear if women who did not complete treatment are included in the final results.
Blockeel,C., Riva,A., De,Vos M., Haentjens,P., Devroey,P., Administration of a gonadotropin-releasing hormone antagonist during the 3 days before the initiation of the in vitro fertilization/intracytoplasmic sperm injection treatment cycle: impact on ovarian stimulation. A pilot study, Fertility and Sterility, 95, 1714-1719, 2011	Not a comparison of interest - compares outcomes in women with different progesterone levels
Blockeel,C., Sterrenburg,M.D., Broekmans,F.J., Eijkemans,M.J., Smitz,J., Devroey,P., Fauser,B.C., Follicular phase endocrine characteristics during ovarian stimulation and GnRH antagonist cotreatment for IVF: RCT comparing recFSH initiated on cycle day 2 or 5, Journal of Clinical Endocrinology and Metabolism, 96, 1122-1128, 2011	Not a comparison of interest
Bodri,D., Sunkara,S.K., Coomarasamy,A., Gonadotropin-releasing hormone agonists versus antagonists for controlled ovarian hyperstimulation in oocyte donors: a systematic review and meta-analysis, Fertility and Sterility, 95, 164-169, 2011	A Cochrane review answering the same question but with a more relevant population (ie not oocyte donors/recipients) has been included in the current review
Borm,G., Mannaerts,B., Treatment with the gonadotrophin-releasing hormone antagonist ganirelix in women undergoing ovarian stimulation with recombinant follicle stimulating hormone is effective, safe and convenient: results of a controlled, randomized, multicentre trial. The European Orgalutran Study Group.[Erratum appears in Hum Reprod 2000 Aug;15(8):1877], Human Reproduction, 15, 1490-1498, 2000	Included in Al-Inany (2011) Cochrane review
Check,M.L., Check,J.H., Choel,J.K., Davies,E., Kiefer,D., Effect of antagonists vs agonists on in vitro fertilization outcome, Clinical and Experimental Obstetrics and Gynecology, 31, 257-259, 2004	Included in Al-Inany (2011) Cochrane review
Cheung,L.P., Lam,P.M., Lok,I.H., Chiu,T.T., Yeung,S.Y., Tjer,C.C., Haines,C.J., GnRH antagonist versus long GnRH agonist protocol in poor responders undergoing IVF: a randomized controlled trial, Human Reproduction, 20, 616-621, 2005	Included in Al-Inany (2011) Cochrane review

Bibliographic information	Reason for exclusion
D'Amato,G., Caroppo,E., Pasquadibisceglie,A., Carone,D., Vitti,A., Vizziello,G.M., A novel protocol of ovulation induction with delayed gonadotropin-releasing hormone antagonist administration combined with high-dose recombinant follicle-stimulating hormone and clomiphene citrate for poor responders and women over 35 years1977, Fertility and Sterility, 81, 1572-1577, 2004	Method of randomisation inadequate (based on day of first presentation at clinic)
Daya,S., Gonadotropin releasing hormone agonist protocols for pituitary desensitization in in vitro fertilization and gamete intrafallopian transfer cycles, Cochrane database of systematic reviews (Online), #2000. Date of Publication, CD001299-, 2000	Withdrawn by the Cochrane library as it has not been updated since 1998
Depalo,R., Lorusso,F., Palmisano,M., Bassi,E., Totaro,I., Vacca,M., Trerotoli,P., Masciandaro,P., Selvaggi,L., Follicular growth and oocyte maturation in GnRH agonist and antagonist protocols for in vitro fertilisation and embryo transfer, Gynecological Endocrinology, 25, 328-334, 2009	Included in Al-Inany (2011) Cochrane review
Engmann,L., DiLuigi,A., Schmidt,D., Nulsen,J., Maier,D., Benadiva,C., The use of gonadotropin-releasing hormone (GnRH) agonist to induce oocyte maturation after cotreatment with GnRH antagonist in high-risk patients undergoing in vitro fertilization prevents the risk of ovarian hyperstimulation syndrome: a prospective randomized controlled study, Fertility and Sterility, 89, 84-91, 2008	Included in Al-Inany (2011) Cochrane review
European and Middle East Orgalutran Study Group., Comparable clinical outcome using the GnRH antagonist ganirelix or a long protocol of the GnRH agonist triptorelin for the prevention of premature LH surges in women undergoing ovarian stimulation2750, Human Reproduction, 16, 644-651, 2001	Included in Al-Inany (2011) Cochrane review
Firouzabadi,R.D., Ahmadi,S., Oskouian,H., Davar,R., Comparing GnRH agonist long protocol and gnrh antagonist protocol in outcome the first cycle of ART, Archives of Gynecology and Obstetrics, 281, 81-85, 2010	Included in Al-Inany (2011) Cochrane review
Fluker,M., Grifo,J., Leader,A., Levy,M., Meldrum,D., Muasher,S.J., Rinehart,J., Rosenwaks,Z., Scott,R.T.,Jr., Schoolcraft,W., Shapiro,D.B., North American Ganirelix Study Group., Efficacy and safety of ganirelix acetate versus leuprolide acetate in women undergoing controlled ovarian hyperstimulation, Fertility and Sterility, 75, 38-45, 2001	Included in Al-Inany (2011) Cochrane review
Franco Jr,J.G., Baruffi,R.L.R., Petersen,C.G., Mauri,A.L., Felipe,V., Contart,P., Comparison of Ovarian Stimulation with Recombinant FSH After 2 nd Phase Protocols with GnRH Analogs (I - estradiol + Ganirelix Versus II - Nafarelin)7482, Jornal Brasileiro de Reproducao Assistida, 7, 26-32, 2003	Included in Al-Inany (2011) Cochrane review
Franco,J.G.,Jr., Baruffi,R.L., Mauri,A.L., Petersen,C.G., Felipe,V., Cornicelli,J., Cavagna,M., Oliveira,J.B., GnRH agonist versus GnRH antagonist in poor ovarian responders: a meta-analysis, Reproductive Biomedicine Online, 13, 618-627, 2006	Clinical pregnancy was not reported per woman randomised. No other outcomes of interest were reported. Individual studies were considered separately for inclusion in the current review
Friedler,S., Gilboa,S., Schachter,M., Raziel,A., Strassburger,D., Ron,El R., Luteal phase characteristics following GnRH antagonist or agonist treatment - a comparative study, Reproductive Biomedicine Online, 12, 27-32, 2006	Included in Al-Inany (2011) Cochrane review

Bibliographic information	Reason for exclusion
Gilliam,M.L., Gonadotrophin-releasing hormone antagonists for assisted reproductive technology, Obstetrics and Gynecology, 118, 706-707, 2011	Abstract - full paper considered for inclusion
Heijnen,E.M., Eijkemans,M.J., de,Klerk C., Polinder,S., Beckers,N.G., Klinkert,E.R., Broekmans,F.J., Passchier,J., te Velde,E.R., Macklon,N.S., Fauser,B.C., A mild treatment strategy for in-vitro fertilisation: a randomised non-inferiority trial.[Reprint in Ned Tijdschr Geneeskd. 2008 Apr 5;152(14):809-16; PMID: 18491824], Lancet, 369, 743-749, 2007	Included in Al-Inany (2011) Cochrane review
Hohmann,F.P., Macklon,N.S., Fauser,B.C., A randomized comparison of two ovarian stimulation protocols with gonadotropin-releasing hormone (GnRH) antagonist cotreatment for in vitro fertilization commencing recombinant follicle-stimulating hormone on cycle day 2 or 5 with the standard long GnRH agonist protocol, Journal of Clinical Endocrinology and Metabolism, 88, 166-173, 2003	Included in Al-Inany (2011) Cochrane review
Homburg,R., Levy,T., Ben-Rafael,Z., A comparative prospective study of conventional regimen with chronic low- dose administration of follicle-stimulating hormone for anovulation associated with polycystic ovary syndrome, Fertility and Sterility, 63, 729-733, 1995	Women were not randomised to treatment groups
Hughes,E.G., Fedorkow,D.M., Daya,S., Sagle,M.A., Van de,Koppel P., Collins,J.A., The routine use of gonadotropin-releasing hormone agonists prior to in vitro fertilization and gamete intrafallopian transfer: a meta-analysis of randomized controlled trials, Fertility and Sterility, 58, 888-896, 1992	Of the included studies, 4 studies were quasi-randomised and another 4 studies did not clearly report the method of randomisation used. Only two studies were truly randomised. These were assessed individually to be included in the current review (Polson, 1991 and Antoine, 1990)
Hughes,Edward, Collins,John, Vandekerckhove,Patrick, Gonadotrophin-releasing hormone analogue as an adjunct to gonadotropin therapy for clomiphene-resistant polycystic ovarian syndrome, Cochrane Database of Systematic Reviews, -, 2009	This review has been withdrawn by the Cochrane library
Huirne,J.A., van Loenen,A.C., Donnez,J., Pirard,C., Homburg,R., Schats,R., McDonnell,J., Lambalk,C.B., Effect of an oral contraceptive pill on follicular development in IVF/ICSI patients receiving a GnRH antagonist: a randomized study, Reproductive Biomedicine Online, 13, 235-245, 2006	Included in Al-Inany (2011) Cochrane review
Hwang,J.L., Seow,K.M., Lin,Y.H., Huang,L.W., Hsieh,B.C., Tsai,Y.L., Wu,G.J., Huang,S.C., Chen,C.Y., Chen,P.H., Tzeng,C.R., Ovarian stimulation by concomitant administration of cetrorelix acetate and HMG following Diane-35 pre-treatment for patients with polycystic ovary syndrome: a prospective randomized study, Human Reproduction, 19, 1993-2000, 2004	Included in Al-Inany (2011) Cochrane review
Inza,R., Van,Thillo G., Lombardi,E., Bisioli,C., Diradourian,M., Kenny,A., Reproductive performance in second IVF cycles treated with the use of either GnRH anatgonists (-antag) vs GnRH agonists (-ag) after failure with long protocols with GnRH agonists: a prospective randomized trial, Fertility and Sterility, Vol.82 Suppl 2, pp.S233-234, 2004., -234, 2004	Included in Al-Inany (2011) Cochrane review
Karimzadeh,M.A., Ahmadi,S., Oskouian,H., Rahmani,E., Comparison of mild stimulation and conventional stimulation in ART outcome, Archives of Gynecology and Obstetrics, 281, 741-746, 2010	Included in Al-Inany (2011) Cochrane review

Bibliographic information	Reason for exclusion
Kim,C.H., Jeon,G.H., Cheon,Y.P., Jeon,I., Kim,S.H., Chae,H.D., Kang,B.M., Comparison of GnRH antagonist protocol with or without oral contraceptive pill pretreatment and GnRH agonist low-dose long protocol in low responders undergoing IVF/intracytoplasmic sperm injection, Fertility and Sterility, 92, 1758-1760, 2009	Included in Al-Inany (2011) Cochrane review
Koichi,K., Yukiko,N., Shima,K., Sachiko,S., Efficacy of low-dose human chorionic gonadotropin (hCG) in a GnRH antagonist protocol, Journal of Assisted Reproduction and Genetics, 23, 223-228, 2006	It is not clear if this is an IVF/ICSI study or whether IUI was also performed
Kumbak,B., Akbas,H., Sahin,L., Karlikaya,G., Karagozoglu,H., Kahraman,S., Ovarian stimulation in women with high and low body mass index: GnRH agonist versus GnRH antagonist, Reproductive Biomedicine Online, 20, 314-319, 2010	Retrospective study
Kumbak,B., Akbas,H., Sahin,L., Karlikaya,G., Karagozoglu,H., Kahraman,S., Ovarian stimulation in women with high and low body mass index: GnRH agonist versus GnRH antagonist, Reproductive Biomedicine Online, 20, 314-319, 2010	Retrospective study
Kurzawa,R., Ciepiela,P., Baczkowski,T., Safranow,K., Brelik,P., Comparison of embryological and clinical outcome in GnRH antagonist vs. GnRH agonist protocols for in vitro fertilization in PCOS non-obese patients. A prospective randomized study, Journal of Assisted Reproduction and Genetics, 25, 365-374, 2008	Included in Al-Inany (2011) Cochrane review
Kyono,K., Fuchinoue,K., Nakajo,Y., Yagi,A., Sasaki,K., A prospective randomized study of three ovulation induction protocols for IVF: GnRH agonist versus antagonist with and without low dose hCG, Fertility and Sterility, Vol.82 Suppl 2, pp.S31, 2004., -, None	Included in Al-Inany (2011) Cochrane review
Lainas,T.G., Petsas,G.K., Zorzovilis,I.Z., Iliadis,G.S., Lainas,G.T., Cazlaris,H.E., Kolibianakis,E.M., Initiation of GnRH antagonist on Day 1 of stimulation as compared to the long agonist protocol in PCOS patients. A randomized controlled trial: effect on hormonal levels and follicular development, Human Reproduction, 22, 1540-1546, 2007	Included in Al-Inany (2011) Cochrane review
Lainas,T.G., Sfontouris,I.A., Zorzovilis,I.Z., Petsas,G.K., Lainas,G.T., Alexopoulou,E., Kolibianakis,E.M., Flexible GnRH antagonist protocol versus GnRH agonist long protocol in patients with polycystic ovary syndrome treated for IVF: a prospective randomised controlled trial (RCT), Human Reproduction, 25, 683-689, 2010	Included in Al-Inany (2011) Cochrane review
Lin,Y.H., Hwang,J.L., Seow,K.M., Huang,L.W., Hsieh,B.C., Tzeng,C.R., Comparison of outcome of clomiphene citrate/human menopausal gonadotropin/cetrorelix protocol and buserelin long protocol--a randomized study, Gynecological Endocrinology, 22, 297-302, 2006	Included in Al-Inany (2011) Cochrane review
Loutradis,D., Stefanidis,K., Drakakis,P., Milingos,S., Antsaklis,A., Michalas,S., A modified gonadotropin-releasing hormone (GnRH) antagonist protocol failed to increase clinical pregnancy rates in comparison with the long GnRH protocol, Fertility and Sterility, 82, 1446-1448, 2004	Included in Al-Inany (2011) Cochrane review
Ludwig,M., Felberbaum,R.E., Devroey,P., Albano,C., ller-Winzen,H., ler,A., Engel,W., Diedrich,K., Significant reduction of the incidence of ovarian hyperstimulation syndrome (OHSS) by using the LHRH antagonist Cetrorelix (Cetrotide) in controlled ovarian stimulation for assisted reproduction, Archives of Gynecology and Obstetrics, 264, 29-32, 2000	Duplicate publication of data in Albano (2000), which is included in the Al-Inany (2011) Cochrane review

Bibliographic information	Reason for exclusion
Mancini,Fulvia, Tur,Rosa, Martinez,Francisca, Coroleu,Buenaventura, Rodriguez,Ignacio, Barri,Pedro N., Gonadotrophin-releasing hormone-antagonists vs long agonist in in-vitro fertilization patients with polycystic ovary syndrome: a meta-analysis, Gynecological Endocrinology,Gynecol Endocrinol, 27, 150-155, 2010	Results were reported per cycle
Mansour,R., Aboulghar,M., Serour,G.I., Al-Inany,H.G., Fahmy,I., Amin,Y., The use of clomiphene citrate/human menopausal gonadotrophins in conjunction with GnRH antagonist in an IVF/ICSI program is not a cost effective protocol, Acta Obstetricia et Gynecologica Scandinavica, 82, 48-52, 2003	Couples were not truly randomised - allocation was based on financial status
Marci,R., Caserta,D., Dolo,V., Tatone,C., Pavan,A., Moscarini,M., GnRH antagonist in IVF poor-responder patients: results of a randomized trial, Reproductive Biomedicine Online, 11, 189-193, 2005	Included in Al-Inany (2011) Cochrane review
Marci,R., Caserta,D., Farina,M., Dessole,S., Germond,M., Tatone,C., Colonna,M., Moscarini,M., A prospective, randomized comparison of two short stimulation protocols with agonist and antagonist of GnRH in poor responders patients undergoing IVF Preliminary report, Human Reproduction, Vol.18 suppl 1, pp.113, 2003., -, -32676	Preliminary report of a paper that is a duplicate publication of a study included in the Al-Inany (2011) Cochrane review
Mashiach,S., Dor,J., Goldenberg,M., Shalev,J., Blankstein,J., Rudak,E., Shoam,Z., Finelt,Z., Nebel,L., Goldman,B., Protocols for induction of ovulation. The concept of programmed cycles, Annals of the New York Academy of Sciences, 541, 37-45, 1988	Unclear how many women were included in the denominator Unclear how randomisation was performed Unclear how the control group was chosen Unclear how many women received GnRH analogue
Meldrum,D.R., Patient preparation and standard stimulation regimens using gonadotropin-releasing hormone agonists, Clinical Obstetrics and Gynecology, 49, 4-11, 2006	Narrative review
Moraloglu,O., Kilic,S., Karayalcin,R., Yuksel,B., Tasdemir,N., Isik,A., Ugur,M., Comparison of GnRH agonists and antagonists in normoresponder IVF/ICSI in Turkish female patients, Advances in Therapy, 25, 266-273, 2008	Included in Al-Inany (2011) Cochrane review
Muasher,S., 'The use of GnRH-a in a luteal suppression vs follicular "flare-up" in conjunction with gonadotropins for ovarian hyperstimulation for in vitro fertilisation (IVF) in patients with normal basal gonadotropin levels: A randomised prospective study', Fertility and Sterility, 56, S42, 1991	Conference abstract
Myers,E.R., McCrory,D.C., Mills,A.A., Price,T.M., Swamy,G.K., Tantibhedhyangkul,J., Wu,J.M., Matchar,D.B., Effectiveness of assisted reproductive technology (ART), Evidence report/technology assessment, 1-195),;#2008. Date of Publication, -195, 2008	Review with no meta-analysis
Nargund,G., Waterstone,J., Bland,J.M., Philips,Z., Parsons,J., Campbell,S., Cumulative conception and live birth rates in natural (unstimulated) IVF cycles, Human Reproduction, 16, 259-262, 2001	Non-comparative study
Nugent,David, Vanderkerchove,Patrick, Hughes,Edward, Arnot,M., Lilford,Richard, Gonadotrophin therapy for ovulation induction in subfertility associated with polycystic ovary syndrome, Cochrane Database of Systematic Reviews, -, 2009	Women did not receive IVF or ICSI
Oehninger,S., Hodgen,G.D., Induction of ovulation for assisted reproduction programmes, Bailliere's Clinical Obstetrics and Gynaecology, 4, 541-573, 1990	Narrative review

Bibliographic information	Reason for exclusion
Olivennes,F., Belaisch-Allart,J., Emperaire,J.C., Dechaud,H., Alvarez,S., Moreau,L., Nicollet,B., Zorn,J.R., Bouchard,P., Frydman,R., Prospective, randomized, controlled study of in vitro fertilization-embryo transfer with a single dose of a luteinizing hormone-releasing hormone (LH-RH) antagonist (cetrorelix) or a depot formula of an LH-RH agonist (triptorelin), Fertility and Sterility, 73, 314-320, 2000	Included in Al-Inany (2011) Cochrane review
Pu,D., Wu,J., Liu,J., Comparisons of GnRH antagonist versus GnRH agonist protocol in poor ovarian responders undergoing IVF, Human Reproduction, 26, 2742-2749, 2011	Three of the studies were already included in the current review. The methods of the other included studies were not reported in enough detail to determine the method of randomisation. The quality of the included studies was not reported
Rogers,P., Molloy,D., Healy,D., McBain,J., Howlett,D., Bourne,H., Thomas,A., Wood,C., Johnston,I., Trounson,A., Cross-over trial of superovulation protocols from two major in vitro fertilization centers, Fertility and Sterility, 46, 424-431, 1986	Women were not randomised
Sauer,M.V., Thornton,I.I.M.H., Schoolcraft,W., Frishman,G.N., Comparative efficacy and safety of cetrorelix with or without mid-cycle recombinant LH and leuprolide acetate for inhibition of premature LH surges in assisted reproduction, Reproductive Biomedicine Online, 9, 487-493, 2004	Included in Al-Inany (2011) Cochrane review
Sbracia,M., Colabianchi,J., Giallonardo,A., Giannini,P., Piscitelli,C., Morgia,F., Montigiani,M., Schimberni,M., Cetrorelix protocol versus gonadotropin-releasing hormone analog suppression long protocol for superovulation in intracytoplasmic sperm injection patients older than 40, Fertility and Sterility, 91, 1842-1847, 2009	Included in Al-Inany (2011) Cochrane review
Serafini,P., Yadid,I., Alegretti,J., Panzan,M., Cosloversusky,M., Motta,E., A prospective, randomized trial of three ovulation induction protocols for IVF including a novel approach with low-dose HCG ahd GnRH antagaonist in the mid-late follicular phase, Human Reproduction, Vol.18 suppl 1, pp.1, 2003., -, -32676	Included in Al-Inany (2011) Cochrane review
Shanis,B.S., Check,J.H., Efficacy of gonadotropin-releasing hormone agonists to induce ovulation following low-dose human menopausal gonadotropin stimulation, Recent Progress in Hormone Research, 50, 483-486, 1995	It is unclear if women received IVF or ICSI. Method of randomisation was not reported
Smitz,J., Picton,H.M., Platteau,P., Rutherford,A., Cortvrindt,R., Clyde,J., Nogueira,D., Devroey,P., Lyby,K., Grondahl,C., Principal findings from a multicenter trial investigating the safety of follicular-fluid meiosis-activating sterol for in vitro maturation of human cumulus-enclosed oocytes, Fertility and Sterility, 87, 949-964, 2007	Relevant outcomes were not reported. Women were randomised to different culture mediums
Tazegul,A., Gorkemli,H., Ozdemir,S., Aktan,T.M., Comparison of multiple dose GnRH antagonist and minidose long agonist protocols in poor responders undergoing in vitro fertilization: a randomized controlled trial, Archives of Gynecology and Obstetrics, 278, 467-472, 2008	Included in Al-Inany (2011) Cochrane review
Tehraninejad,E.S., Nasiri,R., Rashidi,B., Haghollahi,F., Ataie,M., Comparison of GnRH antagonist with long GnRH agonist protocol after OCP pretreatment in PCOs patients, Archives of Gynecology and Obstetrics, 282, 319-325, 2010	Included in Al-Inany (2011) Cochrane review

Bibliographic information	Reason for exclusion
Van Horne,A.K., Bates,G.W.,Jr., Robinson,R.D., Arthur,N.J., Propst,A.M., Recombinant follicle-stimulating hormone (rFSH) supplemented with low-dose human chorionic gonadotropin compared with rFSH alone for ovarian stimulation for in vitro fertilization, Fertility and Sterility, 88, 1010-1013, 2007	Retrospective study
Van,der Auwera,I, Meuleman,C., Koninckx,P.R., Human menopausal gonadotrophin increases pregnancy rate in comparison with clomiphene citrate during replacement cycles of frozen/thawed pronucleate ova, Human Reproduction, 9, 1556-1560, 1994	Only used frozen/thawed ova
Verberg,M.F.G., Macklon,N.S., Nargund,G., Frydman,R., Devroey,P., Broekmans,F.J., Fauser,B.C.J.M., Mild ovarian stimulation for IVF, Human Reproduction Update, 15, 13-29, 2009	Narrative review
Vlaisavljevic,V., Reljic,M., Lovrec,V.G., Kovacic,B., Comparable effectiveness using flexible single-dose GnRH antagonist (cetrorelix) and single-dose long GnRH agonist (goserelin) protocol for IVF cycles--a prospective, randomized study, Reproductive Biomedicine Online, 7, 301-308, 2003	Quasi-randomised trial
Wong,J.M., Forrest,K.A., Snabes,S.Z., Zhao,S.Z., Gersh,G.E., Kennedy,S.H., Efficacy of nafarelin in assisted reproductive technology: a meta-analysis, Human Reproduction Update, 7, 92-101, 2001	Comparison of different GnRH agonist drugs
Xavier,P., Gamboa,C., Calejo,L., Silva,J., Stevenson,D., Nunes,A., Martinez-de-Oliveira,J., A randomised study of GnRH antagonist (cetrorelix) versus agonist (busereline) for controlled ovarian stimulation: effect on safety and efficacy, European Journal of Obstetrics, Gynecology, and Reproductive Biology, 120, 185-189, 2005	Included in Al-Inany (2011) Cochrane review
Xiao,J.S., Chen,S.Y., Zhang,C.L., Chang,S., Effectiveness of GnRH antagonist in vitro fertilization-embryo transfer (IVF-ET) in PCOS patients: A systematic review, Chinese Journal of Evidence-Based Medicine, 11, 811-818, 2011	Foreign language paper
Ye,H., Huang,G.N., Zeng,P.H., Pei,L., IVF/ICSI outcomes between cycles with luteal estradiol (E2) pre-treatment before GnRH antagonist protocol and standard long GnRH agonist protocol: a prospective and randomized study, Journal of Assisted Reproduction and Genetics, 26, 105-111, 2009	Included in Al-Inany (2011) Cochrane review
Zikopoulos,K., Kaponis,A., Adonakis,G., Sotiriadis,A., Kalantaridou,S., Georgiou,I., Paraskevaidis,E., A prospective randomized study comparing gonadotropin-releasing hormone agonists or gonadotropin-releasing hormone antagonists in couples with unexplained infertility and/or mild oligozoospermia, Fertility and Sterility, 83, 1354-1362, 2005	Women received IUI rather than IVF/ICSI

IVF ovarian stimulation

Table G.11 What is the effectiveness of different ovarian strategies as part of an ovarian stimulation protocol in women undergoing IVF or ICSI treatment?

Bibliographic information	Reason for exclusion
Abate,A., Nazzaro,A., Salerno,A., Marzano,F., Pavone Cossut,M.R., Perino,M., Efficacy of recombinant versus human derived follicle stimulating hormone on the oocyte and embryo quality in IVF-ICSI cycles: Randomised, controlled, multi-centre trial, Gynecological Endocrinology, 25, 479-484, 2009	Included in van Wely (2010) Cochrane review
Aboulghar,M.A., Mansour,R.T., Serour,G.I., Al-Inany,H.G., Amin,Y.M., Aboulghar,M.M., Increasing the dose of human menopausal gonadotrophins on day of GnRH antagonist administration: randomized controlled trial, Reproductive Biomedicine Online, 8, 524-527, 2004	Unable to calculate clinical outcome data
Abu-Heija,A.T., Yates,R.W., Barrett,T., Jamieson,M.E., Fleming,R., Coutts,J.R., A comparison of two starting doses of human menopausal gonadotrophin for follicle stimulation in unselected patients for in-vitro fertilization, Human Reproduction, 10, 801-803, 1995	Women were not randomised to treatment groups
Abyholm,T., Andersen,A.N., Balen,A.H., Braat,D.D.M., Devroey,P., D'Hooghe,T.H., Felberbaum,R., Fauser,B.J.C.M., Fridstrom,M., Hillensjo,T., Keck,C., Kurunmaki,H., Lindenberg,S., Ombelet,W., Tapanainen,J., Varila,E., Wramsby,H., Koper,N.P., De,HaanA, Struys,M.J., Mannaerts,B.M., Koper,N., A randomized dose-response trial of a single injection of corifollitropin alfa to sustain multifollicular growth during controlled ovarian stimulation, Human Reproduction, 23, 2484-2492, 2008	Compares two types of rFSH
Agrawal,R., Holmes,J., Jacobs,H.S., Follicle-stimulating hormone or human menopausal gonadotropin for ovarian stimulation in in vitro fertilization cycles: A meta-analysis, Fertility and Sterility, 73, 338-343, 2000	Pregnancy rate reported only per cycle
Al-Inany,H.G., bou-Setta,A.M., Aboulghar,M.A., Mansour,R.T., Serour,G.I., Efficacy and safety of human menopausal gonadotrophins versus recombinant FSH: a meta-analysis, Reproductive Biomedicine Online, 16, 81-88, 2008	All studies in this review are included in the van Wely (2011) Cochrane review for the same comparison (rFSH vs. hMG)
Al-Inany,H.G., bou-Setta,A.M., Aboulghar,M.A., Mansour,R.T., Serour,G.I., Highly purified hMG achieves better pregnancy rates in IVF cycles but not ICSI cycles compared with recombinant FSH: a meta-analysis, Gynecological Endocrinology, 25, 372-378, 2009	The denominator used for the relevant outcomes is not reported
Almog,B., Azem,F., Kapustiansky,R., Azolai,J., Wagman,I., Levin,I., Hauser,R., Pauzner,D., Lessing,J.B., Amit,A., Gamzu,R., Intrafollicular and serum levels of leptin during in vitro fertilization cycles: Comparison between the effects of recombinant follicle-stimulating hormones and human menopausal gonadotrophin, Gynecological Endocrinology, 27, 666-668, 2011	No relevant outcomes reported
Andersen,A.N., Devroey,P., Arce,J.C., Clinical outcome following stimulation with highly purified hMG or recombinant FSH in patients undergoing IVF: a randomized assessor-blind controlled trial, Human Reproduction, 21, 3217-3227, 2006	Included in van Wely (2010) Cochrane review

Bibliographic information	Reason for exclusion
Andoh,K., Mizunuma,H., Liu,X., Kamijo,T., Yamada,K., Ibuki,Y., A comparative study of fixed-dose, step-down, and low-dose step-up regimens of human menopausal gonadotropin for patients with polycystic ovary syndrome, Fertility and Sterility, 70, 840-846, 1998	Women did not receive IVF or ICSI
Antoine,J.M., Salat-Baroux,J., Alvarez,S., Cornet,D., Tibi,C., Mandelbaum,J., Plachot,M., Ovarian stimulation using human menopausal gonadotrophins with or without LHRH analogues in a long protocol for in-vitro fertilization: a prospective randomized comparison, Human Reproduction, 5, 565-569, 1990	Down regulation study. Method of randomisation was not reported
Baart,E.B., Martini,E., Eijkemans,M.J., Van,Opstal D., Beckers,N.G., Verhoeff,A., Macklon,N.S., Fauser,B.C., Milder ovarian stimulation for in-vitro fertilization reduces aneuploidy in the human preimplantation embryo: a randomized controlled trial, Human Reproduction, 22, 980-988, 2007	Included in Al-Inany (2011) Cochrane review
Baker,V.L., Fujimoto,V.Y., Kettel,L.M., Adamson,G.D., Hoehler,F., Jones,C.E., Soules,M.R., Clinical efficacy of highly purified urinary FSH versus recombinant FSH in volunteers undergoing controlled ovarian stimulation for in vitro fertilization: a randomized, multicenter, investigator-blind trial, Fertility and Sterility, 91, 1005-1011, 2009	Included in van Wely (2010) Cochrane review
Balasch,J., bregues,F., Creus,M., arrubia,J., Vidal,E., Carmona,F., Puerto,B., Vanrell,J.A., Follicular development and hormonal levels following highly purified or recombinant follicle-stimulating hormone administration in ovulatory women undergoing ovarian stimulation after pituitary suppression for in vitro fertilization: implications for implantation potential, Journal of Assisted Reproduction and Genetics, 17, 20-27, 2000	Women were not randomised to treatment groups
Balasch,J., Fabregues,F., Creus,M., Casamitjana,R., Puerto,B., Vanrell,J.A., Recombinant human follicle-stimulating hormone for ovulation induction in polycystic ovary syndrome: A prospective, randomized trial of two starting doses in a chronic low-dose step-up protocol, Journal of Assisted Reproduction and Genetics, 17, 561-565, 2000	Women did not receive IVF/ICSI
Balasch,J., Penarrubia,J., Fabregues,F., Vidal,E., Casamitjana,R., Manau,D., Carmona,F., Creus,M., Vanrell,J.A., Ovarian responses to recombinant FSH or HMG in normogonadotrophic women following pituitary desensitization by a depot GnRH agonist for assisted reproduction, Reproductive Biomedicine Online, 7, 35-42, 2003	Included in van Wely (2010) Cochrane review
Balen,A., Is there a risk of prion disease after the administration of urinary-derived gonadotrophins?, Human Reproduction, 17, 1676-1680, 2002	Narrative review with no new data
Balen,A.H., Lumholtz,I.B., Consensus statement on the bio-safety of urinary-derived gonadotrophins with respect to Creutzfeldt-Jakob disease. [39 refs], Human Reproduction, 20, 2994-2999, 2005	Narrative review with no new data
Barreto Melo,M.A., Magnavita,Sabino S., Coelho,G.M., Bellver,J., Pellicer,A., Remohi,J., A prospective, randomized, controlled trial comparing three different gonadotrophin regimens in oocyte donors: ovarian response and IVF outcome, Human Reproduction.European Society of Human Reproduction and Embryology ESHRE 24th Annual Meeting, Barcelona, 6-9 July, 2008. Vol.23 Suppl 1, pp.i101 Abstract No: O-252 Oral, 2008., O-252, 2008	Oocyte donors were randomised to gonadotrophin regimens. The number of recipients was greater than the number of donors, and it is not clear how many eggs each donor provided

Bibliographic information	Reason for exclusion
Barri,P.N., Tur,R., Martinez,F., Coroleu,B., Mild stimulation in assisted reproduction, Gynecological Endocrinology, 26, 261-264, 2010	Study design unclear. Methodology unclear. Irrelevant approach to review question.
Baruffi,R.L., Mauri,A.L., Petersen,C.G., Felipe,V., Martins,A.M., Cornicelli,J., Cavagna,M., Oliveira,J.B., Franco,J.G.,Jr., Recombinant LH supplementation to recombinant FSH during induced ovarian stimulation in the GnRH-antagonist protocol: a meta-analysis, Reproductive Biomedicine Online, 14, 14-25, 2007	Pregnancies are only reported per retrieval
Bassil,S., Wyns,C., Donnez,J., A randomized prospective cross-over study of highly purified follicle-stimulating hormone and human menopausal gonadotrophin for ovarian hyperstimulation in women aged 37-41 years, Journal of Assisted Reproduction and Genetics, 17, 107-112, 2000	Cross over trial - data could not be separated into first and second arms
Bayram,Neriman, van Wely,Madelon, Van der Veen,Fulco, Recombinant FSH versus urinary gonadotrophins or recombinant FSH for ovulation induction in subfertility associated with polycystic ovary syndrome, Cochrane Database of Systematic Reviews, -, 2010	Women did not receive IVF or ICSI
Bentick,B., Shaw,R.W., Iffland,C.A., Burford,G., Bernard,A., A randomized comparative study of purified follicle stimulating hormone and human menopausal gonadotropin after pituitary desensitization with Buserelin for superovulation and in vitro fertilization, Fertility and Sterility, 50, 79-84, 1988	Crossover trial - individual arms of the trial could not be separated
Beretsos,P., Partsinevelos,G.A., Arabatzi,E., Drakakis,P., Mavrogianni,D., Anagnostou,E., Stefanidis,K., Antsaklis,A., Loutradis,D., "hCG priming" effect in controlled ovarian stimulation through a long protocol, Reproductive biology and endocrinology : RBandE, 7, 91, 2009	Outcomes were reported as a rate and the denominator was not clearly reported.
Bergh,C., Howles,C.M., Borg,K., Hamberger,L., Josefsson,B., Nilsson,L., Wikland,M., Recombinant human follicle stimulating hormone (r-hFSH; Gonal-F) versus highly purified urinary FSH (Metrodin HP): results of a randomized comparative study in women undergoing assisted reproductive techniques, Human Reproduction, 12, 2133-2139, 1997	Included in van Wely (2010) Cochrane review
Berkkanoglu,M., Isikoglu,M., Aydin,D., Ozgur,K., Clinical effects of ovulation induction with recombinant follicle-stimulating hormone supplemented with recombinant luteinizing hormone or low-dose recombinant human chorionic gonadotropin in the midfollicular phase in microdose cycles in poor responders, Fertility and Sterility, 88, 665-669, 2007	It was not possible to calculate relevant outcomes per woman randomised
Berkkanoglu,M., Ozgur,K., What is the optimum maximal gonadotropin dosage used in microdose flare-up cycles in poor responders?, Fertility and Sterility, 94, 662-665, 2010	Outcomes were reported as rates per transfer.
Bjercke,S., Tanbo,T., Abyholm,T., Omland,A., ien,H.K., Fedorcsak,P., Clinical outcome following stimulation with highly purified hMG or recombinant FSH in patients undergoing their first treatment cycle of IVF or ICSI, Acta Obstetricia et Gynecologica Scandinavica, 89, 1053-1060, 2010	Women were not truly randomised (treatment allocated on alternate weeks)

Bibliographic information	Reason for exclusion
Blockeel,C., Sterrenburg,M.D., Broekmans,F.J., Eijkemans,M.J., Smitz,J., Devroey,P., Fauser,B.C., Follicular phase endocrine characteristics during ovarian stimulation and GnRH antagonist cotreatment for IVF: RCT comparing recFSH initiated on cycle day 2 or 5, Journal of Clinical Endocrinology and Metabolism, 96, 1122-1128, 2011	Not a comparison of interest
Bosch,E., Ezcurra,D., Individualised controlled ovarian stimulation (iCOS): maximising success rates for assisted reproductive technology patients, Reproductive Biology and Endocrinology, 9, 82-, 2011	No new data reported
Bosch,E., Labarta,E., Crespo,J., Simon,C., Remohi,J., Pellicer,A., Impact of luteinizing hormone administration on gonadotropin-releasing hormone antagonist cycles: an age-adjusted analysis, Fertility and Sterility, 95, 1031-1036, 2011	Outcomes are reported as rates per started cycle and the number of started cycles were not reported
Bosch,E., Vidal,C., Labarta,E., Simon,C., Remohi,J., Pellicer,A., Highly purified hMG versus recombinant FSH in ovarian hyperstimulation with GnRH antagonists--a randomized study, Human Reproduction, 23, 2346-2351, 2008	Included in van Wely (2010) Cochrane review
Centre for Reviews and Dissemination., Urinary hMG versus recombinant FSH for controlled ovarian hyperstimulation following an agonist long down-regulation protocol in IVF or ICSI treatment: a systematic review and meta-analysis (Structured abstract), Database of Abstracts of Reviews of Effects, -, 2010	Abstract - full review considered for inclusion
Chang,P., Kenley,S., Burns,T., Denton,G., Currie,K., DeVane,G., O'Dea,L., Recombinant human chorionic gonadotropin (rhCG) in assisted reproductive technology: results of a clinical trial comparing two doses of rhCG (Ovidrel) to urinary hCG (Profasi) for induction of final follicular maturation in in vitro fertilization-embryo transfer, Fertility and Sterility, 76, 67-74, 2001	Included in Youssef (2011) Cochrane review
Chen,X.-N., Lu,G.-X., Yan,J.-M., Chen,Z.-J., Xiao,H.-M., Chen,G., An open, prospective, randomized, multicenter study to compare recombinant human follicle stimulating hormone (rec-FSH; follitropin-; Puregon(R) solution) with highly purified urinary FSH (uFSH, urofollitropin (highly purified), Metrodin(R) HP) in Chinese women undergoing in vitro fertilization (IVF), Fertility and Sterility, Vol.82 Suppl 2, pp.S228, 2004., -, None	Conference abstract
Cheon,K.W., Byun,H.K., Yang,K.M., Song,I.O., Choi,K.H., Yoo,K.J., Efficacy of recombinant human follicle-stimulating hormone in improving oocyte quality in assisted reproductive techniques, Journal of Reproductive Medicine, 49, 733-738, 2004	Included in van Wely (2010) Cochrane review
Chou,L.L., Hwu,Y.M., Lin,M.H., Lin,S.Y., Lee,R.K., Outcomes of high initial daily doses of gonadotropin in patients with poor ovarian reserve, Taiwanese Journal of Obstetrics and Gynecology, 49, 442-448, 2010	Retrospective study
Christin-Maitre,S., Hugues,J.N., A comparative randomized multicentric study comparing the step-up versus step-down protocol in polycystic ovary syndrome, Human Reproduction, 18, 1626-1631, 2003	Women did not receive IVF or ICSI
Chung,K., Fogle,R., Bendikson,K., Christenson,K., Paulson,R., Microdose gonadotropin-releasing hormone agonist in the absence of exogenous gonadotropins is not sufficient to induce multiple follicle development, Fertility and Sterility, 95, 317-319, 2011	Not a comparative study. No relevant outcomes reported

Bibliographic information	Reason for exclusion
Coomarasamy,A., Afnan,M., Cheema,D., van,der,V, Bossuyt,P.M., van,Wely M., Urinary hMG versus recombinant FSH for controlled ovarian hyperstimulation following an agonist long down-regulation protocol in IVF or ICSI treatment: a systematic review and meta-analysis. [28 refs], Human Reproduction, 23, 310-315, 2008	A more recent Cochrane review (Van Wely, 2011) has reviewed all of the included studies for the same comparison
Corifollitropin alfa Ensure Study Group., Corifollitropin alfa for ovarian stimulation in IVF: a randomized trial in lower-body-weight women, Reproductive Biomedicine Online, 21, 66-76, 2010	Comparison of two types of rFSH
D'Amato,G., Caroppo,E., Pasquadibisceglie,A., Carone,D., Vitti,A., Vizziello,G.M., A novel protocol of ovulation induction with delayed gonadotropin-releasing hormone antagonist administration combined with high-dose recombinant follicle-stimulating hormone and clomiphene citrate for poor responders and women over 35 years1977, Fertility and Sterility, 81, 1572-1577, 2004	Method of randomisation inadequate (based on day of first presentation at clinic)
D'Angelo,A., Amso,N., "Coasting" (withholding gonadotrophins) for preventing ovarian hyperstimulation syndrome, Cochrane database of systematic reviews (Online), #2002. Date of Publication, CD002811-, 2002	Not an intervention of interest
Daya,S., Gunby,J., Hughes,E.G., Collins,J.A., Sagle,M.A., Follicle-stimulating hormone versus human menopausal gonadotropin for in vitro fertilization cycles: a meta-analysis, Fertility and Sterility, 64, 347-354, 1995	Pregnancy rate only reported per cycle
Daya,S., Gunby,J., Hughes,E.G., Collins,J.A., Sagle,M.A., Randomized controlled trial of follicle stimulating hormone versus human menopausal gonadotrophin in in-vitro fertilization, Human Reproduction, 10, 1392-1396, 1995	Study ongoing at time of publication of paper
Daya,Salim, Follicle-stimulating hormone and human menopausal gonadotropin for ovarian stimulation in assisted reproduction cycles, Cochrane Database of Systematic Reviews, -, 2011	Withdrawn from the Cochrane library as it has not been updated since 1996. It has now been superseded by van Wely (2011)
De,GreefR, Zandvliet,A.S., De,HaanA, Ijzerman-Boon,P.C., Marintcheva-Petrova,M., Mannaerts,B.M.J.L., Dose selection of corifollitropin alfa by modeling and simulation in controlled ovarian stimulation, Clinical Pharmacology and Therapeutics, 88, 79-87, 2010	Not a randomised controlled trial
De,Placido G., Alviggi,C., Mollo,A., Strina,I., Ranieri,A., Alviggi,E., Wilding,M., Varricchio,M.T., Borrelli,A.L., Conforti,S., Effects of recombinant LH (rLH) supplementation during controlled ovarian hyperstimulation (COH) in normogonadotrophic women with an initial inadequate response to recombinant FSH (rFSH) after pituitary downregulation, Clinical Endocrinology, 60, 637-643, 2004	The number of clinical pregnancies and live births was not reported. Ongoing pregnany was reported as a rate and the denominator used was unclear
De,Placido G., Alviggi,C., Perino,A., Strina,I., Lisi,F., Fasolino,A., De,Palo R., Ranieri,A., Colacurci,N., Mollo,A., Italian Collaborative Group on Recombinant Human Luteinizing Hormone., Recombinant human LH supplementation versus recombinant human FSH (rFSH) step-up protocol during controlled ovarian stimulation in normogonadotrophic women with initial inadequate ovarian response to rFSH. A multicentre, prospective, randomized controlled trial, Human Reproduction, 20, 390-396, 2005	Outcomes were reported as a rate and the denominator was not clearly reported

Bibliographic information	Reason for exclusion
Devroey,P., Boostanfar,R., Koper,N.P., Mannaerts,B.M., Ijzerman-Boon,P.C., Fauser,B.C., ENGAGE,Investigators, A double-blind, non-inferiority RCT comparing corifollitropin alfa and recombinant FSH during the first seven days of ovarian stimulation using a GnRH antagonist protocol, Human Reproduction, 24, 3063-3072, 2009	Comparison of two types of rFSH
Devroey,P., Fauser,B.C., Platteau,P., Beckers,N.G., Dhont,M., Mannaerts,B.M., Induction of multiple follicular development by a single dose of long-acting recombinant follicle-Stimulating hormone (FSH-CTP, corifollitropin alfa) for controlled ovarian stimulation before in vitro fertilization, Journal of Clinical Endocrinology and Metabolism, 89, 2062-2070, 2004	Compares different types of rFSH. Method of randomisation is not reported.
Devroey,P., Polyzos,N.P., Blockeel,C., An OHSS-Free Clinic by segmentation of IVF treatment, Human Reproduction, 26, 2593-2597, 2011	No raw data reported
Devroey,P., Tjandraprawira,K., Mannaerts,B., Coelingh,Bennink H., Smitz,J., Bonduelle,M., De,Brabanter A., Van Steirteghem,A.C., A randomized, assessor-blind, group-comparative efficacy study to compare the effects of Normegon and Metrodin in infertile female patients undergoing in-vitro fertilization, Human Reproduction, 10, 332-337, 1995	Not a comparison of interest (different doses of LH)
Devroey,P., Tournaye,H., Van,SteirteghemA, Hendrix,P., Out,H.J., The use of a 100 IU starting dose of recombinant follicle stimulating hormone (Puregon) in in-vitro fertilization, Human Reproduction, 13, 565-566, 1998	Not a comparative study
Dickey,R., Nichols,J., Steinkampf,M., Gocial,B., Crain,J., Webster,B., Scobey,M., Marshall,D., Bravelle (highly purified hFSH) vs Follistim (rFSH) in IVF: pooled analysis from two prospective, randomized clinical trials, Fertility and Sterility, 80, S17, 2003	
Dickey,R.P., Nichols,J.E., Steinkampf,M.P., Gocial,B., Thornton,M., Webster,B.W., Bello,S.M., Crain,J., Marshall,D.C., Bravelle IVF Study Group., Highly purified human-derived follicle-stimulating hormone (Bravelle) has equivalent efficacy to follitropin-beta (Follistim) in infertile women undergoing in vitro fertilization, Reproductive Biology and Endocrinology, 1, 63-, 2003	Included in van Wely (2010) Cochrane review
Dickey,R.P., Thornton,M., Nichols,J., Marshall,D.C., Fein,S.H., Nardi,R.V., Bravelle IVF Study Group., Comparison of the efficacy and safety of a highly purified human follicle-stimulating hormone (Bravelle) and recombinant follitropin-beta for in vitro fertilization: a prospective, randomized study, Fertility and Sterility, 77, 1202-1208, 2002	Included in van Wely (2010) Cochrane review
Dor,J., Seidman,D.S., Amudal,E., Bider,D., Levran,D., Mashiach,S., Adjuvant growth hormone therapy in poor responders to in-vitro fertilization: A prospective randomized placebo-controlled double-blind study, Human Reproduction, 10, 40-43, 1995	Included in the Duffy et al. (2010) Cochrane review
Drakakis,P., Loutradis,D., Kallianidis,K., Bletsa,R., Milingos,S., onyssiou-Asteriou,A., Michalas,S., A comparative study of the effect of ovarian stimulation protocols with different gonadotropin preparations on the biological and clinical parameters of the outcome of intracytoplasmic sperm injection, Clinical and Experimental Obstetrics and Gynecology, 29, 286-289, 2002	Participation in the groups was affected by the availability of the drugs and therefore women were not truly randomised. It was not possible to determine outcomes per woman.

Bibliographic information	Reason for exclusion
Drakakis,P., Loutradis,D., Kallianidis,K., Milingos,S., onyssiou-Asteriou,A., Michalas,S., The clinical efficacy of recombinant FSH (r-FSH) as compared to highly purified urinary gonadotrophin (hMG-FD) and the use of a low starting dose of r-FSH in IVF or ICSI. A randomized prospective study, Italian Journal of Gynaecology and Obstetrics, 14, 64-68, 2002	Included in Van Wely (2011) Cochrane review
Ehimen,EgbaseP, Al,SharhanM, Grudzinskas,J.G., A comparison of a step-up protocol with high fixed dose gonadotropin administration for controlled ovarian stimulation in obese patients without polycystic ovarian syndrome: A prospective randomized trial, Middle East Fertility Society Journal, 7, 199-204, 2002	It is not possible to calculate the clinical pregnancy rate per woman - it is presented per embryo transfer and it is not clear how many embryo transfers took place in each group. Live birth rate is not reported.
Engel,J.B., Olivennes,F., Fanchin,R., Frydman,N., Le,D., Blanchet,V., Frydman,R., Single dose application of cetrorelix in combination with clomiphene for friendly IVF: results of a feasibility study, Reproductive Biomedicine Online, 6, 444-447, 2003	Method of randomisation was not clear. Only five women were included in each group
Engmann,L., Shaker,A., White,E., Bekir,J.S., Jacobs,H.S., Tan,S.L., A prospective randomized study to assess the clinical efficacy of gonadotrophins administered subcutaneously and intramuscularly, Human Reproduction, 13, 836-840, 1998	Comparison of route of administration of the same gonadotrophin
European and Israeli Study Group on Highly Purified Menotropin versus Recombinant Follicle-Stimulating Hormone., Efficacy and safety of highly purified menotropin versus recombinant follicle-stimulating hormone in in vitro fertilization/intracytoplasmic sperm injection cycles: a randomized, comparative trial, Fertility and Sterility, 78, 520-528, 2002	Included in van Wely (2011) Cochrane review
Feichtinger,W., Kindermann,C., Pohl,M., Krischker,U., Hohlagschwandtner,M., Weigert,M., Clomid in combination with recombinant FSH and recombinant LH, versus the GNRHA-long protocol A prospective randomized study on two different stimulations for IVF, 11th World Congress on In Vitro Fertilization and Human Reproductive Genetics, 134, 1999	Conference abstract
Feigenbaum,S.L., Miller,P., Kaufmann,R., Elkind-Hirsch,K., Fein,S.H., Marshall,D.C., A new highly purified human-derived FSH, Bravelle, is as effective and well tolerated as recombinant follitropin beta in ovulation induction in infertile women with ovulatory dysfunction, Today's Therapeutic Trends, 19, 297-313, 2001	Some women received IUI - it is not clear how many. No subgroup analysis for those who did not receive IUI is reported.
Fenichel,P., Grimaldi,M., Hieronimus,S., Olivero,J.F., Donzeau,A., Benoit,B., Fiorentini,M., Tran,D.K., Harter,M., Gillet,J.Y., Luteinizing hormone inhibition with an LH-RH analogue, triptorelin, in ovarian stimulation for in vitro fertilization. Choice of the therapeutic regimen, Presse Medicale, 17, 719-722, 1988	French language paper
Filicori,M., Cognigni,G.E., Pocognoli,P., Tabarelli,C., Ferlini,F., Perri,T., Parmegiani,L., Comparison of controlled ovarian stimulation with human menopausal gonadotropin or recombinant follicle-stimulating hormone, Fertility and Sterility, 80, 390-397, 2003	Women were not truly randomised - assigned to age and weight matched groups
Fisch,B., Avrech,O.M., Pinkas,H., Neri,A., Rufas,O., Ovadia,J., Loumaye,E., Superovulation before IVF by recombinant versus urinary human FSH (combined with a long GnRH analog protocol): a comparative study, Journal of Assisted Reproduction and Genetics, 12, 26-31, 1995	No outcomes of interest reported. Method of randomisation not reported

Bibliographic information	Reason for exclusion
Franco,J.G.,Jr., Baruffi,R.L., Coelho,J., Mauri,A.L., Petersen,C.G., Garbellini,E., A prospective and randomized study of ovarian stimulation for ICSI with recombinant FSH versus highly purified urinary FSH2951, Gynecological Endocrinology, 14, 5-10, 2000	Included in van Wely (2011) Cochrane review
Frydman,R., Howles,C.M., Truong,F., A double-blind, randomized study to compare recombinant human follicle stimulating hormone (FSH; Gonal-F) with highly purified urinary FSH (Metrodin) HP) in women undergoing assisted reproductive techniques including intracytoplasmic sperm injection. The French Multicentre Trialists, Human Reproduction, 15, 520-525, 2000	Included in van Wely (2010) Cochrane review
Gallego,Pastor E., Fernandez-Shaw,S., Mayoral,M., Rodriguez,L., Grande,C., Pons,I., Martinez,V., Garcia del,Real E., The treatment with recombinant FSH improvement the embryo quality in IVF cycles: a prospective randomiced study, Revista Iberoamericana de Fertilidad y Reproduccion Humana, 20, 43-50, 2003	Included in van Wely (2010) Cochrane review
Garcia-Velasco,J.A., Bennink,H.J., Epifanio,R., Escudero,E., Pellicer,A., Simon,C., High-dose recombinant LH add-back strategy using high-dose GnRH antagonist is an innovative protocol compared with standard GnRH antagonist.[Reprint of Reprod Biomed Online. 2007 Sep;15(3):280-7; PMID: 17854525], Reproductive Biomedicine Online, 22 Suppl 1, S52-S59, 2011	Compared a group who received a high dose GnRH antagonist and rFSH alone with a group who received low dose GnRH antagonist, rFSH and rLH. Not a comparison of interest
Garcia-Velasco,J.A., Coelingh Bennink,H.J., Epifanio,R., Escudero,E., Pellicer,A., Simon,C., High-dose recombinant LH add-back strategy using high-dose GnRH antagonist is an innovative protocol compared with standard GnRH antagonist, Reproductive Biomedicine Online, 15, 280-287, 2007	Compared a group who received a high dose GnRH antagonist and rFSH alone with a group who received low dose GnRH antagonist, rFSH and rLH. Not a comparison of interest
Gleicher,N., Weghofer,A., Barad,D.H., Improvement in diminished ovarian reserve after dehydroepiandrosterone supplementation, Reproductive Biomedicine Online, 21, 360-365, 2010	Retrospective cross-sectional study and longitudinal analysis
Gordon,U.D., Harrison,R.F., Fawzy,M., Hennelly,B., Gordon,A.C., A randomized prospective assessor-blind evaluation of luteinizing hormone dosage and in vitro fertilization outcome, Fertility and Sterility, 75, 324-331, 2001	Included in van Wely (2011) Cochrane review
Griesinger,G., Shapiro,D.B., Luteinizing hormone add-back: is it needed in controlled ovarian stimulation, and if so, when?, Journal of Reproductive Medicine, 56, 279-300, 2011	No new data reported
Grivel,T., Weil,E., Allaert,F.A., Audebert,A., Barriere,P., Christin-Maire,S., Giacomini,P., Janny,L., Letur-Konirsch,H., Nicollet,B., Olivennes,F., Pouly,J.L., Evaluation of the quality of life in patients undergoing in vitro fertilization procedures, Reproductive Technologies, 10, 338-343, 2001	Not a comparative study
Hedon,B., Hugues,J.N., Emperaire,J.C., Chabaud,J.J., Barbereau,D., Boujenah,A., Howles,C.M., Truong,F., A comparative prospective study of a chronic low dose versus a conventional ovulation stimulation regimen using recombinant human follicle stimulating hormone in anovulatory infertile women, Human Reproduction, 13, 2688-2692, 1998	Women did not receive IVF or ICSI

Bibliographic information	Reason for exclusion
Hedon,B., Out,H.J., Hugues,J.N., Camier,B., Cohen,J., Lopes,P., Zorn,J.R., van der,Heijden B., Coelingh Bennink,H.J., Efficacy and safety of recombinant follicle stimulating hormone (Puregon) in infertile women pituitary-suppressed with triptorelin undergoing in-vitro fertilization: a prospective, randomized, assessor-blind, multicentre trial, Human Reproduction, 10, 3102-3106, 1995	Included in van Wely (2010) Cochrane review
Heijnen,E.M., Eijkemans,M.J., de,Klerk C., Polinder,S., Beckers,N.G., Klinkert,E.R., Broekmans,F.J., Passchier,J., te Velde,E.R., Macklon,N.S., Fauser,B.C., A mild treatment strategy for in-vitro fertilisation: a randomised non-inferiority trial.[Reprint in Ned Tijdschr Geneeskd. 2008 Apr 5;152(14):809-16; PMID: 18491824], Lancet, 369, 743-749, 2007	More relevant to the comparison of GnRH agonists and GnRH antagonists – considered for inclusion in the down regulation review
Hohmann,F.P., Macklon,N.S., Fauser,B.C., A randomized comparison of two ovarian stimulation protocols with gonadotropin-releasing hormone (GnRH) antagonist cotreatment for in vitro fertilization commencing recombinant follicle-stimulating hormone on cycle day 2 or 5 with the standard long GnRH agonist protocol, Journal of Clinical Endocrinology and Metabolism, 88, 166-173, 2003	Included in Al-Inany (2011) Cochrane review
Homburg,R., Levy,T., Ben-Rafael,Z., A comparative prospective study of conventional regimen with chronic low- dose administration of follicle-stimulating hormone for anovulation associated with polycystic ovary syndrome, Fertility and Sterility, 63, 729-733, 1995	Women were not randomised to treatment groups
Hompes,P.G., Broekmans,F.J., Hoozemans,D.A., Schats,R., FIRM group., Effectiveness of highly purified human menopausal gonadotropin vs. recombinant follicle-stimulating hormone in first-cycle in vitro fertilization-intracytoplasmic sperm injection patients, Fertility and Sterility, 89, 1685-1693, 2008	Included in van Wely (2010) Cochrane review
Hoomans,E.H., Andersen,A.N., Loft,A., Leerentveld,R.A., van Kamp,A.A., Zech,H., A prospective, randomized clinical trial comparing 150 IU recombinant follicle stimulating hormone (Puregon((R))) and 225 IU highly purified urinary follicle stimulating hormone (Metrodin-HP((R))) in a fixed-dose regimen in women undergoing ovarian stimulation, Human Reproduction, 14, 2442-2447, 1999	Included in van Wely (2011) systematic review
Hugues,J.N., Bry-Gauillard,H., ndig,B., Uzan,M., Cedrin-Durnerin,I., Comparison of recombinant and urinary follicle-stimulating hormone preparations in short-term gonadotropin releasing hormone agonist protocol for in vitro fertilization-embryo transfer, Journal of Assisted Reproduction and Genetics, 18, 191-196, 2001	Included in van Wely (2010) Cochrane review
Hugues,J.N., Cedrin-Durnerin,I., Howles,C.M., The use of a decremental dose regimen in patients treated with a chronic low-dose step-up protocol for WHO Group II anovulation: a prospective randomized multicentre study, Human Reproduction, 21, 2817-2822, 2006	Women did not receive IVF/ICSI
Hull,M.G., Armatage,R.J., McDermott,A., Use of follicle-stimulating hormone alone (urofollitropin) to stimulate the ovaries for assisted conception after pituitary desensitization, Fertility and Sterility, 62, 997-1003, 1994	Not a comparative study

Bibliographic information	Reason for exclusion
Humaidan,P., Bungum,M., Bungum,L., Yding,Andersen C., Effects of recombinant LH supplementation in women undergoing assisted reproduction with GnRH agonist down-regulation and stimulation with recombinant FSH: an opening study1987, Reproductive Biomedicine Online, 8, 635-643, 2004	Conflicting results on numbe rof clinical pregancies for no LH supplementation group. n = 35 in table 4 and 37 in table 6
Ismail,A.F., Hesham,A.I., Salah,Z., Khaled,M., Fouad,N., Ashraf,N., Hatem,S., Hamdi,B., A prospective comparative study on IVF outcomes with either purified FSH or human menopausal gonadotrophin in downregulated normogonadotrophic women, Gynecologic and Obstetric Investigation, 53, 220-223, 2002	Women were not randomised to treatment groups
Jansen,C.A., van Os,H.C., Out,H.J., Coelingh Bennink,H.J., A prospective randomized clinical trial comparing recombinant follicle stimulating hormone (Puregon) and human menopausal gonadotrophins (Humegon) in non-down-regulated in-vitro fertilization patients, Human Reproduction, 13, 2995-2999, 1998	Included in van Wely (2011) Cochrane review
Jayaprakasan,K., Hopkisson,J., Campbell,B., Johnson,I., Thornton,J., Raine-Fenning,N., A randomised controlled trial of 300 versus 225 IU recombinant FSH for ovarian stimulation in predicted normal responders by antral follicle count, BJOG: An International Journal of Obstetrics and Gynaecology, 117, 853-862, 2010	Women were not truly randomised - pseudorandomisation used to stratify age and BMI
Jee,B.C., Suh,C.S., Kim,Y.B., Kim,S.H., Moon,S.Y., Clinical efficacy of highly purified hMG versus recombinant FSH in IVF/ICSI cycles: A meta-analysis, Gynecologic and Obstetric Investigation, 70, 132-137, 2010	Pregnancy rate was only reported by cycle and embryo transfer
Kansal,Kalra S., Ratcliffe,S., Gracia,C.R., Martino,L., Coutifaris,C., Barnhart,K.T., Randomized controlled pilot trial of luteal phase recombinant FSH stimulation in poor responders, Reproductive Biomedicine Online, 17, 745-750, 2008	Women in both groups received rFSH during the stimulation phase
Karimzadeh,M.A., Mashayekhy,M., Mohammadian,F., Moghaddam,F.M., Comparison of mild and microdose GnRH agonist flare protocols on IVF outcome in poor responders, Archives of Gynecology and Obstetrics, 283, 1159-1164, 2011	Outcomes were reported as rates/transfer. It was not possible to calculate results per woman.
Kilani,Z., Dakkak,A., Ghunaim,S., Cognigni,G.E., Tabarelli,C., Parmegiani,L., Filicori,M., A prospective, randomized, controlled trial comparing highly purified hMG with recombinant FSH in women undergoing ICSI: ovarian response and clinical outcomes, Human Reproduction, 18, 1194-1199, 2003	Included in van Wely (2011) Cochrane review
Kolibianakis,E.M., Venetis,C.A., Diedrich,K., Tarlatzis,B.C., Griesinger,G., Addition of growth hormone to gonadotrophins in ovarian stimulation of poor responders treated by in-vitro fertilization: a systematic review and meta-analysis. [25 refs], Human Reproduction Update, 15, 613-622, 2009	Only three of the six included studies were truly randomised. Individual studies were considered separately for inclusion in the current review.
Kosmas,I.P., Zikopoulos,K., Georgiou,I., Paraskevaidis,E., Blockeel,C., Tournaye,H., Van der,Elst J., Devroey,P., Low-dose HCG may improve pregnancy rates and lower OHSS in antagonist cycles: a meta-analysis, Reproductive Biomedicine Online, 19, 619-630, 2009	The denominator for the outcomes was not reported
Kucuk,T., Kozinoglu,H., Kaba,A., Growth hormone co-treatment within a GnRH agonist long protocol in patients with poor ovarian response: a prospective, randomized, clinical trial, Journal of Assisted Reproduction and Genetics, 25, 123-127, 2008	Included in the Duffy et al. (2010) Cochrane review [cited as Kueuk et al., 2008]

Bibliographic information	Reason for exclusion
Kurzawa,R., Ciepiela,P., Baczkowski,T., Safranow,K., Brelik,P., Comparison of embryological and clinical outcome in GnRH antagonist vs. GnRH agonist protocols for in vitro fertilization in PCOS non-obese patients. A prospective randomized study622, Journal of Assisted Reproduction and Genetics, 25, 365-374, 2008	Compares GnRH agonist and GnRH antagonist - considered in the more relevant review on down regulation
Kyrou,D., Kolibianakis,E.M., Fatemi,H.M., Camus,M., Tournaye,H., Tarlatzis,B.C., Devroey,P., High exposure to progesterone between the end of menstruation and the day of triggering final oocyte maturation is associated with a decreased probability of pregnancy in patients treated by in vitro fertilization and intracytoplasmic sperm injection, Fertility and Sterility, 96, 884-888, 2011	Observational study
Leader,A., Improved monofollicular ovulation in anovulatory or oligo-ovulatory women after a low-dose step-up protocol with weekly increments of 25 international units of follicle-stimulating hormone, Fertility and Sterility, 85, 1766-1773, 2006	Some women received IUI. Results for IUI and IVF/ICSI cycles are not reported separately
Lee,V.C.Y., Chan,C.C.W., Ng,E.H.Y., Yeung,W.S.B., Ho,P.C., Sequential use of letrozole and gonadotrophin in women with poor ovarian reserve: A randomized controlled trial, Reproductive Biomedicine Online, 23, 380-388, 2011	Not a comparison of interest
Legro,R.S., Metformin as adjuvant therapy to IVF in women with PCOS: when is intention-to-treat unintentional?, Human Reproduction, 26, 2043-2044, 2011	Narrative review with no new data reported
Lehert,P., Schertz,J.C., Ezcurra,D., Recombinant human follicle-stimulating hormone produces more oocytes with a lower total dose per cycle in assisted reproductive technologies compared with highly purified human menopausal gonadotrophin: a meta-analysis, Reproductive Biology and Endocrinology, 8, 112-, 2010	Includes quasi-randomised studies and data from abstracts
Lisi,F., Rinaldi,L., Fishel,S., Caserta,D., Lisi,R., Campbell,A., Evaluation of two doses of recombinant luteinizing hormone supplementation in an unselected group of women undergoing follicular stimulation for in vitro fertilization, Fertility and Sterility, 83, 309-315, 2005	About 30 percent of the women in a group did not receive the intervention they were allocated to.
Loumaye,E., Beltrami,V., Galazka,A., Hansson,C., Howles,C., Dupont,F., Pernin,M.O., Demoulin,A., Salat-Baroux,J., Alvarez,S., Frydman,R., Fanchin,R., Hazout,A., Barri,P., Bergh,T., Gudmunsson,J., Germond,M., Hull,M., Barlow,D.H., Clinical assessment of recombinant human follicle-stimulating hormone in stimulating ovarian follicular development before in vitro fertilization, Fertility and Sterility, 63, 77-86, 1995	Included in van Wely (2011) Cochrane review
MacLachlan,V., Besanko,M., O'Shea,F., Wade,H., Wood,C., Trounson,A., Healy,D.L., A controlled study of luteinizing hormone-releasing hormone agonist (buserelin) for the induction of folliculogenesis before in vitro fertilization, New England Journal of Medicine, 320, 1233-1237, 1989	Women were not randomised to treatment groups
Manassiev,N.A., Tenekedjier,K.I., Collins,J., Does the use of recombinant follicle-stimulating hormone instead of urinary follicle-stimulating hormone lead to higher pregnancy rates in in vitro fertilization-embryo transfer cycles?, Assisted Reproduction, 9, 7-12, 1999	All of the included studies were also considered in a more recent Cochrane review (van Wely, 2011)

Bibliographic information	Reason for exclusion
Mansour,R., Aboulghar,M., Serour,G.I., Al-Inany,H.G., Fahmy,I., Amin,Y., The use of clomiphene citrate/human menopausal gonadotrophins in conjunction with GnRH antagonist in an IVF/ICSI program is not a cost effective protocol, Acta Obstetricia et Gynecologica Scandinavica, 82, 48-52, 2003	Couples were not truly randomised - allocation was based on financial status
Mantzavinos,T., Phocas,I., Vitoratos,N., Photopoulos,S., Hassiakos,D., Antoniou,G., Comparison between steroid hormones and cortisol in serum and follicular fluid in stimulated and unstimulated cycles of in vitro fertilization patients, Gynecological Endocrinology, 11, 163-168, 1997	Not clear if women were randomised. Method of randomisation was not reported
Mashiach,S., Dor,J., Goldenberg,M., Shalev,J., Blankstein,J., Rudak,E., Shoam,Z., Finelt,Z., Nebel,L., Goldman,B., Protocols for induction of ovulation. The concept of programmed cycles, Annals of the New York Academy of Sciences, 541, 37-45, 1988	Unclear how many women were included in the denominator Unclear how randomisation was performed Unclear how the control group was chosen Unclear how many women received GnRH analogue
Matorras,R., Prieto,B., Exposito,A., Mendoza,R., Crisol,L., Herranz,P., Burgues,S., Mid-follicular LH supplementation in women aged 35-39 years undergoing ICSI cycles: a randomized controlled study.[Reprint of Reprod Biomed Online. 2009 Dec;19(6):879-87; PMID: 20031032], Reproductive Biomedicine Online, 22 Suppl 1, S43-S51, 2011	A previously printed version of this study is already included in the review. The text was checked and no relevant new information was reported.
Mayenga,J.M., Belaisch-Allart,J., Chouraqui,A., Tesquier,L., Serkine,A.M., Cohen,J., Plachot,M., Mandelbaum,J., Comparison between FSH-HP and hMG in IVF. Contraception Fertilite Sexualite, 25, 371-374, 1997	French language paper
Meden-Vrtovec,H., Pure FSH (Metrodin) for ovarian stimulation in the IVF-ET programme, Clinical and Experimental Obstetrics and Gynecology, 22, 9-13, 1995	It is not clear whether women were randomised to treatment groups
Meldrum,D.R., Patient preparation and standard stimulation regimens using gonadotropin-releasing hormone agonists, Clinical Obstetrics and Gynecology, 49, 4-11, 2006	Narrative review
Mikkelsen,A.L., Lindenberg,S., Benefit of FSH priming of women with PCOS to the in vitro maturation procedure and the outcome: a randomized prospective study, Reproduction, 122, 587-592, 2001	Randomisation was performed per cycle. Method of randomisation was not reported. Inconsistencies between figures reported in table and in text
Mitchell,R., Buckler,H.M., Matson,P., Lieberman,B., Burger,H.G., Hilton,B., Horne,G., Dyson,M., Robertson,W.R., Oestradiol and immunoreactive inhibin-like secretory patterns following controlled ovarian hyperstimulation with urinary (Metrodin) or recombinant follicle stimulating hormone (Puregon), Human Reproduction, 11, 962-967, 1996	Women were included in the Out (1995) study, which is included in the van Wely (2011) Cochrane review
Mohamed,M.A., Sbracia,M., Pacchiarotti,A., Micara,G., Linari,A., Tranquilli,D., Espinola,S.M., Aragona,C., Urinary follicle-stimulating hormone (FSH) is more effective than recombinant FSH in older women in a controlled randomized study, Fertility and Sterility, 85, 1398-1403, 2006	Included in van Wely (2011) Cochrane review
Moran,L., Tsagareli,V., Norman,R., Noakes,M., Diet and IVF pilot study: Short-term weight loss improves pregnancy rates in overweight/obese women undertaking IVF, Australian and New Zealand Journal of Obstetrics and Gynaecology, 51, 455-459, 2011	Not a comparison of interest

Bibliographic information	Reason for exclusion
Muasher,S., 'The use of GnRH-a in a luteal suppression vs follicular "flare-up" in conjunction with gonadotropins for ovarian hyperstimulation for in vitro fertilisation (IVF) in patients with normal basal gonadotropin levels: A randomised prospective study', Fertility and Sterility, 56, S42, 1991	Abstract only
Murber,A., Fancsovits,P., Ledo,N., Szakacs,M., Rigo,J., Urbancsek,J., Impact of highly purified versus recombinant follicle stimulating hormone on oocyte quality and embryo development in intracytoplasmic sperm injection cycles, Acta Biologica Hungarica, 62, 255-264, 2011	It is not clear which study this is a follow up to - the study it references is not an RCT. Described as a 'retrospective secondary analysis'. Relevant outcomes cannot be calculated per woman.
Musters,A.M., de Bekker-Grob,E.W., Mochtar,M.H., van,der,V, van Mello,N.M., Women's perspectives regarding subcutaneous injections, costs and live birth rates in IVF, Human Reproduction, 26, 2425-2431, 2011	Does not report any outcomes of interest
Myers,E.R., McCrory,D.C., Mills,A.A., Price,T.M., Swamy,G.K., Tantibhedhyangkul,J., Wu,J.M., Matchar,D.B., Effectiveness of assisted reproductive technology (ART), Evidence report/technology assessment, 1-195),;#2008. Date of Publication, -195, 2008	Review with no meta-analysis
Nakagawa,K., Ohgi,S., Kojima,R., Sugawara,K., Horikawa,T., Ito,M., Irahara,M., Saito,H., Recombinant-follicle stimulating hormone is more effective than urinary human menopausal gonadotropin in ovarian hyperstimulation for assisted reproductive technology treatment, Reproductive Medicine and Biology, 6, 27-32, 2007	Women were not truly randomised (allocation based on day of the week that treatment was started)
Nardo,L.G., Bellanca,S.A., Messina,K., Nardo,F., Efficacy of recombinant follicle stimulating hormone versus urinary follicle stimulating hormone in in-vitro fertilization: A prospective, randomized, assessor-blind study, Italian Journal of Gynaecology and Obstetrics, 12, 49-53, 2000	Included in van Wely (2010) Cochrane review
Nardo,L.G., Fleming,R., Howles,C.M., Bosch,E., Hamamah,S., Ubaldi,F.M., Hugues,J.N., Balen,A.H., Nelson,S.M., Conventional ovarian stimulation no longer exists: Welcome to the age of individualized ovarian stimulation, Reproductive Biomedicine Online, 23, 141-148, 2011	Narrative review with no new data
Nargund,G., Waterstone,J., Bland,J.M., Philips,Z., Parsons,J., Campbell,S., Cumulative conception and live birth rates in natural (unstimulated) IVF cycles, Human Reproduction, 16, 259-262, 2001	Non-comparative study
Nassar,Z., Massad,Z., Abdo,G., Fakih,M., Ovarian stimulation for in vitro fertilization (IVF): a prospective randomized comparison of recombinant FSH alone or in combination with human menopausal gonadotropins, Fertility and Sterility, 76, S92, 2001-, 2001	Conference abstract
Neyro,J.L., Moreno,J., Echanojauregui,A., Mallabiabarrena,G., Mendoza,R., Aparicio,M.V., Prospective and randomized study about two models of ovaric stimulation for IVF under hypophysary inhibition with GnRH agonists, Progresos En Obstetricia y Ginecologia, 38, 471-477, 1995	Spanish language paper
Ng,E.H., Lau,E.Y., Yeung,W.S., Ho,P.C., HMG is as good as recombinant human FSH in terms of oocyte and embryo quality: a prospective randomized trial, Human reproduction (Oxford, England), 16, 319-325, 2001	Included in van Wely (2010) Cochrane review

Bibliographic information	Reason for exclusion
Nugent,David, Vanderkerchove,Patrick, Hughes,Edward, Arnot,M., Lilford,Richard, Gonadotrophin therapy for ovulation induction in subfertility associated with polycystic ovary syndrome, Cochrane Database of Systematic Reviews, -, 2009	Does not compare ovulation induction drugs used in IVF treatment
Nyboe,Andersen A., Humaidan,P., Fried,G., Addition of rLH (Luveris) to rFSH during the fiinal days of follicular maturation in IVF/ICSI treated patients. A Nordic randomized multicentre trial, Human Reproduction, 21, i54, 2006-, 2006	Conference abstract
Nyboe,AndersenA, Pellicer,A., Devroey,P., Arce,J.C., A randomised trial (MEGASET) comparing highly purified menotropin and recombinant FSH in a GnRH antagonist cycle with single blastocyst transfer, Human Reproduction, 26, i118-, 2011	Conference abstract
Oehninger,S., Hodgen,G.D., Induction of ovulation for assisted reproduction programmes, Bailliere's Clinical Obstetrics and Gynaecology, 4, 541-573, 1990	Narrative review
Oliveira,J.B., Mauri,A.L., Petersen,C.G., Martins,A.M., Cornicelli,J., Cavanha,M., Pontes,A., Baruffi,R.L., Franco,J.G.,Jr., Recombinant luteinizing hormone supplementation to recombinant follicle-stimulation hormone during induced ovarian stimulation in the GnRH-agonist protocol: a meta-analysis1027, Journal of Assisted Reproduction and Genetics, 24, 67-75, 2007	Relevant outcomes are only reported per oocyte retrival
Olivennes,F., Belaich,Allart J., Alvarez,S., Bouchard,P., Frydman,R., A prospective randomized study comparing the use of HMG versus rec-FSH with the single dose GnRH antagonist (Cetrorelix) protocol in IVF-embryo transfer, Human Reproduction, 14, 61, 1999	Conference abstract
Olivennes,F., Belaich,Allart J., Alvarez,S., Bouchard,P., Frydman,R., The use of hMG versus rec-FSH with the single dose GnRH antagonist (Cetrorelix) protocol in IVF-ET: a prospective randomized study, Fertility and Sterility, 72, S114-S115, 1999	Conference abstract
Orvieto,R., Meltcer,S., Liberty,G., Rabinson,J., Anteby,E.Y., Nahum,R., Human menopausal gonadotropin versus highly purified-hMG in controlled ovarian hyperstimulation for in-vitro fertilisation: does purity improve outcome?, Gynecological Endocrinology, 26, 733-735, 2010	Retrospective study
Orvieto,R., Meltcer,S., Liberty,G., Rabinson,J., Anteby,E.Y., Nahum,R., A combined approach to patients with repeated IVF failures, Fertility and Sterility, 94, 2462-2464, 2010	Not an intervention of interest
Out,H.J., Driessen,S.G.A.J., Mannaerts,B.M.J.L., Coelingh,BenninkH, A pregnancy and children follow-up study of three randomised clinical trials with recombinant follicle-stimulating hormone (Puregon) in in-vitro fertilisation, Middle East Fertility Society Journal, 4, 28-34, 1999	Pooling of three studies that are included in the more up-to-date Van Wely (2011) Cochrane review
Out,H.J., Driessen,S.G.A.J., Mannaerts,B.M.J.L., Coelingh,BenninkH, Recombinant follicle-stimulating hormone (follitropin beta, Puregon) yields higher pregnancy rates in in vitro fertilization than urinary gonadotropins, Fertility and Sterility, 69, 40S-44S, 1998	A more up to date meta-analysis is available that includes the same comparisons (van Wely, 2011)
Out,H.J., Mannaerts,B.M., Driessen,S.G., Bennink,H.J., A prospective, randomized, assessor-blind, multicentre study comparing recombinant and urinary follicle stimulating hormone (Puregon versus Metrodin) in in-vitro fertilization, Human Reproduction, 10, 2534-2540, 1995	Included in van Wely (2011) Cochrane review

Bibliographic information	Reason for exclusion
Owen,E.J., West,C., Mason,B.A., Jacobs,H.S., Co-treatment with growth hormone of sub-optimal responders in IVF-ET, Human Reproduction, 6, 524-528, 1991	No relevant outcomes were reported. It is not clear if women were randomised to treatment.
Padilla,S.L., Dugan,K., Maruschak,V., Shalika,S., Smith,R.D., Use of the flare-up protocol with high dose human follicle stimulating hormone and human menopausal gonadotropins for in vitro fertilization in poor responders, Fertility and Sterility, 65, 796-799, 1996	Women were allocated to treatment based on predicted response to drugs. Women were not randomised to treatment
Padilla,S.L., Smith,R.D., Garcia,J.E., The Lupron screening test: tailoring the use of leuprolide acetate in ovarian stimulation for in vitro fertilization.[Erratum appears in Fertil Steril 1991 Dec;56(6):1210], Fertility and Sterility, 56, 79-83, 1991	It is not clear which gonadotrophins the flare up protocol group received
Palagiano,A., Nesti,E., Pace,L., FSH: urinary and recombinant. [25 refs], European Journal of Obstetrics, Gynecology, and Reproductive Biology, 115 Suppl 1, S30-S33, 2004	Narrative review
Papanikolaou,E.G., Polyzos,N.P., Humaidan,P., Pados,G., Bosch,E., Tournaye,H., Tarlatzis,B., Aromatase inhibitors in stimulated IVF cycles, Reproductive Biology and Endocrinology, 9, 85-, 2011	Not a comparison of interest
Platteau,P., Andersen,A.N., Balen,A., Devroey,P., Sorensen,P., Helmgaard,L., Arce,J.C., Similar ovulation rates, but different follicular development with highly purified menotrophin compared with recombinant FSH in WHO Group II anovulatory infertility: A randomized controlled study, Human Reproduction, 21, 1798-1804, 2006	Women did not receive IVF or ICSI
Platteau,P., Nyboe,Andersen A., Loft,A., Smitz,J., Danglas,P., Devroey,P., Highly purified HMG versus recombinant FSH for ovarian stimulation in IVF cycles, Reproductive Biomedicine Online, 17, 190-198, 2008	Analysis of two trials included in Van Wely Cochrane review
Pournaropoulos,F., Tarlatzis,B., Zepiridis,L., Bili,H., Grimbizis,G., Pados,G., Papadimas,J., Bontis,J., Prospective, blind, randomized evaluation of exogenous LH supplementation in the long GnRHa/recFSH stimulation protocol for IVF/ICSI, Human Reproduction, 19, i119, 2004	Conference abstract
Prak,F.M., Bots,R.S., Evers,J.L., Intravenous pulsatile administration of gonadotrophins in an in-vitro fertilization programme, Human Reproduction, 7, 176-179, 1992	It is not clear if women were randomised to the treatment groups
Propst,A.M., Bates,G.W., Robinson,R.D., Arthur,N.J., Martin,J.E., Neal,G.S., A randomized controlled trial of increasing recombinant follicle-stimulating hormone after initiating a gonadotropin-releasing hormone antagonist for in vitro fertilization-embryo transfer, Fertility and Sterility, 86, 58-63, 2006	Not possible to determine outcomes per woman
Pruksananonda,K., Suwajanakorn,S., Sereepapong,W., Virutamasen,P., Comparison of two different fixed doses of follitropin-beta in controlled ovarian hyperstimulation: A prospective randomized, double blind clinical trial, Journal of the Medical Association of Thailand, 87, 1151-1155, 2004	Outcome data is missing for 26% of women in one group and 30% in the other group
Rabinowitz,R., Simon,A., Lewin,A., Bar-Hava,I., Schenker,J.G., Laufer,N., Manipulating the follicular phase in IVF cycles: a comparison of two hMG stimulation protocols, Gynecological Endocrinology, 3, 117-123, 1989	Not a comparison of interest. Method of randomisation was not reported

Bibliographic information	Reason for exclusion
Rama,DeviP, Chatterjee,C., Rajyalakshmi,A., Navatha,P., Arshiya,F., A friendly IVF protocol, Journal of Obstetrics and Gynecology of India, 61, 77-80, 2011	It is not clear if women were randomised to treatment groups
Ramsewak,S.S., Cooke,I.D., Li,T.C., Kumar,A., Monks,N.J., Lenton,E.A., Are factors that influence oocyte fertilization also predictive? An assessment of 148 cycles of in vitro fertilization without gonadotropin stimulation, Fertility and Sterility, 54, 470-474, 1990	Included in van Wely (2010) Cochrane review
Ransom,M.X., Bohrer,M., Blotner,M.B., Kemmann,E., The difference in miscarriage rates between menotropin-induced and natural cycle pregnancies is not surveillance related, Fertility and Sterility, 59, 567-570, 1993	Women were not randomised to treatment groups. Some women received IUI and the results were not separated from those receiving IVF/ICSI
Rashidi,B.H., Sarvi,F., Tehrani,E.S., Zayeri,F., Movahedin,M., Khanafshar,N., The effect of HMG and recombinant human FSH on oocyte quality: a randomized single-blind clinical trial, European Journal of Obstetrics, Gynecology, and Reproductive Biology, 120, 190-194, 2005	Included in van Wely (2011) Cochrane review
Revelli,A., Poso,F., Gennarelli,G., Moffa,F., Grassi,G., Massobrio,M., Recombinant versus highly-purified, urinary follicle-stimulating hormone (r-FSH vs. HP-uFSH) in ovulation induction: a prospective, randomized study with cost-minimization analysis, Reproductive biology and endocrinology : RBandE, Vol.4, pp.38, 2006., -, -32676	Women did not receive IVF or ICSI
Rogers,P., Molloy,D., Healy,D., McBain,J., Howlett,D., Bourne,H., Thomas,A., Wood,C., Johnston,I., Trounson,A., Cross-over trial of superovulation protocols from two major in vitro fertilization centers, Fertility and Sterility, 46, 424-431, 1986	Women were not randomised
Schats,R., Sutter,P.D., Bassil,S., Kremer,J.A., Tournaye,H., Donnez,J., Ovarian stimulation during assisted reproduction treatment: a comparison of recombinant and highly purified urinary human FSH. On behalf of The Feronia and Apis study group, Human Reproduction, 15, 1691-1697, 2000	Included in van Wely (2011) Cochrane review
Scholtes,M.C., Schnittert,B., van,Hoogstraten D., Verhoeven,H.C., Zrener,A., Warne,D.W., A comparison of 3-day and daily follicle-stimulating hormone injections on stimulation days 1-6 in women undergoing controlled ovarian hyperstimulation, Fertility and Sterility, 81, 996-1001, 2004	Women received the same overall dose of FSH (150 IU daily vs 450 IU every 3 days)
Selman,H.A., De,Santo M., Sterzik,K., Coccia,E., El-Danasouri,I., Effect of highly purified urinary follicle-stimulating hormone on oocyte and embryo quality, Fertility and Sterility, 78, 1061-1067, 2002	Included in van Wely (2010) Cochrane review
Shanis,B.S., Check,J.H., Efficacy of gonadotropin-releasing hormone agonists to induce ovulation following low-dose human menopausal gonadotropin stimulation, Recent Progress in Hormone Research, 50, 483-486, 1995	It is unclear if women received IVF or ICSI. Method of randomisation was not reported
Sherwal,V., Malik,S., Bhatia,V., Effect of bromocriptine on the severity of ovarian hyperstimulation syndrome and outcome in high responders undergoing assisted reproduction, Journal of Human Reproductive Sciences, 3, 85-90, 2010	Not a comparison of interest.

Bibliographic information	Reason for exclusion
Smitz,J., Picton,H.M., Platteau,P., Rutherford,A., Cortvrindt,R., Clyde,J., Nogueira,D., Devroey,P., Lyby,K., Grondahl,C., Principal findings from a multicenter trial investigating the safety of follicular-fluid meiosis-activating sterol for in vitro maturation of human cumulus-enclosed oocytes, Fertility and Sterility, 87, 949-964, 2007	Relevant outcomes were not reported. Women were randomised to different culture mediums
Sterrenburg,M.D., Veltman-Verhulst,S.M., Eijkemans,M.J.C., Hughes,E.G., Macklon,N.S., Broekmans,F.J., Fauser,B.C.J.M., Clinical outcomes in relation to the daily dose of recombinant follicle-stimulating hormone for ovarian stimulation in in vitro fertilization in presumed normal responders younger than 39 years: A meta-analysis, Human Reproduction Update, 17, 184-196, 2011	Clinical pregnancy is meta-analysed by cycle rather than per woman. Included studies have been reviewed for the current review on an individual basis
Strehler,E., Abt,M., El-Danasouri,I., De,Santo M., Sterzik,K., Impact of recombinant follicle-stimulating hormone and human menopausal gonadotropins on in vitro fertilization outcome, Fertility and Sterility, 75, 332-336, 2001	Included in van Wely (2010) Cochrane review
Sunkara,S.K., Pundir,J., Khalaf,Y., Effect of androgen supplementation or modulation on ovarian stimulation outcome in poor responders: A meta-analysis, Reproductive BioMedicine Online, 22, 545-555, 2011	A systematic review and meta-analysis with only one relevant study. This study was considered separately for inclusion
Szilagyi,A., Bartfai,G., Manfai,A., Koloszar,S., Pal,A., Szabo,I., Low-dose ovulation induction with urinary gonadotropins or recombinant follicle stimulating hormone in patients with polycystic ovary syndrome, Gynecological Endocrinology, 18, 17-22, 2004	Women did not receive IVF or ICSI
Taketani,Y., Kelly,E., Yoshimura,Y., Hoshiai,H., Irahara,M., Mizunuma,H., Saito,H., Andoh,K., Bebia,Z., Yanaihara,T., Recombinant follicle-stimulating hormone (follitropin alfa) for ovulation induction in Japanese patients with anti-estrogen-ineffective oligo-or anovulatory infertility: Results of a phase II dose-response study, Reproductive Medicine and Biology, 9, 91-97, 2010	Women did not receive IVF or ICSI
van Hooff,M.H., Alberda,A.T., Huisman,G.J., Zeilmaker,G.H., Leerentveld,R.A., Doubling the human menopausal gonadotrophin dose in the course of an in-vitro fertilization treatment cycle in low responders: a randomized study, Human Reproduction, 8, 369-373, 1993	Women were allocated to treatment group by date of first visit
Van Horne,A.K., Bates,G.W.,Jr., Robinson,R.D., Arthur,N.J., Propst,A.M., Recombinant follicle-stimulating hormone (rFSH) supplemented with low-dose human chorionic gonadotropin compared with rFSH alone for ovarian stimulation for in vitro fertilization, Fertility and Sterility, 88, 1010-1013, 2007	Retrospective study
van,Wely M., Westergaard,L.G., Bossuyt,P.M., van,der,V, Effectiveness of human menopausal gonadotropin versus recombinant follicle-stimulating hormone for controlled ovarian hyperstimulation in assisted reproductive cycles: a meta-analysis, Fertility and Sterility, 80, 1086-1093, 2003	A more recent version of this Cochrane review is available (van Wely, 2011) and was considered for inclusion in the current review (van Wely, 2011)
Verberg,M.F.G., Macklon,N.S., Nargund,G., Frydman,R., Devroey,P., Broekmans,F.J., Fauser,B.C.J.M., Mild ovarian stimulation for IVF, Human Reproduction Update, 15, 13-29, 2009	Narrative review

Bibliographic information	Reason for exclusion
Westergaard,L.G., Erb,K., Laursen,S., Rasmussen,P.E., Rex,S., The effect of human menopausal gonadotrophin and highly purified, urine-derived follicle stimulating hormone on the outcome of in-vitro fertilization in down-regulated normogonadotrophic women, Human Reproduction, 11, 1209-1213, 1996	Women were randomised according to the start of their menstrual cycle, therefore not truly randomised
Westergaard,L.G., Erb,K., Laursen,S.B., Rex,S., Rasmussen,P.E., Human menopausal gonadotropin versus recombinant follicle-stimulating hormone in normogonadotropic women down-regulated with a gonadotropin-releasing hormone agonist who were undergoing in vitro fertilization and intracytoplasmic sperm injection: a prospective randomized study, Fertility and Sterility, 76, 543-549, 2001	Included in the van Wely (2011) Cochrane review
Westergaard,Lars W., Bossuyt,MM Patrick, Van der Veen,Fulco, van Wely,Madelon, Human menopausal gonadotropin versus recombinant follicle stimulation hormone for ovarian stimulation in assisted reproductive cycles, Cochrane Database of Systematic Reviews, -, 2011	All included studies were considered for inclusion in the more substantial Cochrane review by van Wely (2011)
Xydias,G., Liarmakopoulou,S., Argyriou,A., Sarella,A., Dimaki,A., Pappa,H., A controlled trial of natural cycles with and without GnRH antagonist administration in poor responder women: Preliminary results, Review of Clinical Pharmacology and Pharmacokinetics, International Edition, 21, 91-92, 2007	Not clear whether women were randomised
Yang,T.S., Wang,B.C., Chang,S.P., Ng,H.T., Comparison of human menopausal gonadotropin and follicle-stimulating hormone with gonadotropin-releasing hormone agonist desensitization for controlled ovarian hyperstimulation in in vitro fertilization, Chung Hua i Hsueh Tsa Chih - Chinese Medical Journal, 55, 452-456, 1995	Women may not have been truly randomised (n=25, n=17)
Yarali,H., Bukulmez,O., Gurgan,T., Urinary follicle-stimulating hormone (FSH) versus recombinant FSH in clomiphene citrate-resistant, normogonadotropic, chronic anovulation: A prospective randomized study, Fertility and Sterility, 72, 276-281, 1999	Women did not receive IVF or ICSI
Yokoi,N., Uemura,T., Murase,M., Kondoh,Y., Ishikawa,M., Hirahara,F., A modified hMG-GnRH method for the induction of ovulation in infertile women with severe hypogonadotropic amenorrhea, Endocrine Journal, 49, 159-164, 2002	Women did not receive IVF or ICSI
Yong,E.L., Ng,S.C., Chan,C.L.K., Kumar,J., Teo,L.S., Ratnam,S.S., Chronic low-dose follicle-stimulating hormone compared with clomiphene/human menopausal gonadotropin for induction of ovulation, Gynecological Endocrinology, 11, 35-42, 1997	Women did not receive IVF or ICSI
Younis,J.S., Ezra,Y., Brzezinnski,A., Fibich,T., Schenker,J.G., Laufer,N., The effect of growth hormone on granulosa cell function during in-vitro fertilization, Human Reproduction, 8, 1588-1592, 1993	Relevant outcomes were not reported. Method of randomisation was not reported
Younis,J.S., Simon,A., Koren,R., Dorembus,D., Schenker,J.G., Laufer,N., The effect of growth hormone supplementation on in vitro fertilization outcome: a prospective randomized placebo-controlled double-blind study, Fertility and Sterility, 58, 575-580, 1992	The study was still ongoing at the time of the paper being written - up to 10/42 (24%) of the women were still pregnant
Zarek,S.M., Muasher,S.J., Mild/minimal stimulation for in vitro fertilization: an old idea that needs to be revisited, Fertility and Sterility, 95, 2449-2455, 2011	Narrative review with retrospective data

Bibliographic information	Reason for exclusion
Ziebe,S., Lundin,K., Janssens,R., Helmgaard,L., Arce,J.C., MERIT (Menotrophin vs Recombinant FSH in vitro Fertilisation Trial) Group., Influence of ovarian stimulation with HP-hMG or recombinant FSH on embryo quality parameters in patients undergoing IVF, Human Reproduction, 22, 2404-2413, 2007	Included in van Wely (2011) Cochrane review

IVF ovulation trigger

Table G.12 Which is the most effective ovulation trigger to use as part of an ovarian stimulation strategy for women undergoing IVF or ICSI treatment?

Bibliographic information	Reason for exclusion
Abdelmassih,V., Oliveira,F.G., Goncalves,S.P., Varella,A.D., Diamond,M.P., Abdelmassih,R., A prospective, randomized and blinded comparison between 10,000 IU urinary and 250 microg recombinant human chorionic gonadotropin for oocyte maturation in in vitro fertilization cycles, Journal of Assisted Reproduction and Genetics, 22, 149-153, 2005	Included in Youssef (2011) Cochrane review
Acevedo,B., Gomez-Palomares,J.L., Ricciarelli,E., ndez,E.R., Triggering ovulation with gonadotropin-releasing hormone agonists does not compromise embryo implantation rates, Fertility and Sterility, 86, 1682-1687, 2006	Included in Youssef (2011) Cochrane review
Agostini,F., Monti,F., De,PascalisL, Paterlini,M., La,SalaG, Blickstein,I., Psychosocial support for infertile couples during assisted reproductive technology treatment, Fertility and Sterility, 95, 707-710, 2011	Compared men's and women's perceived psychosocial support during IVF - not a comparison of interest
Babayof,R., Margalioth,E.J., Huleihel,M., Amash,A., Zylber-Haran,E., Gal,M., Brooks,B., Mimoni,T., Eldar-Geva,T., Serum inhibin A, VEGF and TNFalpha levels after triggering oocyte maturation with GnRH agonist compared with HCG in women with polycystic ovaries undergoing IVF treatment: a prospective randomized trial, Human Reproduction, 21, 1260-1265, 2006	Included in Youssef (2011) Cochrane review
Beckers,N.G., Macklon,N.S., Eijkemans,M.J., Ludwig,M., Felberbaum,R.E., Diedrich,K., Bustion,S., Loumaye,E., Fauser,B.C., Nonsupplemented luteal phase characteristics after the administration of recombinant human chorionic gonadotropin, recombinant luteinizing hormone, or gonadotropin-releasing hormone (GnRH) agonist to induce final oocyte maturation in in vitro fertilization patients after ovarian stimulation with recombinant follicle-stimulating hormone and GnRH antagonist cotreatment, The Journal of clinical endocrinology and metabolism, 88, 4186-4192, 2003	Included in Youssef (2011) Cochrane review
Buckett,W.M., Bentick,B., Shaw,R.W., Induction of the endogenous gonadotrophin surge for oocyte maturation with intra-nasal gonadotrophin-releasing hormone analogue (buserelin): effective minimal dose, Human Reproduction, 13, 811-814, 1998	Not a comparison of interest (compares different dosages of GnRH agonist for triggering)
Buckett,W.M., Chian,R.C., Tan,S.L., Human chorionic gonadotropin for in vitro oocyte maturation: does it improve the endometrium or implantation?2044, Journal of Reproductive Medicine, 49, 93-98, 2004	Results were reported per cycle

Bibliographic information	Reason for exclusion
Chang,P., Kenley,S., Burns,T., Denton,G., Currie,K., DeVane,G., O'Dea,L., Recombinant human chorionic gonadotropin (rhCG) in assisted reproductive technology: results of a clinical trial comparing two doses of rhCG (Ovidrel) to urinary hCG (Profasi) for induction of final follicular maturation in in vitro fertilization-embryo transfer, Fertility and Sterility, 76, 67-74, 2001	Included in Youssef (2011) Cochrane review
D'Amato,G., Caroppo,E., Pasquadibisceglie,A., Carone,D., Vitti,A., Vizziello,G.M., A novel protocol of ovulation induction with delayed gonadotropin-releasing hormone antagonist administration combined with high-dose recombinant follicle-stimulating hormone and clomiphene citrate for poor responders and women over 35 years1977, Fertility and Sterility, 81, 1572-1577, 2004	Method of randomisation inadequate (based on day of first presentation at clinic)
D'Angelo,A., Amso,N., "Coasting" (withholding gonadotrophins) for preventing ovarian hyperstimulation syndrome, Cochrane database of systematic reviews (Online), #2002. Date of Publication, CD002811-, 2002	Coasting vs. early aspiration - not relevant to the trigger phase of IVF
Dayal,M.B., Frankfurter,D., O'Hern,C., Peak,D., Dubey,A., Gindoff,P.R., The use of lead follicle diameter to initiate gonadotropin-releasing hormone antagonist does not affect in vitro fertilization clinical pregnancy, implantation, or live birth rates: a prospective, randomized study, Fertility and Sterility, 92, 2047-2049, 2009	Compares when GnRH antagonist is administered - both groups received the same drugs
DiLuigi,A.J., Engmann,L., Schmidt,D.W., Maier,D.B., Nulsen,J.C., Benadiva,C.A., Gonadotropin-releasing hormone agonist to induce final oocyte maturation prevents the development of ovarian hyperstimulation syndrome in high-risk patients and leads to improved clinical outcomes compared with coasting, Fertility and Sterility, 94, 1111-1114, 2010	Women were not randomised to treatment groups
Emperaire,J.C., Parneix,I., Ruffie,A., Triggering of ovulation without HCG, GYNECOL REV GYNECOL, 2, 269-274, 1994	French language paper
Emperaire,J.C., Ruffie,A., Audeberg,A.J.M., Induction of ovulation triggered by endogenous lutenising hormone after giving and LHRH agonist following stimulation of the follicles for IVF. et biologie de la reproduction, 21, 489-494, 1992	French language paper
Engmann,L., DiLuigi,A., Schmidt,D., Nulsen,J., Maier,D., Benadiva,C., Prevention of Ovarian Hyperstimulation Syndrome (OHSS) With the Use of Gonadotropin Releasing Hormone (GnRH) Agonist to Trigger Final Oocyte Maturation After Cotreatment With GnRH Antagonist in Patients With Polycystic Ovarian Syndrome (PCOS) or Previous High Response Undergoing IVF Treatment-A Prospective Randomized Clinical Trial, Fertility and Sterility, Vol.84 Suppl 1, pp.S96, 2005., -, None	Retrospective study
Engmann,L., DiLuigi,A., Schmidt,D., Nulsen,J., Maier,D., Benadiva,C., The use of gonadotropin-releasing hormone (GnRH) agonist to induce oocyte maturation after cotreatment with GnRH antagonist in high-risk patients undergoing in vitro fertilization prevents the risk of ovarian hyperstimulation syndrome: a prospective randomized controlled study, Fertility and Sterility, 89, 84-91, 2008	IVF protocols varied in terms of pretreatment, down regulation, trigger and luteal phase support between the two groups. It is not possible to conclude which aspect of the IVF protocol was responsible for any significant differences in results.

Bibliographic information	Reason for exclusion
Engmann,L., Romak,J., Nulsen,J., Benadiva,C., Peluso,J., In vitro viability and secretory capacity of human luteinized granulosa cells after gonadotropin-releasing hormone agonist trigger of oocyte maturation, Fertility and Sterility, 96, 198-202, 2011	No relevant outcomes reported
European Recombinant LH Study Group., Human recombinant luteinizing hormone is as effective as, but safer than, urinary human chorionic gonadotropin in inducing final follicular maturation and ovulation in in vitro fertilization procedures: results of a multicenter double-blind study, Journal of Clinical Endocrinology and Metabolism, 86, 2607-2618, 2001	Included in the Youssef (2011) Cochrane review
Galindo,A., Bodri,D., Guillen,J.J., Colodron,M., Vernaeve,V., Coll,O., Triggering with HCG or GnRH agonist in GnRH antagonist treated oocyte donation cycles: a randomised clinical trial, Gynecological Endocrinology, 25, 60-66, 2009	Included in Youssef (2011) Cochrane review
Gomes,M.K.O., Vieira,C.S., Moura,M.D., Manetta,L.A., Leite,S.P., Reis,R.M., Ferriani,R.A., Controlled ovarian stimulation with exclusive FSH followed by stimulation with hCG alone, FSH alone or hMG, European Journal of Obstetrics Gynecology and Reproductive Biology, 130, 99-106, 2007	This is a luteal phase support study - included in Q14E
Gonen,Y., Balakier,H., Powell,W., Casper,R.F., Use of gonadotropin-releasing hormone agonist to trigger follicular maturation for in vitro fertilization, Journal of Clinical Endocrinology and Metabolism, 71, 918-922, 1990	Four women crossed over and received both treatments in different cycles. The data are not reported separately.
Griesinger,G., Diedrich,K., Devroey,P., Kolibianakis,E.M., GnRH agonist for triggering final oocyte maturation in the GnRH antagonist ovarian hyperstimulation protocol: a systematic review and meta-analysis. [44 refs], Human Reproduction Update, 12, 159-168, 2006	All studies in this meta-analysis are included in the more recent Youssef (2011) Cochrane review
Homburg,R., Levy,T., Ben-Rafael,Z., A comparative prospective study of conventional regimen with chronic low- dose administration of follicle-stimulating hormone for anovulation associated with polycystic ovary syndrome, Fertility and Sterility, 63, 729-733, 1995	Women were not randomised to treatment groups
Hugues,J.N., Induction of ovulation in World Health Organization group II anovulatory women undergoing follicular stimulation with recombinant human follicle-stimulating hormone: A comparison of recombinant human chorionic gonadotropin (rhCG) and urinary hCG, Fertility and Sterility, 75, 1111-1118, 2001	Women received either IUI or timed intercourse
Humaidan,P., Bredkjaer,H.E., Bungum,L., Bungum,M., ndahl,M.L., Westergaard,L., Andersen,C.Y., GnRH agonist (buserelin) or hCG for ovulation induction in GnRH antagonist IVF/ICSI cycles: a prospective randomized study, Human Reproduction, 20, 1213-1220, 2005	Included in Youssef (2011) Cochrane review
Humaidan,P., Bungum,L., Bungum,M., Yding,Andersen C., Rescue of corpus luteum function with peri-ovulatory HCG supplementation in IVF/ICSI GnRH antagonist cycles in which ovulation was triggered with a GnRH agonist: a pilot study, Reproductive Biomedicine Online, 13, 173-178, 2006	Included in Youssef (2011) Cochrane review
Humaidan,P., Ejdrup,Bredkjaer H., Westergaard,L.G., Yding,Andersen C., 1,500 IU human chorionic gonadotropin administered at oocyte retrieval rescues the luteal phase when gonadotropin-releasing hormone agonist is used for ovulation induction: a prospective, randomized, controlled study, Fertility and Sterility, 93, 847-854, 2010	Included in cochrane review (Youssef 2010)

Bibliographic information	Reason for exclusion
Humaidan,P., Kol,S., Papanikolaou,E.G., GnRH agonist for triggering of final oocyte maturation: Time for a change of practice?, Human Reproduction Update, 17, 510-524, 2011	A Cochrane Review covering the same search dates is available with more relevant outcomes reported. The same studies are included except one (Engmann, 1998), which will be considered separately for the current review
Induction of final follicular maturation and early luteinization in women undergoing ovulation induction for assisted reproduction treatment--recombinant HCG versus urinary HCG. The European Recombinant Human Chorionic Gonadotrophin Study Group, Human Reproduction, 15, 1446-1451, 2000	Included in Youssef (2011) Cochrane review
Kahraman,S., Karlikaya,G., Kavrut,M., Karagozoglu,H., A prospective, randomized, controlled study to compare two doses of recombinant human chorionic gonadotropin in serum and follicular fluid in woman with high body mass index, Fertility and Sterility, 93, -2087, 2010	Not a comparison of interest - compares dose of trigger
Koichi,K., Yukiko,N., Shima,K., Sachiko,S., Efficacy of low-dose human chorionic gonadotropin (hCG) in a GnRH antagonist protocol10945, Journal of Assisted Reproduction and Genetics, 23, 223-228, 2006	It is not clear if this is an IVF/ICSI study or whether IUI was also performed
Kol,S., Humaidan,P., Itskovitz-Eldor,J., GnRH agonist ovulation trigger and hCG-based, progesterone-free luteal support: A proof of concept study, Human Reproduction, 26, 2874-2877, 2011	Non-comparative observational study
Kolibianakis,E.M., Schultze-Mosgau,A., Schroer,A., Van,Steirteghem A., Devroey,P., Diedrich,K., Griesinger,G., A lower ongoing pregnancy rate can be expected when GnRH agonist is used for triggering final oocyte maturation instead of HCG in patients undergoing IVF with GnRH antagonists, Human Reproduction, 20, 2887-2892, 2005	Included in Youssef (2011) Cochrane review
Kosmas,I.P., Zikopoulos,K., Georgiou,I., Paraskevaidis,E., Blockeel,C., Tournaye,H., Van der,Elst J., Devroey,P., Low-dose HCG may improve pregnancy rates and lower OHSS in antagonist cycles: a meta-analysis, Reproductive Biomedicine Online, 19, 619-630, 2009	Denominator for outcomes was not reported
Kovacs,P., Kovats,T., Bernard,A., Zadori,J., Szmatona,G., Kaali,S.G., Comparison of serum and follicular fluid hormone levels with recombinant and urinary human chorionic gonadotropin during in vitro fertilization, Fertility and Sterility, 90, 2133-2137, 2008	Included in Youssef (2011) Cochrane review
Loumaye,E., Recombinant human luteinizing hormone is as effective as, but safer than, urinary human chorionic gonadotropin in inducing final follicular maturation and ovulation in in vitro fertilization procedures: Results of a multicenter double-blind study, Journal of Clinical Endocrinology and Metabolism, 86, 2607-2618, 2001	Included in Youssef (2011) review
Manau,D., bregues,F., Arroyo,V., nez,W., Vanrell,J.A., Balasch,J., Hemodynamic changes induced by urinary human chorionic gonadotropin and recombinant luteinizing hormone used for inducing final follicular maturation and luteinization, Fertility and Sterility, 78, 1261-1267, 2002	Included in Youssef (2011) Cochrane review
Meldrum,D.R., Patient preparation and standard stimulation regimens using gonadotropin-releasing hormone agonists, Clinical Obstetrics and Gynecology, 49, 4-11, 2006	Narrative review

Bibliographic information	Reason for exclusion
Melo,M., Busso,C.E., Bellver,J., Alama,P., Garrido,N., Meseguer,M., Pellicer,A., Remoh, J., GnRH agonist versus recombinant HCG in an oocyte donation programme: a randomized, prospective, controlled, assessor-blind study, Reproductive Biomedicine Online, 19, 486-492, 2009	Donor oocytes were used
Melo,M.A.B., Busso,C.E., Alama,P., Meseguer,M., Garrido,N., Remohi, A randomized, prospective, assessor-blind, parallel groups, comparing GnRHa versus rhCG as a trigger final oocyte maturation in GNRH antagonist IVF/ICSI cycles, Fertility and Sterility, Vol.88 Suppl 1, pp.43, Abstract no: 114, 2007., 114, 2007-, 2007	Conference abstract. Results included in Youssef (2011) Cochrane review
Myers,E.R., McCrory,D.C., Mills,A.A., Price,T.M., Swamy,G.K., Tantibhedhyangkul,J., Wu,J.M., Matchar,D.B., Effectiveness of assisted reproductive technology (ART), Evidence report/technology assessment, 1-195),;#2008. Date of Publication, -195, 2008	Review with no meta-analysis
Nargund,G., Waterstone,J., Bland,J.M., Philips,Z., Parsons,J., Campbell,S., Cumulative conception and live birth rates in natural (unstimulated) IVF cycles, Human Reproduction, 16, 259-262, 2001	Non-comparative study
Nassar,Z., Massad,Z., Abdo,G., Fakih,M., Ovarian stimulation for in vitro fertilization (IVF): a prospective randomized comparison of recombinant FSH alone or in combination with human menopausal gonadotropins, Fertility and Sterility, 76, S92, 2001-, 2001	Conference abstract
Nevo,O., Eldar-Geva,T., Kol,S., Itskovitz-Eldor,J., Lower levels of inhibin A and pro-alphaC during the luteal phase after triggering oocyte maturation with a gonadotropin-releasing hormone agonist versus human chorionic gonadotropin, Fertility and Sterility, 79, 1123-1128, 2003	Observational uncontrolled study
Oehninger,S., Hodgen,G.D., Induction of ovulation for assisted reproduction programmes, Bailliere's Clinical Obstetrics and Gynaecology, 4, 541-573, 1990	Narrative review
Ossina,E., Yavorovskaya,K., Kuzmichev,L., Kornilov,N., Belikov,V., Belikova,O., Samoilova,A., Yanchuk,T., Beloborodov,S., Triggering of final oocyte maturation in GnRH antagonist IVF protocols: triptorelin 0.1 mg versus hCG. A randomized multicenter trial, Human Reproduction, 19, i102-i103p, 2004	Conference abstract
Palagiano,A., Nesti,E., Pace,L., FSH: urinary and recombinant. [25 refs], European Journal of Obstetrics, Gynecology, and Reproductive Biology, 115 Suppl 1, S30-S33, 2004	Narrative review
Papanikolaou,E.G., Bourgain,C., Fatemi,H., Verpoest,W., Polyzos,N.P., De,Brabanter A., Kolibianakis,E., Tarlatzis,B., Devroey,P., Tournaye,H., Endometrial advancement after triggering with recombinant or urinary HCG: a randomized controlled pilot study, Reproductive Biomedicine Online, 21, 50-55, 2010	Study conducted by the same authors over the same study dates as in Papanikolaou (2010) 'Higher birth rate after recombinant hCG triggering compared with urinary-derived hCG in single-blastocyst IVF antagonist cycles: a randomised controlled trial'. The other study has included more women and reported on more outcomes and so will be considered for inclusion above this study.

Bibliographic information	Reason for exclusion
Pirard,C., Donnez,J., Loumaye,E., GnRH agonist as luteal phase support in assisted reproduction technique cycles: results of a pilot study, Human Reproduction, 21, 1894-1900, 2006	Included in Youssef (2011) Cochrane review
Rogers,P., Molloy,D., Healy,D., McBain,J., Howlett,D., Bourne,H., Thomas,A., Wood,C., Johnston,I., Trounson,A., Cross-over trial of superovulation protocols from two major in vitro fertilization centers, Fertility and Sterility, 46, 424-431, 1986	Women were not randomised
Shalev,E., Geslevich,Y., Matilsky,M., Ben-Ami,M., Gonadotrophin-releasing hormone agonist compared with human chorionic gonadotrophin for ovulation induction after clomiphene citrate treatment, Human Reproduction, 10, 2541-2544, 1995	Women did not receive IVF or ICSI
Shanis,B.S., Check,J.H., Efficacy of gonadotropin-releasing hormone agonists to induce ovulation following low-dose human menopausal gonadotropin stimulation, Recent Progress in Hormone Research, 50, 483-486, 1995	It is unclear if women received IVF or ICSI. Method of randomisation was not reported
Shapiro,B.S., Daneshmand,S.T., Garner,F.C., Aguirre,M., Thomas,S., Gonadotropin-releasing hormone agonist combined with a reduced dose of human chorionic gonadotropin for final oocyte maturation in fresh autologous cycles of in vitro fertilization683, Fertility and Sterility, 90, 231-233, 2008	Retrospective study
Verberg,M.F.G., Macklon,N.S., Nargund,G., Frydman,R., Devroey,P., Broekmans,F.J., Fauser,B.C.J.M., Mild ovarian stimulation for IVF, Human Reproduction Update, 15, 13-29, 2009	Narrative review
Yokoi,N., Uemura,T., Murase,M., Kondoh,Y., Ishikawa,M., Hirahara,F., A modified hMG-GnRH method for the induction of ovulation in infertile women with severe hypogonadotropic amenorrhea, Endocrine Journal, 49, 159-164, 2002	Women did not receive IVF or ICSI
Youssef,Mohamed A.F.M., Van der Veen,Fulco, Al-Inany,Hesham G., Griesinger,Georg, Mochtar,Monique H., van Wely,Madelon, Gonadotropin-releasing hormone agonist versus HCG for oocyte triggering in antagonist assisted reproductive technology cycles, Cochrane Database of Systematic Reviews, -, 2009	There is a 2011 version of this Cochrane review available (Youssef, 2011)

IVF embryo transfer strategies

Table G.13 What is the effectiveness and safety of different embryo transfer strategies?

Bibliographic information	Reason for exclusion
Baruffi,R.L., Mauri,A.L., Petersen,C.G., Nicoletti,A., Pontes,A., Oliveira,J.B., Franco,J.G.,Jr., Single-embryo transfer reduces clinical pregnancy rates and live births in fresh IVF and Intracytoplasmic Sperm Injection (ICSI) cycles: a meta-analysis, Reproductive Biology and Endocrinology, 7, 36-, 2009	Reviews the same papers as those included.
Bhattacharya,S., Templeton,A., What is the most relevant standard of success in assisted reproduction? Redefining success in the context of elective single embryo transfer: evidence, intuition and financial reality. [29 refs], Human Reproduction, 19, 1939-1942, 2004	Review

Bibliographic information	Reason for exclusion
Blake,D.A., Farquhar,C.M., Johnson,N., Proctor,M., Cleavage stage versus blastocyst stage embryo transfer in assisted conception. [95 refs][Update of Cochrane Database Syst Rev. 2005;(4):CD002118; PMID: 16235296], Cochrane Database of Systematic Reviews, CD002118-, 2007	This review has since been updated
Blake,Debbie, Farquhar,Cindy, Johnson,Neil, Proctor,Michelle, Cleavage stage versus blastocyst stage embryo transfer in assisted reproductive technology, Cochrane Database of Systematic Reviews, -, 2010	Individual relevant studies from this review have been included
Cutting,R., Morroll,D., Roberts,S.A., Pickering,S., Rutherford,A., BFS and ACE., Elective single embryo transfer: guidelines for practice British Fertility Society and Association of Clinical Embryologists, Human Fertility, 11, 131-146, 2008	Background/ context
Dare,M.R., Crowther,C.A., Dodd,J.M., Norman,R.J., Single or multiple embryo transfer following in vitro fertilisation for improved neonatal outcome: a systematic review of the literature. [53 refs], Australian and New Zealand Journal of Obstetrics and Gynaecology, 44, 283-291, 2004	Review of older observational papers. Includes abstracts.
Davis,L.B., Lathi,R.B., Westphal,L.M., Milki,A.A., Elective single blastocyst transfer in women older than 35, Fertility and Sterility, 89, 230-231, 2008	Letter no data
de,Klerk C., Heijnen,E.M., Macklon,N.S., Duivenvoorden,H.J., Fauser,B.C., Passchier,J., Hunfeld,J.A., The psychological impact of mild ovarian stimulation combined with single embryo transfer compared with conventional IVF, Human Reproduction, 21, 721-727, 2006	Study compared single embryo transfer plus mild overain stimulation with double embryo transfer with conventional ovarian stimulation
De,Neubourg D., Daels,C., Elseviers,M., Mangelschots,K., Vercruyssen,M., Van,Royen E., Cumulative live-birth delivery after IVF/ICSI since the progressive introduction of single-embryo transfer, Reproductive Biomedicine Online, 20, 836-842, 2010	
De,Neubourg D., Gerris,J., Van,Royen E., Mangelschots,K., Vercruyssen,M., Impact of a restriction in the number of embryos transferred on the multiple pregnancy rate, European Journal of Obstetrics, Gynecology, and Reproductive Biology, 124, 212-215, 2006	Background material
Dean,N.L., Phillips,S.J., Buckett,W.M., Biljan,M.M., Tan,S.L., Impact of reducing the number of embryos transferred from three to two in women under the age of 35 who produced three or more high-quality embryos, Fertility and Sterility, 74, 820-823, 2000	Older paper when policy on embryo transfer was different
Fauque,P., Jouannet,P., Davy,C., Guibert,J., Viallon,V., Epelboin,S., Kunstmann,J.M., Patrat,C., Cumulative results including obstetrical and neonatal outcome of fresh and frozen-thawed cycles in elective single versus double fresh embryo transfers, Fertility and Sterility, 94, 927-935, 2010	Small single site study
Fiddelers,A.A., van Montfoort,A.P., Dirksen,C.D., Dumoulin,J.C., Land,J.A., Dunselman,G.A., Janssen,J.M., Severens,J.L., Evers,J.L., Single versus double embryo transfer: cost-effectiveness analysis alongside a randomized clinical trial, Human Reproduction, 21, 2090-2097, 2006	

Bibliographic information	Reason for exclusion
Frattarelli,J.L., Leondires,M.P., McKeeby,J.L., Miller,B.T., Segars,J.H., Blastocyst transfer decreases multiple pregnancy rates in in vitro fertilization cycles: a randomized controlled trial, Fertility and Sterility, 79, 228-230, 2003	No standard embryo transfer strategy used
Gelbaya,T.A., Tsoumpou,I., Nardo,L.G., The likelihood of live birth and multiple birth after single versus double embryo transfer at the cleavage stage: a systematic review and meta-analysis. [42 refs], Fertility and Sterility, 94, 936-945, 2010	Reviews same papers as NCC review
Gerris,J.M., Single embryo transfer and IVF/ICSI outcome: a balanced appraisal. [212 refs], Human Reproduction Update, 11, 105-121, 2005	General review paper
Henman,M., Catt,J.W., Wood,T., Bowman,M.C., de Boer,K.A., Jansen,R.P., Elective transfer of single fresh blastocysts and later transfer of cryostored blastocysts reduces the twin pregnancy rate and can improve the in vitro fertilization live birth rate in younger women, Fertility and Sterility, 84, 1620-1627, 2005	Single centre with only 121 couples
Hu,Y., Maxson,W.S., Hoffman,D.I., Ory,S.J., Eager,S., Dupre,J., Lu,C., Maximizing pregnancy rates and limiting higher-order multiple conceptions by determining the optimal number of embryos to transfer based on quality, Fertility and Sterility, 69, 650-657, 1998	Single site small cohort study
Kallen,B., Finnstrom,O., Lindam,A., Nilsson,E., Nygren,K.G., Olausson,P.O., Blastocyst versus cleavage stage transfer in in vitro fertilization: differences in neonatal outcome?, Fertility and Sterility, 94, 1680-1683, 2010	Included in Q3b
Korosec,S., Virant-Klun,I., Tomazevic,T., Zech,N.H., Meden-Vrtovec,H., Single fresh and frozen-thawed blastocyst transfer using hyaluronan-rich transfer medium, Reproductive Biomedicine Online, 15, 701-707, 2007	Study compared fresh single embryo transfer with frozen/thawed embryo transfer
Leniaud,L., Poncelet,C., Porcher,R., Martin-Pont,B., Cedrin-Durnerin,I., Hugues,J.N., Wolf,J.P., Sifer,C., Prospective evaluation of elective single-embryo transfer versus double-embryo transfer following in vitro fertilization: a two-year French hospital experience. [French], Gynecologie, Obstetrique and Fertilite, 36, 159-165, 2008	
Levitas,E., Lunenfeld,E., Har-Vardi,I., Albotiano,S., Sonin,Y., Hackmon-Ram,R., Potashnik,G., Blastocyst-stage embryo transfer in patients who failed to conceive in three or more day 2-3 embryo transfer cycles: a prospective, randomized study, Fertility and Sterility, 81, 567-571, 2004	No standardised embryo transfer strategy used - more than 2 embryos.
Lieberman,B., Ali,R., Rangarajan,S., Towards the elective replacement of a single embryo (eSET) in the United Kingdom, Human Fertility, 10, 123-127, 2007	Discussion paper and general review
Luke,B., Brown,M.B., Grainger,D.A., Cedars,M., Klein,N., Stern,J.E., Society for Assisted Reproductive Technology Writing Group., Practice patterns and outcomes with the use of single embryo transfer in the United States, Fertility and Sterility, 93, 490-498, 2010	Included in Q3b
Luke,B., Brown,M.B., Stern,J.E., Grainger,D.A., Klein,N., Cedars,M., Effect of embryo transfer number on singleton and twin implantation pregnancy outcomes after assisted reproductive technology, Journal of Reproductive Medicine, 55, 387-394, 2010	Included in Q3b. Subset of study 3397

Bibliographic information	Reason for exclusion
Lundin,K., Bergh,C., Cumulative impact of adding frozen-thawed cycles to single versus double fresh embryo transfers, Reproductive Biomedicine Online, 15, 76-82, 2007	Single centre retrospective analysis
Maheshwari,A., Griffiths,S., Bhattacharya,S., Global variations in the uptake of single embryo transfer, Human Reproduction Update, 17, 107-120, 2011	General review on uptake of SET
Margreiter,M., Weghofer,A., Kogosowski,A., Mahmoud,K.Z., Feichtinger,W., A prospective randomized multicenter study to evaluate the best day for embryo transfer: does the outcome justify prolonged embryo culture?, Journal of Assisted Reproduction and Genetics, 20, 91-94, 2003	Study do not provide data on Day 5/6 embryo transfer
Min,J.K., Hughes,E., Young,D., Gysler,M., Hemmings,R., Cheung,A.P., Goodrow,G.J., Senikas,V., Wong,B.C., Sierra,S., Carranza-Mamane,B., Case,A., Dwyer,C., Graham,J., Havelock,J., Lee,F., Liu,K., Vause,T., Joint Society of Obstetricians and Gynaecologists of Canada-Canadian Fertility and Andrology Society Clinical Practice Guidelines Committee., Elective single embryo transfer following in vitro fertilization, Journal of Obstetrics and Gynaecology Canada: JOGC, 32, 363-377, 2010	Background/context
Montag,M., van,der,V, Dorn,C., van,der,V, Extended embryo culture reduces the implantation rate on day 4 and day 5 when only a maximum of three embryos are cultured beyond the pronuclear stage, European Journal of Obstetrics, Gynecology, and Reproductive Biology, 124, 65-69, 2006	Potentially includes more than two embryos
Moragianni,V.A., Cohen,J.D., Smith,S.E., Schinfeld,J.S., Somkuti,S.G., Lee,A., Barmat,L.I., Outcomes of day-1, day-3, and blastocyst cryopreserved embryo transfers, Fertility and Sterility, 93, 1353-1355, 2010	Correspondence
Moustafa,M.K., Sheded,S.A., El Aziz Mousta,M.A., Elective single embryo transfer versus double embryo transfer in assisted reproduction, Reproductive Biomedicine Online, 17, 82-87, 2008	Poor study quality
Moustafa,M.K., Sheded,S.A., El Aziz Mousta,M.A., Elective single embryo transfer versus double embryo transfer in assisted reproduction, Reproductive Biomedicine Online, 17, 82-87, 2008	Poor study quality
Multiple births from fertility treatment in the UK: A Consensus statement, Human Fertility, 14, 151-153, 2011	To be used a background/context reference
Pandian,Z., Bhattacharya,S., Ozturk,O., Serour,G., Templeton,A., Number of embryos for transfer following in-vitro fertilisation or intra-cytoplasmic sperm injection. [55 refs][Update of Cochrane Database Syst Rev. 2004;(4):CD003416; PMID: 15495053], Cochrane Database of Systematic Reviews, CD003416-, 2009	Individual relevant studies from this review have been included
Pantos,K., Makrakis,E., Chronopoulou,M., Biba,M., Perdikaris,A., Dafereras,A., Day 4 versus day 3 embryo transfer: a prospective study of clinical outcomes, Fertility and Sterility, 89, 573-577, 2008	Study did not include embryo transfer on day 5/6
Pantos,K., Makrakis,E., Stavrou,D., Karantzis,P., Vaxevanoglou,T., Tzigounis,V., Comparison of embryo transfer on day 2, day 3, and day 6: a prospective randomized study, Fertility and Sterility, 81, 454-455, 2004	Correspondence

Bibliographic information	Reason for exclusion
Prades,M., Golmard,J.L., Vauthier,D., bvre,G., Poirot,C., Can cumulative pregnancy rates be increased by freezing and thawing single embryos?, Fertility and Sterility, 91, 395-400, 2009	Results from a single centre
Roberts,S., McGowan,L., Hirst,W., Brison,D., Vail,A., Lieberman,B., Towards single embryo transfer? Modelling clinical outcomes of potential treatment choices using multiple data sources: predictive models and patient perspectives, Health Technology Assessment (Winchester, England), 14, 1-237, 2010	Duplicate
Roberts,S.A., Fitzgerald,C.T., Brison,D.R., Modelling the impact of single embryo transfer in a national health service IVF programme, Human Reproduction, 24, 122-131, 2009	Paper based on main HTA report already included in review
Roberts,S.A., Hirst,W.M., Brison,D.R., Vail,A., toward SET,collaboration, Embryo and uterine influences on IVF outcomes: an analysis of a UK multi-centre cohort, Human Reproduction, 25, 2792-2802, 2010	Paper based on main HTA report already included in review
Roberts,S.A., McGowan,L., Hirst,W.M., Brison,D.R., Vail,A., Lieberman,B.A., Towards single embryo transfer? modelling clinical outcomes of potential treatment choices using multiple data sources: Predictive models and patient perspectives, Health Technology Assessment, 14, 1-237, 2010	Included in Q3b
Roberts,S.A., McGowan,L., Mark,Hirst W., Vail,A., Rutherford,A., Lieberman,B.A., Brison,D.R., toward SET,Collaboration, Reducing the incidence of twins from IVF treatments: predictive modelling from a retrospective cohort, Human Reproduction, 26, 569-575, 2011	Publication based on main HTA reported that is already included.
Sazonova,A., Kallen,K., Thurin-Kjellberg,A., Wennerholm,U.B., Bergh,C., Obstetric outcome after in vitro fertilization with single or double embryo transfer, Human Reproduction, 26, 442-450, 2011	Included in Q3b
Stillman,R.J., Richter,K.S., Banks,N.K., Graham,J.R., Elective single embryo transfer: a 6-year progressive implementation of 784 single blastocyst transfers and the influence of payment method on patient choice, Fertility and Sterility, 92, 1895-1906, 2009	Not review question. Single centre
Utsunomiya,T., Ito,H., Nagaki,M., Sato,J., A prospective, randomized study: Day 3 versus hatching blastocyst stage, Human Reproduction, #19, 1598-1603, 2004	No relevant comparisons
van Heesch,M.M., Bonsel,G.J., Dumoulin,J.C., Evers,J.L., van der Hoeven,M.A., Severens,J.L., Dykgraaf,R.H., van,der,V, Tonch,N., Nelen,W.L., van,Zonneveld P., van Goudoever,J.B., Tamminga,P., Steiner,K., Koopman-Esseboom,C., van Beijsterveldt,C.E., Boomsma,D.I., Snellen,D., Dirksen,C.D., Long term costs and effects of reducing the number of twin pregnancies in IVF by single embryo transfer: the TwinSing study, BMC Pediatrics, 10, 75-, 2010	Not relevant to research question
van Montfoort,A.P., Dumoulin,J.C., Land,J.A., Coonen,E., Derhaag,J.G., Evers,J.L., Elective single embryo transfer (eSET) policy in the first three IVF/ICSI treatment cycles, Human Reproduction, 20, 433-436, 2005	Included in Q3b
Verberg,M.F., Eijkemans,M.J., Macklon,N.S., Heijnen,E.M., Fauser,B.C., Broekmans,F.J., Predictors of ongoing pregnancy after single-embryo transfer following mild ovarian stimulation for IVF, Fertility and Sterility, 89, 1159-1165, 2008	Model based on small patient population

Bibliographic information	Reason for exclusion
Virant-Klun,I., Tomazevic,T., Zorn,B., Bacer-Kermavner,L., Mivsek,J., Meden-Vrtovec,H., Blastocyst formation--good indicator of clinical results after ICSI with testicular spermatozoa, Human Reproduction, 18, 1070-1076, 2003	Study was not an RCT - used alternated days to randomise
Wang,Y.A., Chapman,M., Costello,M., Sullivan,E.A., Better perinatal outcomes following transfer of fresh blastocysts and blastocysts cultured from thawed cleavage embryos: a population-based study, Human Reproduction, 25, 1536-1542, 2010	Included in Q3b
Wang,Y.A., Kovacs,G., Sullivan,E.A., Transfer of a selected single blastocyst optimizes the chance of a healthy term baby: a retrospective population based study in Australia 2004-2007, Human Reproduction, 25, 1996-2005, 2010	Included in Q3b
Weissman,A., Biran,G., Nahum,H., Glezerman,M., Levran,D., Blastocyst culture and transfer: Lessons from an unselected, difficult IVF population, Reproductive Biomedicine Online, 17, 220-228, 2008	Not an RCT - Women allocated depending on day of week oocyte retrieval was carried out

IVF luteal phase support

Table G.14 What is the effectiveness of luteal phase support as part of an ovarian stimulation strategy for women undergoing IVF or ICSI treatment?

Bibliographic information	Reason for exclusion
Abate,A., Brigandi,A., Abate,F.G., Manti,F., Unfer,V., Perino,M., Luteal phase support with 17alpha-hydroxyprogesterone versus unsupported cycles in in vitro fertilization: a comparative randomized study, Gynecologic and Obstetric Investigation, 48, 78-80, 1999	Included in the van der Linden et al. (2011) Cochrane review
Abate,A., Perino,M., Abate,F.G., Brigandi,A., Costabile,L., Manti,F., Intramuscular versus vaginal administration of progesterone for luteal phase support after in vitro fertilization and embryo transfer. A comparative randomized study, Clinical and Experimental Obstetrics and Gynecology, 26, 203-206, 1999	Included in the van der Linden et al. (2011) Cochrane review
Agostini,F., Monti,F., De,PascalisL, Paterlini,M., La,SalaG, Blickstein,I., Psychosocial support for infertile couples during assisted reproductive technology treatment, Fertility and Sterility, 95, 707-710, 2011	Compared men's and women's perceived psychosocial support during IVF - not a comparison of interest
Albert,J., Luteal phase hormone levels in in vitro fertilisation and embryo transfer (IVF-ET): a prospective randomised trial of human gonadotropin (hCG) vs intramuscular (im) progesterone (p) for luteal phase support following stimulation with GnRH-a and hMG, Fertility and Sterility, Vol.56, pp.S18, 1991., -, None	Conference abstract
Araujo E Jr, Bernardini,L., Frederick,J.L., Asch,R.H., Balmaceda,J.P., Prospective randomized comparison of human chorionic gonadotropin versus intramuscular progesterone for luteal-phase support in assisted reproduction4174, Journal of Assisted Reproduction and Genetics, 11, 74-78, 1994	Women were not truly randomised
Artini,P.G., Volpe,A., Angioni,S., Galassi,M.C., Battaglia,C., Genazzani,A.R., A comparative, randomized study of three different progesterone support of the luteal phase following IVF/ET program, Journal of Endocrinological Investigation, 18, 51-56, 1995	Unclear reported outcomes

Bibliographic information	Reason for exclusion
Ata,B., Urman,B., Single dose GnRH agonist administration in the luteal phase of assisted reproduction cycles: is the effect dependent on the type of GnRH analogue used for pituitary suppression?, Reproductive Biomedicine Online, 20, 165-166, 2010	Letter
Ata,B., Yakin,K., Balaban,B., Urman,B., GnRH agonist protocol administration in the luteal phase in ICSI-ET cycles stimulated with the long GnRH agonist protocol: a randomized, controlled double blind study793, Human Reproduction, 23, 668-673, 2008	Included in the van der Linden et al. (2011) Cochrane review
Beckers,N.G., Laven,J.S., Eijkemans,M.J., Fauser,B.C., Follicular and luteal phase characteristics following early cessation of gonadotrophin-releasing hormone agonist during ovarian stimulation for in-vitro fertilization, Human Reproduction, 15, 43-49, 2000	No outcomes of interest reported (only reported pregnancy was biochemical pregnancy)
Belaisch-Allart,J., De,Mouzon J., Lapousterle,C., Mayer,M., The effect of HCG supplementation after combined GnRH agonist/HMG treatment in an IVF programme, Human Reproduction, 5, 163-166, 1990	Included in the van der Linden et al. (2011) Cochrane review
Belaisch-Allart,J., Effect of luteal phase supplementation in an IVF programme after ovarian stimulation by LH-RH analogs: multicentric analysis, Contraception, Fertilite, Sexualite, 16, 654-656, 1988	In French
Belaisch-Allart,J., Testart,J., Fries,N., Forman,R.G., Frydman,R., The effect of dydrogesterone supplementation in an IVF programme, Human Reproduction, 2, 183-185, 1987	Included in the van der Linden et al. (2011) Cochrane review
Buvat,J., Marcolin,G., Guittard,C., Herbaut,J.C., Louvet,A.L., Dehaene,J.L., Luteal support after luteinizing hormone-releasing hormone agonist for in vitro fertilization: superiority of human chorionic gonadotropin over oral progesterone, Fertility and Sterility, 53, 490-494, 1990	Quasi randomised (randomisation based on date)
Buvat,J., Marcolin,G., Herbaut,J.C., Dehaene,J.L., Verbecq,P., Fourlinnie,J.C., A randomized trial of human chorionic gonadotropin support following in vitro fertilization and embryo transfer, Fertility and Sterility, 49, 458-461, 1988	Quasi randomised trial
Casper,R.F., Wilson,E., Collins,J.A., Brown,S.F., Parker,J.A., Enhancement of human implantation by exogenous chorionic gonadotropin, Lancet, 2, 1191-, 1983	Letter
Claman,P., Domingo,M., Leader,A., Luteal phase support in in-vitro fertilization using gonadotrophin releasing hormone analogue before ovarian stimulation: a prospective randomized study of human chorionic gonadotrophin versus intramuscular progesterone, Human Reproduction, 7, 487-489, 1992	The number of women in the study is not reported. The number of women in each treatment group is not reported. Randomisation was performed per cycle.
Colwell,K.A., Tummon,I.S., Elevation of serum progesterone with oral micronized progesterone after in vitro fertilization: A randomized, controlled trial, Journal of Reproductive Medicine for the Obstetrician and Gynecologist, 36, 170-172, 1991	Method of randomisation was unclear (n=28 in one group, n=42 in the other). It is not clear if the study was still ongoing at the time the paper was written up
Costabile,L., Gerli,S., Manna,C., Rossetti,D., Di Renzo,G.C., Unfer,V., A prospective randomized study comparing intramuscular progesterone and 17alpha-hydroxyprogesterone caproate in patients undergoing in vitro fertilization-embryo transfer cycles, Fertility and Sterility, 76, 394-396, 2001	The number of women in each group is not reported (220 total women and 300 cycles).

Bibliographic information	Reason for exclusion
D'Amato,G., Caroppo,E., Pasquadibisceglie,A., Carone,D., Vitti,A., Vizziello,G.M., A novel protocol of ovulation induction with delayed gonadotropin-releasing hormone antagonist administration combined with high-dose recombinant follicle-stimulating hormone and clomiphene citrate for poor responders and women over 35 years1977, Fertility and Sterility, 81, 1572-1577, 2004	Method of randomisation inadequate (based on day of first presentation at clinic)
D'Angelo,A., Amso,N., "Coasting" (withholding gonadotrophins) for preventing ovarian hyperstimulation syndrome, Cochrane database of systematic reviews (Online), #2002. Date of Publication, CD002811-, 2002	Not relevant to the luteal phase/post implantation phase of IVF/ICSI cycles
Drakakis,P., Loutradis,D., Vomvolaki,E., Stefanidis,K., Kiapekou,E., Anagnostou,E., Anastasiadou,K., Milingos,S., Antsaklis,A., Luteal estrogen supplementation in stimulated cycles may improve the pregnancy rate in patients undergoing in vitro fertilization/intracytoplasmic sperm injection-embryo transfer, Gynecological Endocrinology, 23, 645-652, 2007	Not clear how women were randomised - women may have been randomised by method of ART
Elassar,A., Mann,J.S., Engmann,L., Nulsen,J., Benadiva,C., Luteal phase estradiol versus luteal phase estradiol and antagonist protocol for controlled ovarian stimulation before in vitro fertilization in poor responders, Fertility and Sterility, 95, 324-326, 2011	Retrospective study
Elgindy,E.A., El-Haieg,D.O., Mostafa,M.I., Shafiek,M., Does luteal estradiol supplementation have a role in long agonist cycles?, Fertility and Sterility, 93, 2182-2188, 2010	Included in the van der Linden et al. (2011) Cochrane review
Engmann,L., DiLuigi,A., Schmidt,D., Benadiva,C., Maier,D., Nulsen,J., The effect of luteal phase vaginal estradiol supplementation on the success of in vitro fertilization treatment: a prospective randomized study, Fertility and Sterility, 89, 554-561, 2008	Included in Kolibianakis (2008) review
Farhi,J., Weissman,A., Steinfeld,Z., Shorer,M., Nahum,H., Levran,D., Estradiol supplementation during the luteal phase may improve the pregnancy rate in patients undergoing in vitro fertilization-embryo transfer cycles, Fertility and Sterility, 73, 761-766, 2000	Women were not truly randomised
Fatemi,H.M., Camus,M., Kolibianakis,E.M., Tournaye,H., Papanikolaou,E.G., Donoso,P., Devroey,P., The luteal phase of recombinant follicle-stimulating hormone/gonadotropin-releasing hormone antagonist in vitro fertilization cycles during supplementation with progesterone or progesterone and estradiol, Fertility and Sterility, 87, 504-508, 2007	No pregnancy outcomes were reported
Fatemi,H.M., Kolibianakis,E.M., Camus,M., Tournaye,H., Donoso,P., Papanikolaou,E., Devroey,P., Addition of estradiol to progesterone for luteal supplementation in patients stimulated with GnRH antagonist/rFSH for IVF: a randomized controlled trial, Human Reproduction, 21, 2628-2632, 2006	Included in Kolibianakis (2008) systematic review
Fisch,P., Casper,R.F., Brown,S.E., Wrixon,W., Collins,J.A., Reid,R.L., Simpson,C., Unexplained infertility: evaluation of treatment with clomiphene citrate and human chorionic gonadotropin, Fertility and Sterility, 51, 828-833, 1989	Does not compare luteal phase support
Friedler,S., Raziel,A., Schachter,M., Strassburger,D., Bukovsky,I., Ron-El,R., Luteal support with micronized progesterone following in-vitro fertilization using a down-regulation protocol with gonadotrophin-releasing hormone agonist: a comparative study between vaginal and oral administration, Human Reproduction, 14, 1944-1948, 1999	Comparison of oral and vaginal progesterone

Bibliographic information	Reason for exclusion
Fujii,S., Sato,S., Fukui,A., Kimura,H., Kasai,G., Saito,Y., Continuous administration of gonadotrophin-releasing hormone agonist during the luteal phase in IVF, Human Reproduction, 16, 1671-1675, 2001	Not a comparison of interest
Fujimoto,A., Osuga,Y., Fujiwara,T., Yano,T., Tsutsumi,O., Momoeda,M., Kugu,K., Koga,K., Morita,Y., Wada,O., Taketani,Y., Human chorionic gonadotropin combined with progesterone for luteal support improves pregnancy rate in patients with low late-midluteal estradiol levels in IVF cycles, Journal of Assisted Reproduction and Genetics, 19, 550-554, 2002	Results were presented per cycle (n=51 vs. n=63). Method of randomisation unclear - not clear whether women were truly randomised
Garcia-Velasco,J.A., Motta,L., Lopez,A., Mayoral,M., Cerrillo,M., Pacheco,A., Low-dose human chorionic gonadotropin versus estradiol/progesterone luteal phase support in gonadotropin-releasing hormone agonist-triggered assisted reproductive technique cycles: understanding a new approach, Fertility and Sterility, 94, 2820-2823, 2010	No pregnancy or live birth data reported. Luteal phase support was given to oocyte donors after oocyte collection (embryos were transferred into different women, who were not part of this study)
Gelbaya,T.A., Kyrgiou,M., Tsoumpou,I., Nardo,L.G., The use of estradiol for luteal phase support in in vitro fertilization/intracytoplasmic sperm injection cycles: a systematic review and meta-analysis. [45 refs], Fertility and Sterility, 90, 2116-2125, 2008	Addresses the same review question as Kolibianakis (2008), however most results are reported per embryo transfer or per cycle. Relevant included trials were reviewed on an individual basis
Ghanem,M.E., Sadek,E.E., Elboghdady,L.A., Helal,A.S., Gamal,A., Eldiasty,A., Bakre,N.I., Houssen,M., The effect of luteal phase support protocol on cycle outcome and luteal phase hormone profile in long agonist protocol intracytoplasmic sperm injection cycles: a randomized clinical trial323, Fertility and Sterility, 92, 486-493, 2009	Quasi randomised (Cochrane review authors contacted authors of this trial)
Golan,A., Herman,A., Soffer,Y., Bukovsky,I., Caspi,E., Ron-El,R., Human chorionic gonadotrophin is a better luteal support than progesterone in ultrashort gonadotrophin-releasing hormone agonist/menotrophin in-vitro fertilization cycles, Human Reproduction, 8, 1372-1375, 1993	Included in the van der Linden et al. (2011) Cochrane review
Gorkemli,H., Ak,D., Akyurek,C., Aktan,M., Duman,S., Comparison of pregnancy outcomes of progesterone or progesterone + estradiol for luteal phase support in ICSI-ET cycles, Gynecologic and Obstetric Investigation, 58, 140-144, 2004	It was not possible to calculate results per woman
Herman,A., Raziel,A., Strassburger,D., Soffer,Y., Bukovsky,I., Ron-El,R., The benefits of mid-luteal addition of human chorionic gonadotrophin in in-vitro fertilization using a down-regulation protocol and luteal support with progesterone, Human Reproduction, 11, 1552-1557, 1996	Women were assigned to treatment groups based on their hormonal profile. They were not randomised
Herman,A., Ron-El,R., Golan,A., Raziel,A., Soffer,Y., Caspi,E., Pregnancy rate and ovarian hyperstimulation after luteal human chorionic gonadotropin in in vitro fertilization stimulated with gonadotropin-releasing hormone analog and menotropins, Fertility and Sterility, 53, 92-96, 1990	Women were assigned to treatment by alternating numbers
Homburg,R., Levy,T., Ben-Rafael,Z., A comparative prospective study of conventional regimen with chronic low- dose administration of follicle-stimulating hormone for anovulation associated with polycystic ovary syndrome, Fertility and Sterility, 63, 729-733, 1995	Women were not randomised to treatment groups

Bibliographic information	Reason for exclusion
Hughes,E., Collins,J., Vandekerckhove,P., Gonadotrophin-releasing hormone analogue as an adjunct to gonadotropin therapy for clomiphene-resistant polycystic ovarian syndrome. [3 refs][Update in Cochrane Database Syst Rev. 1996;(1):CD000097; PMID: 17636588], Cochrane Database of Systematic Reviews, CD000097-, 2000	The 2005 version of this review has been withdrawn by the Cochrane library as it has not been updated
Hurd,W.W., Randolph,J.F.,Jr., Christman,G.M., Ansbacher,R., Menge,A.C., Gell,J.S., Luteal support with both estradiol and progesterone after clomiphene citrate stimulation for in vitro fertilization, Fertility and Sterility, 66, 587-592, 1996	Some women received treatment in both groups, although it is not clear how many or what their clinical outcomes were
Isik,A.Z., Caglar,G.S., Sozen,E., Akarsu,C., Tuncay,G., Ozbicer,T., Vicdan,K., Single-dose GnRH agonist administration in the luteal phase of GnRH antagonist cycles: A prospective randomized study, Reproductive Biomedicine Online, #19, 472-477, 2009	Included in the van der Linden et al. (2011) Cochrane review
Isikoglu,M., Ozgur,K., Oehninger,S., Extension of GnRH agonist through the luteal phase to improve the outcome of intracytoplasmic sperm injection908, Journal of Reproductive Medicine, 52, 639-644, 2007	Not a comparison of interest (GnRH agonist vs. none). Different protocols were used for the IVF procedure.
Jee,B.C., Suh,C.S., Kim,S.H., Kim,Y.B., Moon,S.Y., Effects of estradiol supplementation during the luteal phase of in vitro fertilization cycles: a meta-analysis, Fertility and Sterility, 93, 428-436, 2010	Does not report live birth rate. The majority of the studies are included in the systematic review by Kolibianakis (2008), which reports clinical pregnancy and live birth rate. Studies in the Jee (2010) review that are not in the Kolibianakis (2008) review were appraised as independent studies for the current review
Jung,H., Roh,H.K., The effects of E2 supplementation from the early proliferative phase to the late secretory phase of the endometrium in hMG-stimulated IVF-ET, Journal of Assisted Reproduction and Genetics, 17, 28-33, 2000	Clinical pregnancy rate was calculated with the number of cycles with at least one transferred embryo. Raw data not reported. No other outcomes of interest reported
Kolibianakis,E.M., Venetis,C.A., Papanikolaou,E.G., Diedrich,K., Tarlatzis,B.C., Griesinger,G., Estrogen addition to progesterone for luteal phase support in cycles stimulated with GnRH analogues and gonadotrophins for IVF: a systematic review and meta-analysis. [16 refs], Human Reproduction, 23, 1346-1354, 2008	A more recent Cochrane review (van der Linden et al., 2011) includes all four of the studies included in this review
Kupferminc,M.J., Lessing,J.B., Amit,A., Yovel,I., David,M.P., Peyser,M.R., A prospective randomized trial of human chorionic gonadotrophin or dydrogesterone support following in-vitro fertilization and embryo transfer, Human Reproduction, 5, 271-273, 1990	Included in the van der Linden et al. (2011) Cochrane review
Kyrou,D., Kolibianakis,E.M., Fatemi,H.M., Tarlatzi,T.B., Devroey,P., Tarlatzis,B.C., Increased live birth rates with GnRH agonist addition for luteal support in ICSI/IVF cycles: a systematic review and meta-analysis, Human Reproduction Update, 17, 734-740, 2011	Four of the six included studies are included in the van der Linden et al. (2011) Cochrane review. The other two studies are considered separately for inclusion.
Leeton,J., Trounson,A., Jessup,D., Support of the luteal phase in in vitro fertilization programs: results of a controlled trial with intramuscular Proluton, Journal of in Vitro Fertilization and Embryo Transfer, 2, 166-169, 1985	Quasi randomised

Bibliographic information	Reason for exclusion
Lewin,A., Benshushan,A., Mezker,E., Yanai,N., Schenker,J.G., Goshen,R., The role of estrogen support during the luteal phase of in vitro fertilization-embryo transplant cycles: a comparative study between progesterone alone and estrogen and progesterone support, Fertility and Sterility, 62, 121-125, 1994	Included in the van der Linden et al. (2011) Cochrane review
Ludwig,M., Finas,A., Katalinic,A., Strik,D., Kowalcek,I., Schwartz,P., Felberbaum,R., Kupker,W., Schopper,B., Ai-Hasani,S., Diedrich,K., Prospective, randomized study to evaluate the success rates using hCG, vaginal progesterone or a combination of both for luteal phase support, Acta Obstetricia et Gynecologica Scandinavica, 80, 574-582, 2001	Live birth and clinical pregnancy outcomes reported per embryo transfer, but the number of embryo transfers in each group is not reported. The other relevant outcomes are reported by clinical pregnancy, but it is not possible to determine how many pregnancies were in each group.
Lukaszuk,K., Liss,J., Lukaszuk,M., Maj,B., Optimization of estradiol supplementation during the luteal phase improves the pregnancy rate in women undergoing in vitro fertilization-embryo transfer cycles, Fertility and Sterility, 83, 1372-1376, 2005	Treatment was randomised per cycle. Method of randomisation was not reported. It was not possible to calculate the results per woman. It is not clear how many women were included in each treatment group.
Mansour,R., Tawab,N., Kamal,O., El-Faissal,Y., Serour,A., Aboulghar,M., Serour,G., Intrauterine injection of human chorionic gonadotropin before embryo transfer significantly improves the implantation and pregnancy rates in in vitro fertilization/intracytoplasmic sperm injection: a prospective randomized study, Fertility and Sterility, 96, 1370-1374, 2011	hCG was only given at the time of embryo transfer
Martinez,F., Coroleu,B., Parera,N., Alvarez,M., Traver,J.M., Boada,M., Barri,P.N., Human chorionic gonadotropin and intravaginal natural progesterone are equally effective for luteal phase support in IVF, Gynecological Endocrinology, 14, 316-320, 2000	Women were not truly randomised (randomised by social security number)
Meldrum,D.R., Patient preparation and standard stimulation regimens using gonadotropin-releasing hormone agonists, Clinical Obstetrics and Gynecology, 49, 4-11, 2006	Narrative review
Mochtar,M.H., Hogerzeil,H.V., Mol,B.W., Progesterone alone versus progesterone combined with HCG as luteal support in GnRHa/HMG induced IVF cycles: a randomized clinical trial, Human Reproduction, 11, 1602-1605, 1996	Not possible to determine outcomes per woman (only reported per cycle)
Mousavi,Fatemi H., Kolibianakis,E.M., Camus,M., Tournaye,H., Van,Steirteghem A., Devroey,P., Progesterone Versus Progesterone Combined With Estradiol as Luteal Support in Cycles Stimulated With GnRH Antagonist/rec-FSH for IVF: A Randomized Clinical Trial, Fertility and Sterility, Vol.84 Suppl 1, pp.S322, 2005., -, None	Conference abstract
Mui,Lam P., Chun,Cheung M., Ping,Cheung L., Ingrid,Lok H., John,Haines C., Effects of early luteal-phase vaginal progesterone supplementation on the outcome of in vitro fertilization and embryo transfer, Gynecological Endocrinology, 24, 674-680, 2008	Included in the van der Linden et al. (2011) Cochrane review
Myers,E.R., McCrory,D.C., Mills,A.A., Price,T.M., Swamy,G.K., Tantibhedhyangkul,J., Wu,J.M., Matchar,D.B., Effectiveness of assisted reproductive technology (ART), Evidence report/technology assessment, 1-195),;#2008. Date of Publication, -195, 2008	Review with no meta-analysis

Bibliographic information	Reason for exclusion
Nader,S., Berkowitz,A.S., Ochs,D., Held,B., Winkel,C.A., Luteal-phase support in stimulated cycles in an in vitro fertilization/embryo transfer program: progesterone versus human chorionic gonadotropin5015, Journal of in Vitro Fertilization and Embryo Transfer, 5, 81-84, 1988	Treatment was randomised per cycle rather than per woman. Method of randomisation was not reported. The study was not complete at the time of publication - at least one woman was still pregnant.
Nargund,G., Waterstone,J., Bland,J.M., Philips,Z., Parsons,J., Campbell,S., Cumulative conception and live birth rates in natural (unstimulated) IVF cycles, Human Reproduction, 16, 259-262, 2001	Non-comparative study
Nosarka,S., Kruger,T., Siebert,I., Grove, D., Luteal phase support in in vitro fertilization: meta-analysis of randomized trials, Gynecologic and Obstetric Investigation, 60, 67-74, 2005	Meta-analysis results only reported by outcome. Live birth rate not reported. Relevant included trials were considered separately for inclusion
Oliveira,J.B., Baruffi,R., Petersen,C.G., Mauri,A.L., Cavagna,M., Franco,J.G.,Jr., Administration of single-dose GnRH agonist in the luteal phase in ICSI cycles: a meta-analysis5587, Reproductive Biology and Endocrinology, 8, 107-, 2010	Clinical pregnancy rate was only reported per transfer. Live birth rate was not reported. Individual studies were assessed for inclusion in the current review
Padilla,S.L., Smith,R.D., Garcia,J.E., The Lupron screening test: tailoring the use of leuprolide acetate in ovarian stimulation for in vitro fertilization.[Erratum appears in Fertil Steril 1991 Dec;56(6):1210], Fertility and Sterility, 56, 79-83, 1991	All women received progesterone for luteal phase support
Papanikolaou,E.G., Verpoest,W., Fatemi,H., Tarlatzis,B., Devroey,P., Tournaye,H., A novel method of luteal supplementation with recombinant luteinizing hormone when a gonadotropin-releasing hormone agonist is used instead of human chorionic gonadotropin for ovulation triggering: a randomized prospective proof of concept study, Fertility and Sterility, 95, 1174-1177, 2011	The two groups received different ovulation triggers as well as different types of luteal phase support - it is not possible to tell whether the trigger or support drug affected outcomes
Pirard,C., Donnez,J., Loumaye,E., GnRH agonist as luteal phase support in assisted reproduction technique cycles: results of a pilot study, Human Reproduction, 21, 1894-1900, 2006	Comparison group of interest has only two women
Polson,D.W., Rogers,P.A., Krapez,J.A., Leeton,J.F., Vaginal progesterone as luteal phase support in an IVF/GIFT programme, European Journal of Obstetrics, Gynecology, and Reproductive Biology, 46, 35-38, 1992	Women not truly randomised - assigned to groups by alternating numbers
Pouly,J.L., Luteal phase supplementation with oestrogens does not improve the IVF pregnancy rate: a randomized study, Human Reproduction, 20, i72, 2005	Conference abstract
Pournaropoulos,F., Tarlatzis,B., Zepiridis,L., Bili,H., Grimbizis,G., Pados,G., Papadimas,J., Bontis,J., Prospective, blind, randomized evaluation of exogenous LH supplementation in the long GnRHa/recFSH stimulation protocol for IVF/ICSI, Human Reproduction, 19, i119, 2004	Conference abstract
Pritts,E.A., Atwood,A.K., Luteal phase support in infertility treatment: a meta-analysis of the randomized trials. [46 refs], Human Reproduction, 17, 2287-2299, 2002	Only 7 of the 30 included studies were truly randomised - these were looked at as individual studies

Bibliographic information	Reason for exclusion
Qublan,H., Amarin,Z., Al-Qudah,M., Diab,F., Nawasreh,M., Malkawi,S., Balawneh,M., Luteal phase support with GnRH-a improves implantation and pregnancy rates in IVF cycles with endometrium of <or=7 mm on day of egg retrieval.[Erratum appears in Hum Fertil (Camb). 2008 Jun;11(2):127 Note: Qublah, H [corrected to Qublan, H]; Al-Quda, M [corrected to Al-Qudah, M]], Human Fertility, 11, 43-47, 2008	Included in the van der Linden et al. (2011) Cochrane review
Razieh,D.F., Maryam,A.R., Nasim,T., Beneficial effect of luteal-phase gonadotropin-releasing hormone agonist administration on implantation rate after intracytoplasmic sperm injection267, Taiwanese Journal of Obstetrics and Gynecology, 48, 245-248, 2009	Not a comparison of interest
Rogers,P., Molloy,D., Healy,D., McBain,J., Howlett,D., Bourne,H., Thomas,A., Wood,C., Johnston,I., Trounson,A., Cross-over trial of superovulation protocols from two major in vitro fertilization centers, Fertility and Sterility, 46, 424-431, 1986	Women were not randomised
Serna,J., Adding estradiol patches to the luteal phase of IVF/ICSI cycles did not improve pregnancy nor miscarriage rates, Fertility and Sterility,Fertil Steril, 86, S73-, 2006	Included in Kolibianakis (2008) systematic review
Serna,J., Cholquevilque,J.L., Cela,V., nez-Salazar,J., Requena,A., Garcia-Velasco,J.A., Estradiol supplementation during the luteal phase of IVF-ICSI patients: a randomized, controlled trial, Fertility and Sterility, 90, 2190-2195, 2008	Donor eggs were used. Allocation to treatment was based on day of clinic visit rather than randomisation
Smith,E.M., Anthony,F.W., Gadd,S.C., Masson,G.M., Trial of support treatment with human chorionic gonadotrophin in the luteal phase after treatment with buserelin and human menopausal gonadotrophin in women taking part in an in vitro fertilisation programme, BMJ, 298, 1483-1486, 1989	Women were not truly randomised (randomised by date of ovulation trigger)
Smitz,J., Bourgain,C., Van,Waesberghe L., Camus,M., Devroey,P., Van Steirteghem,A.C., A prospective randomized study on oestradiol valerate supplementation in addition to intravaginal micronized progesterone in buserelin and HMG induced superovulation, Human Reproduction, 8, 40-45, 1993	28% of women did not have IVF or ICSI and the results are not reported separately. Women were randomised by birth date.
Smitz,J., Devroey,P., Camus,M., Deschacht,J., Khan,I., Staessen,C., Van,Waesberghe L., Wisanto,A., Van Steirteghem,A.C., The luteal phase and early pregnancy after combined GnRH-agonist/HMG treatment for superovulation in IVF or GIFT, Human Reproduction, 3, 585-590, 1988	Women received IVF or GIFT - results were not separated by method of ART
Soliman,S., Daya,S., Collins,J., Hughes,E.G., The role of luteal phase support in infertility treatment: a meta-analysis of randomized trials, Fertility and Sterility, 61, 1068-1076, 1994	It is not clear what the denominator for pregnancy is. The majority of the included studies reported pregnancy per cycle. Many of the included studies used quasi randomisation. Some studies were cross-over trials and it is not clear whether only phase one data was used. Individual studies were appraised for the current review
Stovall,D.W., Van Voorhis,B.J., Sparks,A.E., Adams,L.M., Syrop,C.H., Selective early elimination of luteal support in assisted reproduction cycles using a gonadotropin-releasing hormone agonist during ovarian stimulation, Fertility and Sterility, 70, 1056-1062, 1998	Women were not randomised to treatment groups

Bibliographic information	Reason for exclusion
Tay,P.Y., Lenton,E.A., Inhibition of progesterone secretion by oestradiol administered in the luteal phase of assisted conception cycles, Medical journal of Malaysia, 58, 187-195, 2003	Some women received IUI. It is not clear how many received IUI, and the results are not reported separately from the women who received IVF or ICSI.
Tay,P.Y.S., Lenton,E.A., The impact of luteal supplement on pregnancy outcome following stimulated IVF cycles11236, Medical Journal of Malaysia, 60, 151-157, 2005	Relevant outcomes not clearly reported. Method of randomisation unclear (n=35, n=36, n=55, n=35)
Tesarik,J., Hazout,A., Mendoza-Tesarik,R., Mendoza,N., Mendoza,C., Beneficial effect of luteal-phase GnRH agonist administration on embryo implantation after ICSI in both GnRH agonist- and antagonist-treated ovarian stimulation cycles1176, Human Reproduction, 21, 2572-2579, 2006	Both groups of women received the same drugs for luteal phase support
Tomic,V., Tomic,J., Klaic,D.Z., Oral micronized progesterone combined with vaginal progesterone gel for luteal support, Gynecological Endocrinology, 27, 1010-1013, 2011	Not an RCT
Torode,H.W., Porter,R.N., Vaughan,J.I., Saunders,D.M., Luteal phase support after in vitro fertilisation: a trial and rationale for selective use, Clinical Reproduction and Fertility, 5, 255-261, 1987	It is not clear how many women were randomised to each treatment group. Only the number of women who received luteal phase support in each group is reported.
Trounson,A., Howlett,D., Rogers,P., Hoppen,H.O., The effect of progesterone supplementation around the time of oocyte recovery in patients superovulated for in vitro fertilization, Fertility and Sterility, 45, 532-535, 1986	Progesterone or hCG only given at time of oocyte retrieval
Van Steirteghem,A.C., Smitz,J., Camus,M., Van,Waesberghe L., Deschacht,J., Khan,I., Staessen,C., Wisanto,A., Bourgain,C., Devroey,P., The luteal phase after in-vitro fertilization and related procedures, Human Reproduction, 3, 161-164, 1988	Women received IVF or GIFT - results were not separated by ART method
Van,S.A.C., Smitz,J., Camus,M., Deschacht,J., Kahn,I., Staessen,C., Van,W.L., Wisanto,A., Devroey,P., Ovarian stimulation by buserelin-HMG before in vitro fertilization or gamete intrafallopian transfer in patients with previous failed clomid-HMG cycles, CONTRACEPT FERTIL SEX, 16, 295-298, 1988	French language paper
Var,T., Tonguc,E.A., Doganay,M., Gulerman,C., Gungor,T., Mollamahmutoglu,L., A comparison of the effects of three different luteal phase support protocols on in vitro fertilization outcomes: a randomized clinical trial, Fertility and Sterility, 95, 985-989, 2011	Women were not truly randomised - allocated to treatment on the basis of application number
Verberg,M.F.G., Macklon,N.S., Nargund,G., Frydman,R., Devroey,P., Broekmans,F.J., Fauser,B.C.J.M., Mild ovarian stimulation for IVF, Human Reproduction Update, 15, 13-29, 2009	Narrative review
Vimpeli,T., Tinkanen,H., Huhtala,H., Ronnberg,L., Kujansuu,E., Salivary and serum progesterone concentrations during two luteal support regimens used in in vitro fertilization treatment, Fertility and Sterility,Fertil Steril, 76, 847-848, 2001	Letter
Wong,Y.F., Loong,E.P., Mao,K.R., Tam,P.P., Panesar,N.S., Neale,E., Chang,A.M., Salivary oestradiol and progesterone after in vitro fertilization and embryo transfer using different luteal support regimens, Reproduction, Fertility, and Development, 2, 351-358, 1990	Included in the van der Linden et al. (2011) Cochrane review

Bibliographic information	Reason for exclusion
Yanushpolsky,E., Hurwitz,S., Greenberg,L., Racowsky,C., Hornstein,M., Patterns of luteal phase bleeding in in vitro fertilization cycles supplemented with Crinone vaginal gel and with intramuscular progesterone--impact of luteal estrogen: prospective, randomized study and post hoc analysis, Fertility and Sterility, 95, 617-620, 2011	Women in both groups received both estrogen and progesterone
Yovich,J.L., Stanger,J.D., Yovich,J.M., Tuvik,A.I., Assessment and hormonal treatment of the luteal phase of in vitro fertilization cycles, Australian and New Zealand Journal of Obstetrics and Gynaecology, 24, 125-130, 1984	Quasi randomised (Cochrane review authors contacted authors of this trial)

Chapter 19. People with cancer who wish to preserve fertility

Table G.15 What is the effectiveness of cryopreservation (including vitrification) in fertility preservation strategies?

Bibliographic information	Reason for exclusion
Abdelhafez,F.F., Desai,N., bou-Setta,A.M., Falcone,T., Goldfarb,J., Slow freezing, vitrification and ultra-rapid freezing of human embryos: A systematic review and meta-analysis, Reproductive Biomedicine Online, #20, -222, 2010	Meta-analysis
Bergh,T., Ericson,A., Hillensjo,T., Nygren,K.G., Wennerholm,U.B., Deliveries and children born after in-vitro fertilisation in Sweden 1982-95: a retrospective cohort study., Lancet, 354, 1579-1585, 1999	Unable to extract data for children of cancer patients only
Bonduelle,M., Wilikens,A., Buysse,A., Van,Assche E., Devroey,P., Van Steirteghem,A.C., Liebaers,I., A follow-up study of children born after intracytoplasmic sperm injection (ICSI) with epididymal and testicular spermatozoa and after replacement of cryopreserved embryos obtained after ICSI, Human Reproduction, 13 Suppl 1, 196-207, 1998	Unable to extract data for children of cancer patients only
Bonduelle,M., Wilikens,A., Buysse,A., Van,Assche E., Wisanto,A., Devroey,P., Van Steirteghem,A.C., Liebaers,I., Prospective follow-up study of 877 children born after intracytoplasmic sperm injection (ICSI), with ejaculated epididymal and testicular spermatozoa and after replacement of cryopreserved embryos obtained after ICSI, Human Reproduction, 11 Suppl 4, 131-155, 1996	Unable to extract data for children of cancer patients only
Bruinsma,F., Venn,A., Lancaster,P., Speirs,A., Healy,D., Incidence of cancer in children born after in-vitro fertilization, Human Reproduction, 15, 604-607, 2000	Unable to extract data for children of cancer patients only
Ciotti,P.M., Porcu,E., Notarangelo,L., Magrini,O., Bazzocchi,A., Venturoli,S., Meiotic spindle recovery is faster in vitrification of human oocytes compared to slow freezing, Fertility and Sterility, 91, 2399-2407, 2009	Study does not provide any data on outcomes of interest
Cobo,A., Diaz,C., Clinical application of oocyte vitrification: A systematic review and meta-analysis of randomized controlled trials, Fertility and Sterility, 96, 277-285, 2011	Includes same trials already included in review. Also includes fresh vs. frozen comparison.
Cutting,R., Barlow,S., Anderson,R., Human oocyte cryopreservation: Evidence for practice, Human Fertility, 12, 125-136, 2009	Practice parameter
Edelstein,A., Yavetz,H., Kleiman,S.E., Botchan,A., Hauser,R., Paz,G., Yogev,L., Deoxyribonucleic acid-damaged sperm in cryopreserved-thawed specimens from cancer patients and healthy men, Fertility and Sterility, 90, 205-208, 2008	Correspondence
Ginsburg,E.S., Yanushpolsky,E.H., Jackson,K.V., In vitro fertilization for cancer patients and survivors, Fertility and Sterility, 75, 705-710, 2001	Not a randomized controlled trial
Haie-Meder,C., Mlika-Cabanne,N., Michel,G., Briot,E., Gerbaulet,A., Lhomme,C., Cosset,J.M., Sarrazin,D., Flamant,F., Hayat,M., Radiotherapy after ovarian transposition: ovarian function and fertility preservation, International Journal of Radiation Oncology, Biology, Physics, 25, 419-424, 1993	Study on fertility preservation, not cryopreservation or vitrification

Bibliographic information	Reason for exclusion
Hourvitz,A., Goldschlag,D.E., Davis,O.K., Gosden,L.V., Palermo,G.D., Rosenwaks,Z., Intracytoplasmic sperm injection (ICSI) using cryopreserved sperm from men with malignant neoplasm yields high pregnancy rates, Fertility and Sterility, 90, 557-563, 2008	Not a randomized controlled trial
Kuwayama,M., Vajta,G., Ieda,S., Kato,O., Comparison of open and closed methods for vitrification of human embryos and the elimination of potential contamination, Reproductive BioMedicine Online, 11, 608-614, 2005	Not a randomised controlled trial.
Kwon,Y.S., Hahn,H.S., Kim,T.J., Lee,I.H., Lim,K.T., Lee,K.H., Shim,J.U., Mok,J.E., Fertility preservation in patients with early epithelial ovarian cancer, Journal of Gynecologic Oncology, 20, 44-47, 2009	Study on fertility preservation, not cryopreservation or vitrification
Lin,T.K., Su,J.T., Lee,F.K., Lin,Y.R., Lo,H.C., Cryotop vitrification as compared to conventional slow freezing for human embryos at the cleavage stage: survival and outcomes, Taiwanese Journal of Obstetrics and Gynecology, 49, 272-278, 2010	Retrospective study
Loutradi,K.E., Kolibianakis,E.M., Venetis,C.A., Papanikolaou,E.G., Pados,G., Bontis,I., Tarlatzis,B.C., Cryopreservation of human embryos by vitrification or slow freezing: a systematic review and meta-analysis. [48 refs], Fertility and Sterility, 90, 186-193, 2008	Meta-analysis
Moragianni,V.A., Cohen,J.D., Smith,S.E., Schinfeld,J.S., Somkuti,S.G., Lee,A., Barmat,L.I., Outcomes of day-1, day-3, and blastocyst cryopreserved embryo transfers, Fertility and Sterility, 93, 1353-1355, 2010	Type of embryo not type of freezing; useful for Q3
Noyes,N., Labella,P.A., Grifo,J., Knopman,J.M., Oocyte cryopreservation: a feasible fertility preservation option for reproductive age cancer survivors, Journal of Assisted Reproduction and Genetics, 27, 495-499, 2010	Does not compare methods of cryopreservation
Noyes,N., Labella,P.A., Grifo,J., Knopman,J.M., Oocyte cryopreservation: a feasible fertility preservation option for reproductive age cancer survivors, Journal of Assisted Reproduction and Genetics, 27, 495-499, 2010	Not a randomized controlled trial
Oktay,K., Oktem,O., Ovarian cryopreservation and transplantation for fertility preservation for medical indications: report of an ongoing experience, Fertility and Sterility, 93, 762-768, 2010	Not a randomized controlled trial
Paffoni,A., Alagna,F., Somigliana,E., Restelli,L., Brevini,T.A., Gandolfi,F., Ragni,G., Developmental potential of human oocytes after slow freezing or vitrification: a randomized in vitro study based on parthenogenesis, Reproductive Sciences, 15, 1027-1033, 2008	Study using parthenogenetic activation not fertilization with male gametes
Pinborg,A., Loft,A., Aaris,HenningsenA, Rasmussen,S., Andersen,A.N., Infant outcome of 957 singletons born after frozen embryo replacement: The Danish National Cohort Study 1995-2006, Fertility and Sterility, 94, 1320-1327, 2010	Unable to extract data for children of cancer patients only
Ping,P., Zhu,W.B., Zhang,X.Z., Yao,K.S., Xu,P., Huang,Y.R., Li,Z., Sperm banking for male reproductive preservation: a 6-year retrospective multi-centre study in China, Asian Journal of Andrology, 12, 356-362, 2010	Question not included in update of guideline

Bibliographic information	Reason for exclusion
Rezazadeh,Valojerdi M., Eftekhari-Yazdi,P., Karimian,L., Hassani,F., Movaghar,B., Vitrification versus slow freezing gives excellent survival, post warming embryo morphology and pregnancy outcomes for human cleaved embryos, Journal of Assisted Reproduction and Genetics, 26, 347-354, 2009	Not a randomized controlled trial
Shalom-Paz,E., Almog,B., Shehata,F., Huang,J., Holzer,H., Chian,R.C., Son,W.Y., Tan,S.L., Fertility preservation for breast-cancer patients using IVM followed by oocyte or embryo vitrification, Reproductive Biomedicine Online, 21, 566-571, 2010	Does not report relevant outcomes. Reports how many oocytes were retrieved and 'predicted pregnancy rates' based on non-cancer population data
Silber,S., Kagawa,N., Kuwayama,M., Gosden,R., Duration of fertility after fresh and frozen ovary transplantation, Fertility and Sterility, 94, 2191-2196, 2010	Not a randomized controlled trial
Son,W.Y., Chung,J.T., Gidoni,Y., Holzer,H., Levin,D., Chian,R.C., Tan,S.L., Comparison of survival rate of cleavage stage embryos produced from in vitro maturation cycles after slow freezing and after vitrification, Fertility and Sterility, 92, 956-958, 2009	Correspondence
Sunkara,S.K., Siozos,A., Bolton,V.N., Khalaf,Y., Braude,P.R., El-Toukhy,T., The influence of delayed blastocyst formation on the outcome of frozen-thawed blastocyst transfer: a systematic review and meta-analysis, Human Reproduction, 25, 1906-1915, 2010	Type of embryo rather than type of freezing
Sutcliffe,A.G., D'Souza,S.W., Cadman,J., Richards,B., McKinlay,I.A., Lieberman,B., Minor congenital anomalies, major congenital malformations and development in children conceived from cryopreserved embryos, Human Reproduction, 10, 3332-3337, 1995	Unable to extract data for children of cancer patients only
van Casteren,N.J., van Santbrink,E.J., van,Inzen W., Romijn,J.C., Dohle,G.R., Use rate and assisted reproduction technologies outcome of cryopreserved semen from 629 cancer patients, Fertility and Sterility, 90, 2245-2250, 2008	Unclear if particpants who had emnryos frozen ad part of IVF had cancer or not
Wennerholm,U.B., Soderstrom-Anttila,V., Bergh,C., Aittomaki,K., Hazekamp,J., Nygren,K.G., Selbing,A., Loft,A., Children born after cryopreservation of embryos or oocytes: A systematic review of outcome data, Human Reproduction, 24, 2158-2172, 2009	Unable to extract data for children of cancer patients only
Yap,J.K., Davies,M., Fertility preservation in female cancer survivors. [130 refs], Journal of Obstetrics and Gynaecology, 27, 390-400, 2007	Not a randomized controlled trial

Chapter 20. Long-term safety of assisted reproduction treatments in women with infertility and their children

Table G.16 Safety of ovulation stimulating agents in women and long term effects on children conceived via ART

Bibliographic information	Reason for exclusion
Barlow,P., Lejeune,B., Puissant,F., Englert,Y., Van,Rysselberge M., Degueldre,M., Vekemans,M., Leroy,F., Early pregnancy loss and obstetrical risk after in-vitro fertilization and embryo replacement, Human Reproduction, 3, 671-675, 1988	Investigated short term consequences of IVF
Ben-Ami,I., Edel,Y., Barel,O., Vaknin,Z., Herman,A., Maymon,R., Do assisted conception twins have an increased risk for anencephaly?, Human Reproduction, 26, 3466-3471, 2011	Potentially includes other methods of assisted conception.
Bergh,T., Ericson,A., Hillensjo,T., Nygren,K-G, Wennerholm,U-B, Deliveries and children born after IVF in Sweden 1982-1995 - a retrospective cohort study, Lancet, 354, 1579-1585, 1999	Outcomes evaluated are not relevant to the question
Bonduelle,M., Legein,J., Derde,M.P., Buysse,A., Schietecatte,J., Wisanto,A., Devroey,P., Van,Steirteghem A., Liebaers,I., Comparative follow-up study of 130 children born after intracytoplasmic sperm injection and 130 children born after in-vitro fertilization, Human Reproduction, 10, 3327-3331, 1995	Comparison between IVF and ICSI
Bonduelle,M., Legein,J., Buysse,A., Van,Assche E., Wisanto,A., Devroey,P., Van Steirteghem,A.C., Liebaers,I., Prospective follow-up study of 423 children born after intracytoplasmic sperm injection, Human Reproduction, 11, 1558-1564, 1996	Non-comparative study
Bonduelle,M., Wilikens,A., Buysse,A., Van,Assche E., Wisanto,A., Devroey,P., Van Steirteghem,A.C., Liebaers,I., Prospective follow-up study of 877 children born after intracytoplasmic sperm injection (ICSI), with ejaculated epididymal and testicular spermatozoa and after replacement of cryopreserved embryos obtained after ICSI, Human Reproduction, 11 Suppl 4, 131-155, 1996	Non-comparative study
Bonduelle,M., Wilikens,A., Buysse,A., Van,Assche E., Devroey,P., Van Steirteghem,A.C., Liebaers,I., A follow-up study of children born after intracytoplasmic sperm injection (ICSI) with epididymal and testicular spermatozoa and after replacement of cryopreserved embryos obtained after ICSI, Human Reproduction, 13 Suppl 1, 196-207, 1998	Non-comparative study
Bruinsma,F., Venn,A., Lancaster,P., Speirs,A., Healy,D., Incidence of cancer in children born after in-vitro fertilization, Human Reproduction, 15, 604-607, 2000	Includes other ART techniques
Buckett,W.M., Tan,S.L., Congenital abnormalities in children born after assisted reproductive techniques: how much is associated with the presence of infertility and how much with its treatment?. [15 refs], Fertility and Sterility, 84, 1318-1319, 2005	Review

Bibliographic information	Reason for exclusion
Burkman,R.T., Tang,M.T.C., Malone,K.E., Marchbanks,P.A., McDonald,J.A., Folger,S.G., Burger,C.W., Fertility drug use was not associated with an increased risk of breast cancer, Evidence-based Obstetrics and Gynecology, 6, 137-based, 2004	Abstract
Burkman,R.T., Tang,M.T., Malone,K.E., Marchbanks,P.A., McDonald,J.A., Folger,S.G., Norman,S.A., Strom,B.L., Bernstein,L., Ursin,G., Weiss,L.K., Daling,J.R., Simon,M.S., Spirtas,R., Infertility drugs and the risk of breast cancer: findings from the National Institute of Child Health and Human Development Women's Contraceptive and Reproductive Experiences Study, Fertility and Sterility, 79, 844-851, 2003	Specific fertility drugs not reported
Chan,Y.Y., Jayaprakasan,K., Zamora,J., Thornton,J.G., Raine-Fenning,N., Coomarasamy,A., The prevalence of congenital uterine anomalies in unselected and high-risk populations: a systematic review, Human Reproduction Update, 17, 761-771, 2011	Mixed population and results for IVF women were not reported separately.
Cohen,J., Infertile couples, assisted reproduction and increased risks to the children, Reproductive Biomedicine Online, 15, 245-246, 2007	Review
Cusido,M., Fabregas,R., Pere,B.S., Escayola,C., Barri,P.N., Ovulation induction treatment and risk of borderline ovarian tumors, Gynecological Endocrinology, 23, 373-376, 2007	Results were not adjusted for confounders and confidence intervals not reported
Davies,M., Moore,V.M., Willson,K., Chan,A., Haan,E., Comparative risk of birth defects across ART treatment modalities and spontaneous pregnancies within a population cohort, Human Reproduction, 26th Annual Meeting of the European Society of Human Reproduction and Embryology, ESHRE Rome Italy. Conference Start, i54-, 2010	Includes other types of ART
Debaun,M.R., Niemitz,E.L., Feinberg,A.P., Association of in vitro fertilization with Beckwith-Wiedemann syndrome and epigenetic alterations of LIT1 and H19, American Journal of Human Genetics, 72, 156-160, 2003	No p-values or confidence intervals reported
El-Chaar,D., Yang,Q., Gao,J., Bottomley,J., Leader,A., Wen,S.W., Walker,M., Risk of birth defects increased in pregnancies conceived by assisted human reproduction, Fertility and Sterility, 92, 1557-1561, 2009	Fertility drugs used not clearly stated
Gadducci,A., Gargini,A., Palla,E., Genazzani,A.R., Reproductive variables, fertility drugs and epithelial ovarian tumor risk, CME Journal of Gynecologic Oncology, 9, 245-252, 2004	Review
Glud,E., Kjaer,S.K., Troisi,R., Brinton,L.A., Fertility drugs and ovarian cancer, Epidemiologic Reviews,Epidemiol.Rev., 20, 237-257, 1998	A more recent review has been included

Bibliographic information	Reason for exclusion
Golombok,S., Cook,R., Bish,A., Murray,C., Families created by the new reproductive technologies: quality of parenting and social and emotional development of the children, Child Development,Child Dev., 66, 285-298, 1995	Non-relevant comparison -Compares children born from IVF, donor insemination, natural conception and adopted children
Hansen,M., Colvin,L., Petterson,B., Kurinczuk,J.J., de,Klerk N., Bower,C., Admission to hospital of singleton children born following assisted reproductive technology (ART).[Erratum appears in Hum Reprod. 2008 Oct;23(10):2390], Human Reproduction, 23, 1297-1305, 2008	Includes other types of ART
Hvidtjorn,D., Grove,J., Schendel,D., Vaeth,M., Ernst,E., Nielsen,L., Thorsen,P., 'Vanishing embryo syndrome' in IVF/ICSI, Human reproduction (Oxford, England), #20, 2550-2551, 2005	Results were not adjusted for confounders
Hvidtjorn,D., Grove,J., Schendel,D., Svaerke,C., Schieve,L.A., Uldall,P., Ernst,E., Jacobsson,B., Thorsen,P., Multiplicity and early gestational age contribute to an increased risk of cerebral palsy from assisted conception: A population-based cohort study, Human Reproduction, 25, 2115-2123, 2010	Fertility drugs used not clearly stated
Ito,A., Honma,Y., Inamori,E., Yada,Y., Momoi,M.Y., Nakamura,Y., Developmental outcome of very low birth weight twins conceived by assisted reproduction techniques, Journal of Perinatology, 26, 130-133, 2006	Includes other ART types other than IVF and ICSI
Jensen,A., Sharif,H., Frederiksen,K., Susanne,K.K., Use of fertility drugs and risk of ovarian cancer: Danish population based cohort study, Obstetrical and Gynecological Survey, 64, 390-391, 2009	Editorial comment
Kai,C.M., Main,K.M., Andersen,A.N., Loft,A., Chellakooty,M., Skakkebaek,N.E., Juul,A., Serum Insulin-like Growth Factor-I (IGF-I) and growth in children born after assisted reproduction, Journal of Clinical Endocrinology and Metabolism, 91, 4352-4360, 2006	Confidence intervals not reported
Kallen,B., Finnstrom,O., Lindam,A., Nilsson,E., Nygren,K.G., Olausson,P.O., Cancer risk in children and young adults conceived by in vitro fertilization, Pediatrics, 126, 270-276, 2010	Non-relevant comparisons
Kallen,A.J.B., Finnstrom,O.O., Lindam,A.P., Nilsson,E.M.E., Nygren,K.G., Otterblad,OlaussonP, Cerebral palsy in children born after in vitro fertilization. Is the risk decreasing?, European Journal of Paediatric Neurology, 14, 526-530, 2010	Compares IVF children of different age groups.
Kapiteijn,K., de Bruijn,C.S., de,Boer E., de Craen,A.J., Burger,C.W., van Leeuwen,F.E., Helmerhorst,F.M., Does subfertility explain the risk of poor perinatal outcome after IVF and ovarian hyperstimulation?, Human Reproduction, 21, 3228-3234, 2006	Fertility drugs used not clearly stated

Bibliographic information	Reason for exclusion
Kashyap,S., Moher,D., Fung,M.F., Rosenwaks,Z., Assisted reproductive technology and the incidence of ovarian cancer: a meta-analysis, Obstetrics and Gynecology, 103, 785-794, 2004	Fertility drugs used not clearly stated
Katz,D., Paltiel,O., Peretz,T., Revel,A., Sharon,N., Maly,B., Michan,N., Sklair-Levy,M., Allweis,T., Beginning IVF treatments after age 30 increases the risk of breast cancer: results of a case-control study, Breast Journal, 14, 517-522, 2008	Non-relevant risk factor
Kim,J., Oktay,K., Infertility as a risk factor of ovarian and breast cancer, Expert Review of Obstetrics and Gynecology, 6, 153-161, 2011	Non-relevant risk factor
Klemetti,R., Sevon,T., Gissler,M., Hemminki,E., Health of children born after ovulation induction, Fertility and Sterility, 93, 1157-1168, 2010	Fertility drugs used not clearly stated
Klip,H., Burger,C.W., de,KrakerJ, Van,LeeuwenF, Doyle,P., Children born after fertility treatment, including in vitro fertilization, were not at increased risk of childhood cancer, Evidence-based Obstetrics and Gynecology, 4, 140-based, 2002	Includes women that used other types of ART other than IVF
Kurinczuk,J.J., Bower,C., Birth defects in infants conceived by intracytoplasmic sperm injection: an alternative interpretation, BMJ, 315, 1260-1265, 1997	Results were not adjusted for confounding factors
Lerner-Geva,L., Keinan-Boker,L., Blumstein,T., Boyko,V., Olmar,L., Mashiach,S., Rabinovici,J., Potashnik,G., Lunenfeld,E., Schenker,J.G., Shushan,A., Fishman,A., Cohen,I., Vagman,I., Lunenfeld,B., Infertility, ovulation induction treatments and the incidence of breast cancer--a historical prospective cohort of Israeli women, Breast Cancer Research and Treatment, 100, 201-212, 2006	Results not adjusted for confounders
Ludwig,M., Katalinic,A., Malformation rate in fetuses and children conceived after ICSI: results of a prospective cohort study, Reproductive Biomedicine Online, 5, 171-178, 2002	Duration of follow-up was 8 weeks
Maimburg,R.D., Vaeth,M., Do children born after assisted conception have less risk of developing infantile autism?, Human Reproduction, 22, 1841-1843, 2007	It does not specifically evaluate the consequences of IVF
Moll,A.C., Imhof,S.M., Cruysberg,J.R., Schouten-van Meeteren,A.Y., Boers,M., van Leeuwen,F.E., Incidence of retinoblastoma in children born after in-vitro fertilisation, Lancet, 361, 309-310, 2003	Non-comparative study
Ness,R.B., Cramer,D.W., Goodman,M.T., Kruger,KjaerS, Mallin,K., Mosgaard,B.J., Purdie,D.M., Risch,H.A., Vergona,R., Wu,A.H., Cook,L.S., Infertility, but not fertility drug use, was associated with an increased risk of ovarian cancer, Evidence-based Obstetrics and Gynecology, 5, 36-based, 2003	Fertility drugs used not clearly stated

Bibliographic information	Reason for exclusion
Orgeas,C.C., Sanner,K., Hall,P., Conner,P., Holte,J., Nilsson,S.J., Sundfeldt,K., Persson,I., Chia,K.S., Wedren,S., Dickman,P.W., Czene,K., Breast cancer incidence after hormonal infertility treatment in Sweden: a cohort study, American Journal of Obstetrics and Gynecology, 200, 72-77, 2009	Results reported as standardised incidence ratio
Parazzini,F., Pelucchi,C., Talamini,R., Montella,M., La,VecchiaC, Use of fertility drugs and risk of endometrial cancer in an Italian case-control study, European Journal of Cancer Prevention, #19, 428-430, 2010	Specific fertility drugs not reported
Pruksananonda,C., Growth and development of children conceived by intracytoplasmic sperm injection at King Chulalongkorn Memorial Hospital, Journal of the Medical Association of Thailand, 84 Suppl 1, S76-S85, 2001	Non-comparative study
Raimondi,S., Pedotti,P., Taioli,E., Meta-analysis of cancer incidence in children born after assisted reproductive technologies, British Journal of Cancer, 93, 1053-1056, 2005	Includes papers with inappropriate study design
Reid,S.M., Jaques,A.M., Susanto,C., Breheny,S., Reddihough,D.S., Halliday,J., Cerebral palsy and assisted reproductive technologies: a case-control study, Developmental Medicine and Child Neurology, 52, e161-e166, 2010	Includes other assisted reproductive techniques not relevant to the question
Roca-de,Bes M., Gutierrez-Maldonado,J., Gris-Martinez,J.M., Comparative study of the psychosocial risks associated with families with multiple births resulting from assisted reproductive technology (ART) and without ART, Fertility and Sterility, 96, 170-174, 2011	The specific ART used was not mentioned
Schieve,L.A., Cohen,B., Nannini,A., Ferre,C., Reynolds,M.A., Zhang,Z., Jeng,G., Macaluso,M., Wright,V.C., Massachusetts Consortium for Assisted Reproductive Technology Epidemiologic Research (MCARTER), A population-based study of maternal and perinatal outcomes associated with assisted reproductive technology in Massachusetts, Maternal and Child Health Journal, 11, 517-525, 2007	Fertility drugs used not clearly stated
Silva,Idos S., Wark,P.A., McCormack,V.A., Mayer,D., Overton,C., Little,V., Nieto,J., Hardiman,P., Davies,M., MacLean,A.B., Ovulation-stimulation drugs and cancer risks: a long-term follow-up of a British cohort, British Journal of Cancer, 100, 1824-1831, 2009	Results reported as standardised incidence ratios
Sun,Y., Vestergaard,M., Christensen,J., Zhu,J.L., Bech,B.H., Olsen,J., Epilepsy and febrile seizures in children of treated and untreated subfertile couples, Human Reproduction, 22, 215-220, 2007	Fertility drugs used not clearly stated
Terry,K.L., Willett,W.C., Rich-Edwards,J.W., Michels,K.B., A prospective study of infertility due to ovulatory disorders, ovulation induction, and incidence of breast cancer, Archives of Internal Medicine, 166, 2484-2489, 2006	Non-relevant risk factor

Bibliographic information	Reason for exclusion
Van,Golde R., Boada,M., Veiga,A., Evers,J., Geraedts,J., Barri,P., A retrospective follow-up study on intracytoplasmic sperm injection, Journal of Assisted Reproduction and Genetics, 16, 227-232, 1999	Comparison between IVF and ICSI
Venn,A., The use of fertility drugs did not increase the risk of ovarian cancer in infertile women, Evidence-based Obstetrics and Gynecology, 7, 89-based, 2005	Editorial comment
Vlahos,N.F., Economopoulos,K.P., Fotiou,S., Endometriosis, in vitro fertilisation and the risk of gynaecological malignancies, including ovarian and breast cancer. [78 refs], Best Practice and Research in Clinical Obstetrics and Gynaecology, 24, 39-50, 2010	Review
Zadori,J., Kozinszky,Z., Orvos,H., Katona,M., Kaali,S.G., Pal,A., The incidence of major birth defects following in vitro fertilization, Journal of Assisted Reproduction and Genetics, 20, 131-132, 2003	Fertility drugs used not clearly stated

Appendix H Evidence tables

[See separate appendix document]

Appendix I GRADE tables

Table I.6.3 Accuracy of tests of ovarian reserve: area under the curve data

Quality assessment							Summary of findings	
No. of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Pooled area under the curve**	**Quality**
Live full-term singleton birth								
Antral Follicle Count (AFC) on day 3 of cycle								
1 (N = 243) (Li et al., 2010)	Retrospective cohort	Serious[g]	-	Serious[h]	None	None	0.622	Very low
Anti-Mullerian Hormone (AMH) on day 3 of cycle								
1 (N =324) (Lee et al., 2009)	Prospective cohort	None	-	Serious[h]	None	None	0.52	Low
1 (N = 243) (Li et al., 2010)	Retrospective	Serious[g]	-	Serious[h]	None	None	0.682	Very low
Age								
1 (N = 324) (Lee et al., 2009)	Prospective cohort	None	-	Serious[h]	None	None	0.55	Low
Clomifene Citrate Challenge Test (CCCT)								
No evidence reported								

Quality assessment							Summary of findings	
No. of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Pooled area under the curve**	**Quality**
E2								
No evidence reported								
Follicle-Stimulating Hormone (FSH) on day 3 of cycle								
1 (N = 324) (Lee et al., 2009)	Prospective cohort	None	-	Serious[h]	None	None	0.52	Low
1 (N = 243) (Li et al., 2010)	Retrospective	Serious[g]	-	Serious[h]	None	None	0.623	Very low
Inhibin B								
No evidence reported								
Ovarian volume (OV)								
No evidence reported								
Ovarian blood flow								
No evidence reported								
Low response following ovarian stimulation								
AFC on day 2–4 of cycle								
4 (N = 470)[a] (Bancsi et al., 2002; Hendriks et al., 2004; van Rooij et al., 2002; Younis et., al 2010)	Prospective cohort	None	None	None	None	None	0.83	Moderate

Quality assessment							Summary of findings	
No. of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Pooled area under the curve**	**Quality**
AMH on day 2–4 of cycle								
3 (N = 757)[a] (van Rooij et al., 2002; Al-Azemi, 2011; Andersen, 2011)	Prospective cohort	None	None	None	None	None	0.83[i]	Moderate
Age								
5 (N = 618)[a] (Bancsi et al., 2002; Hendriks et al., 2004; Khairy et al., 2008; van Rooij et al., 2002; Younis et al., 2010)	Prospective cohort	None	None	None	None	None	0.73[i]	Moderate
CCCT on day 3 of cycle								
1 (N = 63) (Hendriks et al., 2004)	Prospective cohort	None	-	None	None	None	0.85	Moderate
E2 on day 3 of cycle								
3 (N = 302)[a] (Bancsi et al., 2002; Hendriks et al., 2004; van Rooij et., al 2002)	Prospective cohort	None	None	None	None	None	0.52[i]	Moderate
FSH on day 2–4 of cycle								
4 (N = 470) (Bancsi et al 2002, Hendriks et al 2004, van Rooij et al 2002, Younis et al 2010)	Prospective cohort	None	None	None	None	None	0.81[i]	Moderate

Quality assessment							Summary of findings	
No. of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Pooled area under the curve**	**Quality**
Inhibin B on day 3 of cycle								
3 (N = 302)[a] (Bancsi et al., 2002; Hendriks et al., 2004; van Rooij et al., 2002)	Prospective cohort	None	None	None	None	None	0.76[i]	Moderate
OV on day 2–4 of cycle								
1 (N = 168) (Younis et al., 2010)	Prospective cohort	None	-	None	None	None	0.67	Moderate
Ovarian blood flow								
No evidence reported								
Age + FSH on day 2 – 4 of cycle [b]								
1 (N = 148) (Khairy et al., 2008)	Prospective cohort	None	-	None	None	None	0.75	Moderate
Age +AFC on day 3 of cycle [c]								
1 (N = 148) (Khairy et al., 2008)	Prospective cohort	None	-	None	None	None	0.80	Moderate
FSH on day 2–4 of cycle + AFC on day 3 of cycle[d]								
2 (N =183) (Bancsi et al., 2002; Hendricks et al., 2004)	Prospective cohort	None	None	None	None	None	0.90[i]	Moderate

Quality assessment							Summary of findings	
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Pooled area under the curve	Quality
Age + FSH on day 2–4 of cycle + AFC on day 3 of cycle[b]								
1 (N = 148) (Khairy et al., 2008)	Prospective cohort	None	-	None	None	None	0.81	Moderate
Age + FSH + Inhibin B + AMH								
1 (N = 352) (Al-Azemi et al., 2010)	Prospective cohort	None	-	None	None	None	0.819	Moderate
AMH + Smoking								
1 (N = 119)[e] (Ansersen et al , 2011)	Prospective cohort	None	-	None	None	None	0.85	Moderate
High response following ovarian stimulation								
AFC on day 3 of cycle								
1 (N = 119)[e] van Rooij 2002	Prospective cohort	None	-	NA	None	NA	0.86	Moderate
AMH on day 3 of cycle								
3 (N = 544) [e](van Rooij et al., 2002; Aflatoonian et al., 2009; Andersen et al., 2011)	Prospective cohort	Serious[k] -	-None	Serious[j]	None	-	0.83[i]	Low
Age								
1 (n=143) (Aflatoonian et al., 2009)	Prospective cohort	None	-	None	Serious[l]	-	0.409	Low

Quality assessment							Summary of findings	
No. of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Pooled area under the curve**	**Quality**
E2 on day 3 of cycle								
1 (n=143) (Aflatoonian et al., 2009)	Prospective cohort	None	-	Serious[j]	None		0.474	Low
CCCT on day 3 of cycle								
No evidence reported								
FSH								
1 (n=143) (Aflatoonian et al., 2009)	Prospective cohort	None	-	Serious[j]	None	-	0.385	Low
Inhibin B on day 3 of cycle								
1 (N = 119)[e] (van Rooij et al., 2002)	Prospective cohort	None	-	None	None	None	0.76	Moderate
Ovarian blood flow								
No evidence reported								
AMH + AFC + FSH								
1 (N = 119)[e] (Ansersen et al , 2011)	Prospective cohort	None	-	None	None	None	0.80	Moderate
Cancellation following ovarian stimulation								
AFC on day 2–4 of cycle								
1 (N = 84)[f] (McIlveen et al., 2007)	Prospective cohort	None	-	None	None	None	0.74	Moderate

Quality assessment							Summary of findings	
No. of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Pooled area under the curve**	**Quality**
AMH on day 2 of cycle								
2 (N = 200 (McIlveen et al., 2007; Lee, 2011)	Prospective cohort	Serious[o]	None	None	None		0.77[i]	Low
Age								
No evidence reported								
CCCT								
No evidence reported								
E2 on day 2–4 of cycle								
No evidence reported								
FSH on day 2–4 of cycle								
1 (N = 84) (McIlveen et al., 2007)	Prospective cohort	None	-	None	None	None	0.64	Moderate
Inhibin B on day 2–4 of cycle								
1 (N = 84) (McIlveen et al., 2007)	Prospective cohort	None	-	None	None	None	0.78	Moderate
OV on day 2 of cycle								
1 (N = 84) (McIlveen et al., 2007)	Prospective cohort	None	-	None	None	None	0.78	Moderate
Ovarian blood flow								
No evidence reported								

Quality assessment							Summary of findings	
No. of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Pooled area under the curve**	**Quality**
Pregnancy (no data reported)								
No evidence reported								
AFC (cut-off at <15)								
1 (N = 115; Ben-Haroush, 2011)	Prospective cohort	Very Serious[m, n]	-	None	None	None	0.613	Low
AMH on day 3–5 of cycle								
No evidence reported								
Age								
No evidence reported								
CCCT								
No evidence reported								
E2								
1 (N = 115; Ben-Haroush, 2011)	Prospective cohort	Very Serious[m, n]	-	None	None	None	0.595	Low
FSH								
1 (N = 115; Ben-Haroush, 2011)	Prospective cohort	Very Serious[m, n]	-	None	None	None	0.459	Low
Inhibin B								
No evidence reported								

Quality assessment							Summary of findings	
No. of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Pooled area under the curve**	**Quality**
OV								
1 (N = 115; Ben-Haroush, 2011)	Prospective cohort	Very Serious[m, n]	-	None	None	None	0.513	Low
Ovarian blood flow (based on peak systolic velocity)								
1 (N = 115; Ben-Haroush, 2011)	Prospective cohort	Very Serious[m, n]	-	None	None	None	0.393	Low

AFC: Antral Follicle Count ; AMH: Anti-Mullerian Hormone; FSH: Follicle-Stimulating Hormone; CCCT: Clomiphene Citrate Challenge Test; OV: ovarian volume

[a] Low response defined as < 4 oocytes or cycle cancellation due to < 3 follicles or absent follicular growth

[b] High age + high FSH

[c] High age + low AFC

[d] High FSH + low AFC

[e] High response defined as > 15 oocytes or E2 > 3000pg/ml

[f] Defined as < 4 follicles with a diameter of > 14 mm after 8 days of stimulation or when requirement for hCG not met after 4-5 days or no oocytes retrieved

[g] Retrospective study design is liable to be baised

[h] Live full-term singleton birth not reported, so live birth used as a proxy

[i] Weighted average based on sample size calculated by reviewer in Excel.

[j] uUnclear when measurements taken

[k] Intra-assay coefficient was greater than 10% for AMH test so considered

[l] Wide confidence intervals

[m] Test process not described in detail.

[n] A variety of IVF protocols were used and are likely to influence pregnancy rates, but unclear if this was accounted for in the analysis.

[o] Lee et al restricted to women aged 40 years or over.

Table I.6.4 GRADE findings for evaluation ovarian reserve: likelihood ratios for the Antral Follicle Count (AFC) test

Quality assessment							**Summary of findings**							
								Measure of diagnostic accuracy						
No. of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of women/patients**	**Sensitivity**	**Specificity**	**Positive predictive value**	**Negative predictive value**	**Positive likelihood ratio**	**Negative likelihood ratio**	**Quality**
Low response following ovarian stimulation														
≤ 2 oocytes														
1 (Bancsi et al., 2004a)	Prospective Observational	None	-	-	None	None	N = 120					14.0 (3.30, 59.4)	0.68 (0.54, 0.86)	Moderate
≤ 3 oocytes														
1 (Bancsi et al., 2004a)	Prospective Observational	None	-	-	None	None	N = 120					6.61 (2.84,15.39)	0.57 (0.41, 0.78)	Moderate
≤ 4 oocytes														
1 (Bancsi et al., 2004a)	Prospective Observational	None	-	-	None	None	N = 120					5.13 (2.71, 9.71)	0.44 (0.29, 0.67)	Moderate
≤ 5 oocytes														
1 (Bancsi et al., 2004a)	Prospective Observational	None	-	-	None	None	N =120					4.04 (2.45, 6.68)	0.34 (00.20, 0.58)	Moderate
≤ 6 oocytes														
1 (Bancsi et al., 2004a)	Prospective Observational	None	-	-	None	None	N = 120					3.56 (2.32, 5.46)	0.25 (0.13, 0.49)	Moderate

Quality assessment							Summary of findings							
								Measure of diagnostic accuracy						
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Number of women/patients	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Positive likelihood ratio	Negative likelihood ratio	Quality
≤ 8 oocytes														
1 (Bancsi et al., 2004a)	Prospective observational	None	-	-	None	None	N = 120					2.75 (2.00, 3.78)	0.13 (0.04, 0.37)	Moderate
≤ 10 oocytes														
1 (Bancsi et al., 2004a)	Prospective Observational	None	-	-	None	None	N = 120					2.20 (1.70, 2.86)	0.10 (0.03, 0.38)	Moderate
High response following ovarian stimulation														
>9 oocytes														
1 (Ng et al., 2000)	Prospective cohort	Serious	-	-	-	-	N = 128					2.07	0.56	Low
>10 oocytes														
1 (Kwee et al., 2007)	Prospective Observational	None	-	-	None	None	N = 110					3.24 (2.30, 4.55)	0.08 (0.01, 0.56)	Moderate
>12 oocytes														
1 (Kwee et al., 2007)	Prospective Observational	None	-	-	None	None	N = 110					4.31 (2.79, 6.69)	0.15 (0.04, 0.55)	Moderate
>14 oocytes														
1 (Kwee et al., 2007)	Prospective Observational	None	-	-	None	None	N = 110					7.66 (4.10, 14.32)	0.20 (0.07, 0.55)	Moderate

Quality assessment							Summary of findings							
								Measure of diagnostic accuracy						
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Number of women/patients	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Positive likelihood ratio	Negative likelihood ratio	Quality
1 (Ng et al., 2000)	Prospective cohort	Serious[1]	-	-	-	-	N = 128					3.33	0.85	Low
1 (Van RooiJ et al., 2002)	Prospective cohort	Serious[1]	-	-	-	-	N = 114					2.49	0.13	Low
1 (Eldar-Geva et al., 2005)	Prospective cohort	Serious[1]	-	-	-	-	N = 56					1.40	0.18	Low
>16 oocytes														
1 (Kwee et al 2007)	Prospective Observational	None	-	-	None	None	N = 110					10.94(3.70, 32.32)	0.55.(0.35, 0.87)	Moderate
1 Aflatoonian et al 2009	Prospective cohort	Serious[1]	-	-	None	None	N = 143					11.11	0.12	Low
>18 oocytes														
1 (Kwee et al, 2007)	Prospective Observational	None	-	-	None	None	N = 110					13.68(2.88, 64.84)	0.72 (0.53, 0.98)	Moderate

[1] 95% CI not presented

Table I.6.5 GRADE findings for evaluation of accuracy of tests of ovarian reserve: likelihood ratios for the Anti-Mullerian Hormone (AMH) test

Quality assessment							Summary of findings							
								Measure of diagnostic accuracy						
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Number of women/patients	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Positive likelihood ratio	Negative likelihood ratio	Quality
Low response following ovarian stimulation														
≤ 0.5 ng/ml														
1 (La Marca et al., 2007)	Prospective Observational	None	-	-	None	None	N = 48					4.58 (2.76, 7.64)	0.20 (0.06, 0.72)	Moderate
≤ 0.75 ng/ml														
1 (La Marca et al., 2007)	Prospective Observational	None	-	-	None	None	N = 48					11.00 (4.76, 25.44)	0.27 (0.10, 0.72)	Moderate
≤ 1.25 ng/ml														
1 (McIlveen et al., 2007)	Prospective Observational	None	-	-	None	None	N = 84					2.33 (1.26, 4.31)	0.56 (0.38, 0.82)	Moderate
=1.36														
1 (Al-Azemi et al., 2011)	Prospective Observational	Serious[1]	-	-	-	None	N = 356					2.99	0.34	Low
≤ 2.97 ng/ml (based on poor responder being <5 oocytes														
1 (Kunt et al., 2011)	Prospective Observational	Serious[1]	-	-	-	None	N = 180					7.14	0.14	Low

Quality assessment							Summary of findings							
								Measure of diagnostic accuracy						
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Number of women/patients	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Positive likelihood ratio	Negative likelihood ratio	Quality
High response following ovarian stimulation (as reported in Boer et al, 2011**)**														
=1.59 ng/ml														
1 (Riggs et al., 2008)	Retrospective cohort	Very serious	-	-	-	None	N = 123					2.55	0.24	Very Low
=1.66 ng/ml														
1 (Ebner et al., 2006)	Prospective cohort	Serious [1]	-	-	-	None	N = 135					1.38	0.16	Low
=1.99 ng/ml														
1 (Lee et al., 2008)	Prospective cohort	Serious [1]	-	-	-	None	N = 262					2.37	0.16	Low
= 2.10 ng/ml														
1 (Nelson et al., 2007)	Prospective cohort	Serious [1]	-	-	-	None	N = 314					4.19	0.15	Low
=2.60 ng/ml														
1 (La Marca et al., 2007)	Prospective cohort	Serious [1]	-	-	-	None	N = 48					1.95	0.25	Low
=3.36 ng/ml														
1 (Lee et al., 2008)	Prospective cohort	Serious [1]	-	-	-	None	N = 262					4.77	0.44	Low

Quality assessment							Summary of findings							
								Measure of diagnostic accuracy						
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Number of women/patients	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Positive likelihood ratio	Negative likelihood ratio	Quality
=3.50 ng/ml														
1 (Van RooiJ et al., 2002)	Prospective cohort	Serious [1]	-	-	-	None	N = 114					8.00	0.63	Low
1 (Eldar-Geva et al., 2005)	Prospective cohort	Serious [1]	-	-	-	None	N = 53					6.55	0.31	Low
1 (Nelson et al., 2007)	Prospective cohort	Serious [1]	-	-	-	None	N = 314					14.25	0.45	Low
1 (Nardo et al., 2009)	Prospective cohort	Serious [1]	-	-	-	None	N = 165					2.93	0.17	Low
=4.52 ng/ml														
1 (Ebner et al., 2006)	Prospective cohort	Serious [1]	-	-		None	N = 135					2.89	0.56	Low
= 4.83 ng/ml														
1 (Aflatoonian et al., 2009)	Prospective cohort	Serious [1]	-	-	-	None	N = 159					4.23	0.09	Low
=7.00 ng/ml														
1 (La Marca et al., 2007)	Prospective cohort	Serious [1]	-	-	-	None	N = 48					3.35	0.52	Very low

[1] 95% CI not presented

Table I.6.6 GRADE findings for evaluation of accuracy of tests of ovarian reserve: likelihood ratios for the Follicle-Stimulating Hormone (FSH) test

Quality assessment							Summary of findings							
								Measure of diagnostic accuracy						
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Number of women/patients	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Positive likelihood ratio	Negative likelihood ratio	Quality
Low response following ovarian stimulation														
≥7.0 IU/L														
1 (Al-Azemi et al., 2011)	Prospective Observational	Serious[1]	-	-	-	None	N = 356					2.17	0.46	Low
≥8.9 IU/L														
1 (Bancsi et al., 2004b)	Prospective Observational	None	-	-	None	None	N = 120					6.41 (3.16, 13.04)	0.43 (0.28, 0.65)	Moderate
≥ 10 IU/L														
1 (Hendriks et al., 2004)	Prospective Observational	None	-	-	None	None	N = 63					13.53 (3.26, 55.56)	0.43 (0.24, 0.76)	Moderate
≥11 IU/L														
1 (Bancsi et al., 2004b)	Prospective Observational	None	-	-	None	None	N = 120					6.22 (2.65, 14.60)	0.60 (0.44, 0.81)	Moderate
≥13.4 IU/L														
1 (Bancsi et al., 2004b)	Prospective Observational	None	-	-	None	None	N = 120					7.58 (2.65, 21.68)	0.67 (0.52, 0.86)	Moderate

Quality assessment							Summary of findings							
								Measure of diagnostic accuracy						
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Number of women/patients	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Positive likelihood ratio	Negative likelihood ratio	Quality
≥ 15 IU/L														
1 (Hendriks et al., 2004)	Prospective Observational	None	-	-	None	None	N = 63					13.53 (1.70, 107.62)	0.72 (0.53, 0.98)	Moderate
High response following ovarian stimulation														
≤ 4 IU/L														
1 (Kwee et al., 2006)	Prospective Observational	None	-	-	None	None	N = 110					16.41 (1.81, 148.62)	0.83 (0.67, 1.04)	Moderate
≤ 5 IU/L														
1 (Kwee et al., 2006)	Prospective Observational	None	-	-	None	None	N = 110					4.56 (1.57, 13.27)	0.75 (0.55, 1.03)	Moderate
≤ 6 IU/L														
1 (Kwee et al., 2006)	Prospective Observational	None	-	-	None	None	N = 110					2.74 (1.65, 4.54)	0.46 (0.24, 0.89)	Moderate
≤ 7 IU/L														
1 (Kwee et al., 2006)	Prospective Observational	None	-	-	None	None	N = 110					2.13 (1.52, 2.98)	0.29 (0.10, 0.81)	Moderate
≤ 8 IU/L														
1 (Kwee et al., 2006)	Prospective Observational	None	-	-	None	None	N = 110					1.59 (1.29, 1.96)	0.14 (0.02, 0.98)	Moderate

[1] 95% CI not presented

Table I.6.9 GRADE findings of non-comparative seroconversion data resulting from sperm washing used in association with different ART methods

Quality assessment							Summary of findings				
							Number of people		Effect		
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Sero-con-version	Comparator	Relative (95% CI)	Absolute (95% CI)	Quality
Seroconversion rate in mothers											
IUI with washed sperm from HIV-positive males											
(Savasi et al., 2007)	Prospective cohort	Serious [e]	-	None	None	Yes [r]	0/2400 (0%)	-	-	-	Very low
(Marina et al., 1998)	Prospective cohort	Some [a]	-	None	None	Yes [b]	0/101 (0%)	-	-	-	Very low
(Bujan et al., 2007b)	Retrospective cohort	Some [g]	-	None	None	Yes [s]	0/2840 (0%)	-	-	-	Very low
(Bujan et al., 2007a)	Retrospective cohort	Some [i]	-	None	None	Yes [j]	0/294 (0%)	-	-	-	Very low
							0/5635 (0%)				Very low
ICSI with washed sperm from HIV-positive males											
(Savasi et al., 2007)	Prospective cohort	Serious [e]	-	None	None	Yes [s]	0/283 (0%)	-	-	-	Very low
Mencaglia (2005)	Prospective cohort	None	-	None	None	Yes [h]	0/78 (0%)	-	-	-	low
(Kashima et al., 2009)	Prospective cohort	Some [l]	-	None	None	Yes [m]	0/23 (0%)	-	-	-	Very Low
(Sauer et al., 2009)	Retrospective cohort	Serious [k]	-	None	None	Yes [h]	0/420 (0%)	-	-	-	Very low

Quality assessment							Summary of findings				
							Number of people		Effect		
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Sero-con-version	Comparator	Relative (95% CI)	Absolute (95% CI)	Quality
(Bujan et al., 2007b)	Retrospective cohort	Some [g]	-	None	None	Yes [r]	0/394 (0%)	-	-	-	Very low
(Wu et al., 2011)	Prospective cohort	Some [t]	-	None	None	No	0/14 (0%)	-	-	-	Very low
							0/1212 (0%)				Very low
ICSI with washed sperm from HIV- or HCV-positive males											
(Garrido et al., 2004)	Retrospective cohort	None	-	None	None	Yes [o]	0/113 (0%)	-	-	-	Very low
IVF with washed sperm from HIV-positive males											
Bujan (2007b)	Retrospective cohort	Some [g]	-	None	None	Yes [h]	0/107 (0%)	-	-	-	Very low
(Kashima et al., 2009)	Prospective cohort	Some [l]	-	None	None	Yes [m]	0/13 (0%)	-	-	-	Very low
							0/120 (0%)				Very low
Seroconversion rate in children											
IUI with washed sperm from HIV-positive males											
(Savasi et al., 2007)	Prospective cohort	Serious [e]	-	None	None	Yes [f]	0/2400 (0%)	-	-	-	Very low
(Marina et al., 1998)	Prospective cohort	Some [a]	-	None	None	Yes [b]	0/101 (0%)	-	-	-	Very low

Quality assessment							Summary of findings				
							Number of people		Effect		
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Sero-con-version	Comparator	Relative (95% CI)	Absolute (95% CI)	Quality
(Semprini et al., 1992)	Prospective cohort	Serious [c]	-	None	None	Yes [d]	0/59 (0%)	-	-	-	Very low
(Nicopoullos et al., 2010)	Retrospective cohort	Serious [p]	-	None	None	Yes [q]	0/439 (0%)	-	-	-	Very low
							0/2999 (0%)				Very low
ICSI with washed sperm from HIV-positive males											
(Savasi et al., 2007)	Prospective cohort	Serious [e]	-	None	None	Yes [n]	0/283 (0%)	-	-	-	Very low
Mencaglia (2005)	Prospective cohort	None	-	None	None	Yes [h]	0/78 (0%)	-	-	-	Low
(Kashima et al., 2009)	Prospective cohort	Some [l]	-	None	None	Yes [m]	0/23 (0%)	-	-	-	Very low
(Sauer et al., 2009)	Retrospective cohort	Serious [k]	-	None	None	Yes [h]	0/420 (0%)	-	-	-	Very low
(Nicopoullos et al., 2010)	Retrospective cohort	Serious [p]	-	None	None	Yes [q]	0/117 (0%)	-	-	-	Very low
(Wu et al., 2011)	Prospective cohort	Some [t]	-	None	None	Yes [u]	0/14 (0%)	-	-	-	Very low
							0/935 (0%)				Very low

Quality assessment							Summary of findings				
							Number of people		Effect		
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Sero-con-version	Comparator	Relative (95% CI)	Absolute (95% CI)	Quality
IVF with washed sperm from HIV-positive males											
(Nicopoullos et al., 2010)	Retrospective cohort	Serious [p]	-	None	None	Yes [q]	0/114 (0%)	-	-	-	Very low
(Kashima et al., 2009)	Prospective cohort	Some [l]	-	None	None	Yes [m]	0/13 (0%)	-	-	-	Very low
							0/117 (0%)				Very low

[a] Some women had variations in ovulation in some cases and there was no evidence that this was taken into account during the analysis

[b] Overall, in the study, six of the 101 (5.6%) of the semen samples tested positive for HIV-1 DNA after sperm washing and these samples were not used in IUI. It is not clear what happened when a positive result was found, although the study states that no frozen sperm was used

[c] Baseline characteristics after inclusion criteria were applied were not reported. Women who did not conceive were not tested beyond three months. Five pregnancies were still ongoing when the study was published – it was not possible to tell how many cycles this represents.

[d] Post-wash testing was performed, but it was not reported whether there were positive results, or whether frozen sperm were used if a positive test result was obtained

[e] The follow-up of subjects was not complete enough as there were 72 ongoing pregnancies. The follow-up of subjects was not long enough as there was no reported HIV testing beyond the third month for 256 (44%) of women who did not deliver

[f] Post-wash testing was performed, and samples with a positive result were not used in IUI. Overall in the study, 4% of samples were positive and 2% of kit tests failed, but it is not clear how many of these were in the IUI group

[g] The results for this study were pooled from different studies and it is not clear whether confounding factors in each study were taken into account by the study authors. Follow-up HIV data was unknown in 74 couples (7%) but it is not clear how many cycles they took part in

[h] The use of post-wash testing was not reported. 355 (85%) of the cycles were performed using fresh embryos, the remaining 65 (15%) were performed with frozen embryo transfer

[i] Four women were lost to follow-up

[j] Only frozen sperm were used in this study, in both the control and washed sperm groups. Post-wash testing was performed, but the number of positive results and the number of kit failures was not reported

[k] Seventy six (42%) men had an abnormal semen analysis. Eighteen pregnancies were still ongoing when the study was published

[l] There is a small sample size in the washed sperm group

[m] The washed sperm group used only frozen sperm. Post-wash testing was performed, but the number of positive results and the number of kit failures was not reported

[n] Post-wash testing was performed, and frozen sperm were used in couples where the test had a positive result. Overall, in the study, 4% of samples were positive and 2% of kit tests failed, but it is not clear how many of these were in the ICSI group

[o] Post-wash testing was performed for HIV and HCV. Overall, in the study, there were positive results in 8 (20%) samples for HIV and 10 (18%) for HCV. Positive samples were not used and fresh samples were taken 2 to 3 weeks later and used instead

[p] The study included couples with abnormal fertility results (42%) and no subgroup analysis was undertaken for these couples. Follow up of the participants was not long enough as there were some ongoing pregnancies when the paper was published

[q] Overall, in the study, ten samples had positive post-wash tests and there was one testing kit failure, resulting in cancellation of treatment in nine couples and the use of frozen sperm in the remaining couple

[r] The use of post-wash testing was not reported. It is not clear how many cycles used frozen sperm. Some of the women in this group may also be included in the Savasi study (Savasi study dates: 2002 to 2006; Bujan study dates: 1989 to 2003)

[s] Post-wash testing was performed, and samples with a positive result were not used in IUI. Overall in the study, 4% of samples were positive and 2% of kit tests failed, but it is not clear how many of these were in the IUI group. Some of the women in this group may also be included in the Bujan study (Savasi study dates: 2002 to 2006; Bujan study dates: 1989 to 2003)

[t] Post-wash testing was performed but the results were not reported. It is not clear whether follow-up was complete in women that did not conceive.

[u] Of the 14 couples that participated, there was one case in which an oocyte was fertilised but did not show cleavage and so did not undergo embryo transfer.

Table I.6.10 GRADE findings of Seroconversion data comparing different methods of ART

Quality assessment							**Summary of findings**				
							No. of people		**Effect**		**Quality**
No. of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Intervention**	**Comparator**	**Relative (95% CI)**	**Absolute (95% CI)**	
Seroconversion rate in mothers											
IUI with washed sperm from HIV-positive males compared with ICSI with washed sperm from HIV-positive males											
1 (Savasi et al., 2007)	Prospective cohort	Serious [a]	None	None	None	Yes [f]	0/2400 (0%)	0/283 (0%)	Not calculable	-	Very low
1 (Bujan et al., 2007b)	Retrospective cohort	Some [c]	None	None	None	Yes [g]	0/2840 (0%)	0/394 (0%)	Not calculable	-	Very low
IUI with washed sperm from HIV-positive males compared with IVF with washed sperm from HIV-positive males											
1 (Bujan et al., 2007b)	Retrospective cohort	Some [c]	None	None	None	Yes [d]	0/2840 (0%)	0/107 (0%)	Not calculable	-	Very low

Quality assessment							Summary of findings				
							No. of people		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
IVF with washed sperm from HIV-positive males compared with ICSI with washed sperm from HIV-positive males											
1 (Bujan et al., 2007b)	Retrospective cohort	Some [c]	None	None	None	Yes [d]	0/107 (0%)	0/394 (0%)	Not calculable	-	Very low
Seroconversion rate in children											
IUI with washed sperm from HIV-positive males compared with ICSI with washed sperm from HIV-positive males											
1 (Savasi et al., 2007)	Prospective cohort	Serious [a]	None	None	None	Yes [b]	0/2400 (0%)	0/283 (0%)	Not calculable	-	Very low
1 (Nicopoullos et al., 2010)	Retrospective cohort	None	None	None	None	Yes [e]	0/439 (0%)	0/117 (0%)	Not calculable	-	Very low
IUI with washed sperm from HIV-positive males compared with IVF with washed sperm from HIV-positive males											
1 (Nicopoullos et al., 2010)	Retrospective cohort	None	None	None	None	Yes [e]	0/439 (0%)	0/114 (0%)	Not calculable	-	Very low
IVF with washed sperm from HIV-positive males compared with ICSI with washed sperm from HIV-positive males											
1 (Nicopoullos et al., 2010)	Retrospective cohort	None	None	None	None	Yes [e]	0/114 (0%)	0/117(0%)	Not calculable	-	Very low

[a] There were 72 ongoing pregnancies. There was no reported HIV testing beyond the third month for 256 (44%) of women who did not deliver

[b] Post-wash pre-insemination testing had a 4% positive test rate and 2% of testing kits failed. Only sperm that tested negative post-wash was used in insemination. In the case of a positive test, frozen sperm was used in the ICSI group. No frozen sperm was used in the IUI group

[c] 74 (7.1%) couples were lost to follow-up

[d] Post-wash pre-insemination testing was not reported

[e] Overall, in the study, ten samples had positive post-wash tests and there was one testing kit failure, resulting in cancellation of treatment in nine couples and the use of frozen sperm in the remaining couple

[f] Post-wash pre-insemination testing had a 4% positive test rate and 2% of testing kits failed. Only sperm that tested negative post-wash was used in insemination. In the case of a positive test, frozen sperm was used in the ICSI group. No frozen sperm was used in the IUI group. Some of the women in this group may also be included in the Bujan study (Savasi study dates: 2002 to 2006; Bujan study dates: 1989 to 2003)

[g] Post-wash pre-insemination testing was not reported. Some of the women in this group may also be included in the Savasi study (Savasi study dates: 2002 to 2006; Bujan study dates: 1989 to 2003)

Table I.6.11 GRADE findings for comparing the use of washed sperm from HIV- and/or HCV- positive males with unwashed sperm in control couples

Quality assessment							**Summary of findings**				
							No. of people		**Effect**		**Quality**
No. of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Sperm washed**	**No sperm wash**	**Relative (95% CI)**	**Absolute (95% CI)**	
Live full term singleton birth											
IVF with washed sperm from HIV-positive males compared to IVF in control couples with sperm from HIV-negative males											
1 (Kashmina et al., 2009)	Prospective cohort	Some [a]	-	Some [b]	None	Yes [c]	8/13 (62%)	91/465 (20%)	6.6 (2.1 to 20.6)	526 more per 1000 (from 161 more to 878 more)	Very low
ICSI with washed sperm from HIV-positive males compared to ICSI in control couples with sperm from HIV-negative males											
1 (Kashmina et al., 2009)	Prospective cohort	Some [a]	-	Some [b]	None	Yes [c]	9/23 (39%)	47/209 (22%)	2.2 (0.9 to 5.4)	194 more per 1000 (from 19 fewer to 500 more)	Very low
IUI with washed sperm from HIV-positive males compared to IUI in control couples with sperm from HIV-negative males											
1 (Bujan et al., 2007a)	Retrospective cohort	Serious [d]	-	Some [e]	None	Yes [f]	44/294 (15%)	37/320 (12%)	1.3 (0.8 to 2.2)	35 more per 1000 (from 17 fewer to 109 more)	Very low

Quality assessment							Summary of findings				
							No. of people		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Sperm washed	No sperm wash	Relative (95% CI)	Absolute (95% CI)	
Pre-term birth (<37 weeks)											
No studies											
Multiple births											
IVF with washed sperm from HIV-positive males compared to IVF in control couples with sperm from HIV-negative males											
1 (Kashmina et al., 2009)	Prospective cohort	Some [a]	-	None	None	Yes [c]	3/13 (23%)	15/465 (4%)	9.0 (2.2 to 36.1)	32 fewer per 1000 (from 32 fewer to 37 more)	Very low
ICSI with washed sperm from HIV-positive males compared to ICSI in control couples with sperm from HIV-negative males											
1 (Kashmina et al., 2009)	Prospective cohort	Some [a]	-	None	None	Yes [c]	2/23 (9%)	6/209 (3%)	3.2 (0.6 to 17.0)	58 more per 1000 (from 11 fewer to 306 more)	Very low
IUI with washed sperm from HIV-positive males compared to IUI in control couples with sperm from HIV-negative males											
1 (Bujan et al., 2007a)	Retrospective cohort	Serious [d]	-	Some [g]	None	Yes [f]	7/294 (2%)	7/320 (2%)	1.1 (0.4 to 3.1)	3 more per 1000 (from 21 fewer to 65 more)	Very low

Quality assessment							Summary of findings					
							No. of people		Effect			Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Sperm washed	No sperm wash	Relative (95% CI)	Absolute (95% CI)		
Clinical pregnancy												
ICSI with washed sperm from HIV-positive males compared to frozen semen and TESE/MESA from HIV-negative males												
1 (Wu et al., 2011)	Prospective cohort	Serious[h]	-	None	None	Yes [i]	5/14 (35.7%)	30/68 (44.1%)	20/36 (55.6%)	NS	NS	Very low
Congenital abnormalities												
No studies												
Adverse pregnancy outcome (including miscarriages, ectopic pregnancies, intrauterine deaths)												
IUI with washed sperm from HIV-positive males compared to IUI in control couples with sperm from HIV-negative males												
1 (Bujan et al., 2007a)	Retrospective cohort	Serious [d]	-	None	None	Yes [f]	9/294 (3%)	10/320 (3%)	1.0 (0.4 to 2.4)	1 fewer per 1000 (from 19 fewer to 42 more)		Very low

[a] There is a small sample size in the washed sperm group

[b] This may include births from multiple pregnancy and may include stillbirths as well as live births

[c] The washed sperm group used only frozen sperm. Post-wash testing was performed, but the number of positive results and the number of kit failures was not reported

[d] Characteristics of donor semen and washed sperm were not compared and 4 women were lost to follow-up after pregnancy was determined

[e] It is not clear if this includes still births, live births and/or multiple pregnancies

[f] Only frozen sperm were used in this study, in both the control and washed sperm groups. Post-wash testing was performed, but the number of positive results and the number of kit failures was not reported

[g] This is the number of twin and triplet pregnancies. It is not clear if all of these multiple pregnancies delivered live babies and at what gestational age they were delivered

[h] Results of semen analysis were not compared between these groups

[i] Pregnancy rates from HIV-discordant couples reflect results from fresh cycles only.

Table I.6.12 GRADE findings for comparing the use of washed sperm from HIV-positive men using different ARTs

Quality assessment							Summary of findings				
							No. of people		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Live full term singleton birth											
IUI with washed sperm from HIV-positive males compared with ICSI with washed sperm from HIV-positive males											
1 (Nicopoullos et al., 2010)	Retrospective cohort	Some [a]	None	None	None	Yes [b]	31/439 (7%)	17/117 (15%)	0.4 (0.2 to 0.8)	76 fewer per 1000 (from 21 fewer to 107 fewer)	Very low
IUI with washed sperm from HIV-positive males compared with IVF with washed sperm from HIV-positive males											
1 (Nicopoullos et al., 2010)	Retrospective cohort	Some [a]	None	None	None	Yes [b]	31/439 (7%)	21/114 (18%)	0.3 (0.2 to 0.6)	116 fewer per 1000 (from 65 fewer to 146 fewer)	Very low
IVF with washed sperm from HIV-positive males compared with ICSI with washed sperm from HIV-positive males											
1 (Nicopoullos et al., 2010)	Retrospective cohort	Some [a]	None	None	None	Yes [b]	21/114 (18%)	17/117 (15%)	1.3 (0.7 to 2.7)	41 more per 1000 (from 45 fewer to 181 more)	Very low
Pre-term birth (<37 weeks)											
No evidence											

Quality assessment							Summary of findings				
							No. of people		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Multiple births											
IUI with washed sperm from HIV-positive males compared with IVF with washed sperm from HIV-positive males											
1 (Nicopoullos et al., 2010)	Retrospective cohort	Some [a]	None	None	None	Yes [b]	2/439 (1%)	7/114 (6%)	0.0 (0.0 to 0.1)	61 fewer per 1000 (from 55 fewer to 61 fewer)	Very low
IUI with washed sperm from HIV-positive males compared with ICSI with washed sperm from HIV-positive males											
1 (Nicopoullos et al., 2010)	Retrospective cohort	Some [a]	None	None	None	Yes [b]	2/439 (1%)	5/117 (4%)	0.1 (0.0 to 0.5)	38 fewer per 1000 (from 21 fewer to 43 fewer)	Very low
IVF with washed sperm from HIV-positive males compared with ICSI with washed sperm from HIV-positive males											
1 (Nicopoullos et al., 2010)	Retrospective cohort	Some [a]	None	None	None	Yes [b]	7/114 (6%)	5/117 (4%)	1.5 (0.5 to 4.8)	20 more per 1000 (from 21 fewer to 134 more)	Very low
Congenital abnormalities											
No evidence											

Quality assessment							Summary of findings				
							No. of people		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Adverse pregnancy outcome (including miscarriages, ectopic pregnancies, intrauterine deaths)											
IUI with washed sperm from HIV-positive males compared with IVF with washed sperm from HIV-positive males											
1 (Nicopoullos et al., 2010)	Retrospective cohort	Some [a]	None	None	None	Yes [b]	20/439 (5%)	14/114 (12%)	0.3 (0.2 to 0.7)	78 fewer per 1000 (from 34 fewer to 101 fewer)	Very low
IUI with washed sperm from HIV-positive males compared with ICSI with washed sperm from HIV-positive males											
1 (Nicopoullos et al., 2010)	Retrospective cohort	Some [a]	None	None	None	Yes [b]	20/439 (5%)	7/117 (6%)	0.8 (0.3 to 1.8)	14 fewer per 1000 (from 41 fewer to 45 more)	Very low
IVF with washed sperm from HIV-positive males compared with ICSI with washed sperm from HIV-positive males											
1 (Nicopoullos et al., 2010)	Retrospective cohort	Some [a]	None	None	None	Yes [b]	14/114 (12%)	7/117 (6%)	2.2 (0.9 to 5.7)	65 more per 1000 (from 8 fewer to 212 more)	Very low

[a] The cohort had a combination of couples with normal and abnormal (41.7%) fertility results as well as couples with and without co-morbidities. No subgroup analysis was done by comorbidities or fertility problems

[b] Overall, in the study, ten samples had positive post-wash tests and there was one testing kit failure, resulting in cancellation of treatment in nine couples and the use of frozen sperm in the remaining couple

Table I.6.13 GRADE findings of non-comparative effectiveness data of outcomes for sperm washing in different ART groups

Quality assessment							Summary of findings				
							No. of people		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Sperm washed	Comparator	Relative (95% CI)	Absolute (95% CI)	
Live singleton birth											
IUI with washed sperm from HIV-positive males											
(Savasi et al., 2007)	Prospective cohort	Some [a]	-	Some [b]	None	Yes [c]	325/2400 (14%)	-	-	-	Very low
(Marina et al., 1998)	Prospective cohort	Some [d]	-	None	None	Yes [e]	20/101 (20%)	-	-	-	Very low
(Semprin et al., 1992)	Prospective cohort	Serious [f]	-	None	None	Yes [g]	5/59 (8%)	-	-	-	Very low
(Nicopoullos et al., 2010)	Retrospective cohort	Serious [h]	-	None	None	Yes [i]	31/439 (7%)	-	-	-	Very low
ICSI with washed sperm from HIV-positive males											
(Sauer et al., 2009)	Retrospective cohort	Serious [j]	-	None	None	Yes [k]	68/420 (16%)	-	-	-	Very low
(Nicopoullos et al., 2010)	Retrospective cohort	Serious [h]	-	None	None	Yes [i]	17/117 (15%)	-	-	-	Very low
ICSI with washed sperm from HIV- or HCV-positive males											
Garrido (2004)	Retrospective cohort	None	-	Some l	None	Yes [m]	23/113 (20%)	-	-	-	Very low
IVF with washed sperm from HIV-positive males											
(Nicopoullos et al., 2010)	Retrospective cohort	Serious [h]	-	None	None	Yes [i]	21/114 (18%)	-	-	-	Very low

Quality assessment							Summary of findings				
							No. of people		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Sperm washed	Comparator	Relative (95% CI)	Absolute (95% CI)	
IVF or IUI or ICSI with washed sperm from HIV-positive males											
(Bujan et al., 2007b)	Retrospective cohort	Serious [n]	-	None	None	Yes [k]	368/3341 (11%)	-	-	-	Very low
Pre-term birth (<37 weeks)											
IUI with washed sperm from HIV-positive males											
Semprini (1992)	Prospective cohort	Serious [f]	-	None	None	Yes [g]	1/59 (2%)	-	-	-	Very low
ICSI with washed sperm from HIV-positive males											
(Sauer et al., 2009)	Retrospective	Serious [j]	-	None	None	Yes [k]	74/420 (18%)	-	-	-	Very low
Multiple births											
IUI with washed sperm from HIV-positive males											
Marina (1998)	Prospective cohort	Some [d]	-	None	None	Yes [e]	8/101 (8%)	-	-	-	Very low
(Semprin et al., 1992)	Prospective cohort	Serious [f]	-	None	None	Yes [g]	3/59 (5%)	-	-	-	Very low
(Nicopoullos et al., 2010)	Retrospective cohort	Serious [h]	-	None	None	Yes [i]	2/439 (1%)	-	-	-	Very low
ICSI with washed sperm from HIV-positive males											
(Sauer et al., 2009)	Retrospective cohort	Serious [j]	-	None	None	Yes [k]	48/420 (11%)	-	-	-	Very low
(Nicopoullos et al., 2010)	Retrospective cohort	Serious [h]	-	None	None	Yes [i]	5/117 (4%)	-	-	-	Very low

Quality assessment							Summary of findings				
							No. of people		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Sperm washed	Comparator	Relative (95% CI)	Absolute (95% CI)	
IVF with washed sperm from HIV-positive males											
(Nicopoullos et al., 2010)	Retrospective cohort	Serious [h]	-	None	None	Yes [i]	7/114 (6%)	-	-	-	Very low
IVF or IUI or ICSI with washed sperm from HIV-positive males											
(Bujan et al., 2007b)	Retrospective cohort	Serious [n]	-	None	None	Yes [k]	42/3341 (1%)	-	-	-	Very low
Clinical pregnancy											
ICSI with fresh washed sperm from HIV-positive males											
(Wu et al., 2011)	Prospective cohort	Some[p]	-	None	None	None	5/14 (35.7%)	-	-	-	Very low
Frozen clinical pregnancy											
ICSI with frozen washed sperm from HIV-positive males											
(Wu et al., 2011)	Prospective cohort	Some[p]	-	None	None	None	3/14 (21.4%)	-	-	-	Very low
Multiple pregnancy											
ICSI with washed sperm from HIV-positive males											
(Wu et al., 2011)	Prospective cohort	Some[q]	-	None	None	Yes [r]	2/14 (14.3%)	-	-	-	Very low
Congenital abnormalities											
ICSI with washed sperm from HIV-positive males											
(Sauer et al 2009)	Retrospective	Serious [j]	-	None	None	Yes [n]	1/420 (<1%)	-	-	-	Very low

Quality assessment							Summary of findings				
							No. of people		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Sperm washed	Comparator	Relative (95% CI)	Absolute (95% CI)	
Adverse pregnancy outcomes (including spontaneous abortions, ectopic pregnancies, miscarriages, pre-clinical miscarriages, extra-uterine pregnancies and intrauterine deaths)											
IUI with washed sperm from HIV-positive males											
(Savasi et al., 2007)	Prospective cohort	Some [a]	-	None	None	Yes [c]	59/2400 (2%)	-	-	-	Very low
(Semprin et al., 1992)	Prospective cohort	Serious [f]	-	None	None	Yes [g]	5/59 (8%)	-	-	-	Very low
(Nicopoullos et al., 2010)	Retrospective cohort	Serious [h]	-	None	None	Yes [i]	20/439 (5%)	-	-	-	Very low
ICSI with washed sperm from HIV-positive males											
(Sauer et al 2009)	Retrospective	Serious [j]	NA	None	None	Yes [k]	26/420 (6%)	-	-	-	Very low
(Nicopoullos et al., 2010)	Retrospective cohort	Serious [h]	NA	None	None	Yes [i]	7/117 (6%)	-	-	-	Very low
(Wu et al., 2011)	Prospective cohort	None	NA	None	None	Yes [r]	1/14 (7.1%)	-	-	-	Low
IVF with washed sperm from HIV-positive males											
(Nicopoullos et al., 2010)	Retrospective cohort	Serious [h]	NA	None	None	Yes [i]	14/114 (12%)	-	-	-	Very low
IVF or IUI or ICSI with washed sperm from HIV-positive males											
(Bujan et al., 2007b)	Retrospective cohort	Serious [n]	NA	None	None	Yes [k]	121/3341 (4%)	-	-	-	Very low

[a] The follow-up of subjects was not complete enough as there were 72 ongoing pregnancies

[b] It is not clear if this includes still births, live births and/or multiple pregnancies

[c] Post-wash testing was performed, and samples with a positive result were not used in IUI. Overall in the study, 4% of samples were positive and 2% of kit tests failed, but it is not clear how many of these were in the IUI group

[d] Some women had ovulatory alterations and this was not taken into account during the analysis

[e] Overall, in the study, six of the 101 (5.6%) of the semen samples tested positive for HIV-1 DNA after sperm washing and these samples were not used in IUI. It is not clear what happened when a positive result was found, although the study states that no frozen sperm was used

[f] Baseline characteristics after inclusion criteria were applied were not reported. Women who did not conceive were not tested beyond three months. Five pregnancies were still ongoing when the study was published – it was not possible to tell how many cycles this represents.

[g] Post-wash testing was performed, but it was not reported whether there were positive results, or whether frozen sperm were used if a positive test result was obtained

[h] The study included couples with abnormal fertility results (42%) and no subgroup analysis was undertaken for these couples. Follow up of the participants was not long enough as there were some ongoing pregnancies when the paper was published

[i] Overall, in the study, ten samples had positive post-wash tests and there was one testing kit failure, resulting in cancellation of treatment in nine couples and the use of frozen sperm in the remaining couple. The couples in the Nicopoullos (2010) study may also have been included in the Bujan (2007b) study

[j] Seventy six (42%) men had an abnormal semen analysis. Eighteen pregnancies were still ongoing when the study was published

[k] The use of post-wash testing was not reported. It is not clear how many cycles used frozen sperm. The couples in the Bujan (2007b) study may also have been included in the Nicopoullos (2010) study

[l] The number of delivered live babies from multiple pregnancies was not reported separately. It is not clear if this figure includes twins or triplets

[m] Post-wash testing was performed for HIV and HCV. Overall, in the study, there were positive results in 8 (20%) samples for HIV and 10 (18%) for HCV. Positive samples were not used and fresh samples were taken 2 to 3 weeks later and used instead

[n] The results for this study were pooled from different studies and it is not clear whether confounding factors in each study were taken into account by the study authors. Delivery data was missing from 142 (14%) couples. The number of cycles represented by the couples whose data is missing was not reported[o] The Congenital abnormality was reported in the context of a termination of pregnancy. It is not clear whether the other fetuses in the study were tested for abnormalities

[p] Semen analysis and fertility results of couples were not reported and it is not clear whether there were pre-existing fertility problems that might have affected the results.

[q] The patients received varying numbers of embryo resulting in varying pregnancy outcomes.

[r] It is not clear whether this outcome resulted from the fresh, frozen cycles or both.

Table I.8.2 GRADE findings for comparison of clomifene citrate or tamoxifen with other drugs (first line treatment for PCOS)

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Live full-term singleton birth											
Metformin vs. clomifene citrate											
4 (Johnson et al., 2010; Legro et al., 2007; Palomba et al., 2005; and Zain et al., 2009)	RCTs	Very serious [a, b, c]	Very serious [d]	Serious [e]	Serious [f]	Yes [g, h]	54/331 (16%) women	75/334 (22%) women	RR 0.8 (0.3 to 2.3) [i]	45 fewer per 1000 (from 164 fewer to 301 more)	Very low
Metformin + clomifene citrate vs. clomifene citrate											
5 (Johnson et al., 2010; Legro et al., 2007; Moll et al., 2006; Sahin et al., 2004; and Zain et al., 2009)	RCTs	Very serious [a, b, c]	None	Serious [e]	Serious [f]	Yes [g]	103/404 (25%) women	99/228 (43%) women	RR 1.1 (0.8 to 1.3)	45 fewer per 1000 (from 164 fewer to 301 more)	Very low
Metformin vs. metformin+ clomifene citrate											
3 (Johnson et al., 2010; Legro et al., 2007; and Zain et al., 2009)	RCTs	Very serious [a, b, c]	Serious [j]	Serious [e]	None	Yes [g]	28/281 (10%) women	79/282 (28%) women	RR 0.4 (0.2 to 0.8) [i]	168 fewer per 1000 (from 62 fewer to 221 fewer)	Very low

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Letrozole vs. clomifene citrate											
1 (Dehbashi et al., 2009)	RCT	None	-	Serious [e]	Serious [f]	None	10/50 (20%) women	6/50 (12%) women	RR 1.7 (0.7 to 4.2)	80 more per 1000 (from 41 fewer to 389 more)	Low
rFSH vs. clomifene citrate											
1 (Lopez et al., 2004)	RCT	Serious [k]	-	Serious [e]	Serious [f]	None	11/38 (29%) women	6/38 (16%) women	RR 1.8 (0.8 to 4.5)	131 more per 1000 (from 39 fewer to 545 more)	Very low
Clinical pregnancy											
Metformin vs. clomifene citrate											
5 (Karimzadeh et al., 2010; Zain et al., 2009; Johnson et al., 2010; Palomba et al., 2005; Legro et al., 2007)	RCTs	Very serious [a, b, c]	Very serious [d]	None	Serious [f]	Yes [g, h]	79/421 (19%) women	97/424 (23%) women	RR 0.9 (0.4 to 1.8) [i]	27 fewer per 1000 (from 130 fewer to 185 more)	Very low

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Metformin + clomifene citrate vs. clomifene citrate											
7 (Karimzadeh et al., 2010; Sahin et al., 2004; Dasari et al., 2009; Legro et al., 2007; Zain et al., 2009; Johnson et al., 2010; Moll et al., 2006)	RCTs	Very serious [a, b, c]	None	None	Serious [f]	Yes [g]	158/508 (31%) women	138/522 (26%) women	RR 1.2 (1.0 to 1.4)	45 more per 1000 (from 1 more to 108 more)	Very low
Metformin vs. metformin + clomifene citrate											
4 (Karimzadeh et al., 2010; Legro et al., 2007; Zain et al., 2009; Johnson et al., 2010)	RCTs	Very serious [a, b, c]	Very serious [d]	None	Serious [f]	Yes [g]	48/371 (13%) women	105/370 (28%) women	RR 0.5 (0.3 to 1.0) [i]	133 fewer per 1000 (from 204 fewer to 1 fewer)	Very low
Letrozole vs. clomifene citrate											
3 (Atay et al., 2006; Dehbashi et al., 2009; Elsedeek, 2011)	RCTs	Very serious [a, b, c]	None	None	None	None	44/160 (28%) women	28/162 (17%) women	RR 1.6 (1.0 to 2.4)	99 more per 1000 (from 7 more to 237 more)	Low
rFSH vs. clomifene citrate											
1 (Lopez et al., 2004)	RCT	Serious [k]	-	None	Serious [f]	None	16/38 (42%) women	9/38 (24%) women	RR 1.8 (1.0 to 3.5)	185 more per 1000 (from 24 fewer to 597 more)	Low

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Adverse pregnancy outcomes											
Metformin vs. clomifene citrate (Death of woman)											
1 (Legro et al., 2007)	RCT	Very serious [a, b, c]	-	None	Serious [f]	None	1/208 (1%) women	0/209 (0%) women	RR 3.0 (0.1 to 73.6)	Not estimable	Very low
Metformin vs. clomifene citrate (Miscarriage)											
4 (Zain et al., 2009; Johnson et al., 2010; Palomba et al., 2005 Legro et al. 2007)	RCTs	Very serious [a, b, c]	Serious [j]	None	Serious [f]	Yes [g, h]	17/331 (5%) women	20/334 (6%) women	RR 0.9 (0.3 to 2.4) [i]	9 fewer per 1000 (from 42 fewer to 84 more)	Very low
							17/73 (23%) pregnancies	20/108 (43%) pregnancies	RR 1.4 (0.4 to 5.0) [i]	65 more per 1000 (from 117 fewer to 735 more)	
Metformin vs. clomifene citrate (Ectopic pregnancy)											
2 (Johnson et al., 2010; Legro et al., 2007)	RCTs	Very serious [a, b, c]	- [l]	None	Serious [f]	Yes [g]	0/243 (0%) women	2/245 (1%) women	RR 0.2 (0.0 to 4.2)	7 fewer per 1000 (from 8 fewer to 26 more)	Very low
							0/32 (0%) pregnancies	2/76 (3%) pregnancies	RR 0.7 (0.0 to 13.2)	9 fewer per 1000 (from 26 fewer to 322 more)	

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Metformin vs. clomifene citrate (Gestational hypertension)											
2 (Johnson et al., 2010; Palomba et al., 2005)	RCTs	Very serious [a, b, c]	- [l]	None	Serious [f]	Yes [g, h]	1/85 (1%) women	0/86 (0%) women	RR 3.0 (0.1 to 71.9)	Not estimable	Very low
							1/45 (2%) pregnancies	0/40 (0%) pregnancies	RR 2.5 (0.1 to 59.6)	Not estimable	
Metformin vs. clomifene citrate (Gestational diabetes)											
2 (Johnson et al. 2010; Legro et al., 2007)	RCTs	Very serious [a, b, c]	- [l]	None	Serious [f]	Yes [g]	2/244 (1%) women	9/245 (4%) women	RR 0.2 (0.1 to 1.0)	29 fewer per 1000 (from 35 fewer to 1 more)	Very low
							2/32 (6%) pregnancies	9/64 (14%) pregnancies	RR 0.6 (0.2 to 2.6)	53 fewer per 1000 (from 120 fewer to 224 more)	

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Metformin vs. clomifene citrate (Preterm labour or premature rupture of membranes)											
2 (Johnson et al., 2010; Legro et al., 2007)	RCTs	Very serious [a, b, c]	None	None	Serious [f]	Yes [g]	1/244 (<1%) women	2/245 (1%) women	RR 0.6 (0.1 to 4.5)	3 fewer per 1000 (from 8 fewer to 28 more)	Very low
							1/32 (3%) pregnancies	2/64 (3%) pregnancies	RR 1.0 (0.2 to 5.9)	1 fewer per 1000 (from 26 fewer to 153 more)	
Metformin vs. clomifene citrate (Intrauterine fetal death)											
1 (Palomba et al., 2005)	RCT	None	-	None	Serious [f]	Yes [h]	1/50 (2%) women	1/50 (2%) women	RR 1.0 (0.1 to 15.6)	0 fewer per 1000 (from 19 fewer to 291 more)	Moderate
							1/31 (3%) pregnancies	1/26 (4%) pregnancies	RR 0.8 (0.1 to 12.8)	6 fewer per 1000 (from 36 fewer to 452 more)	

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Metformin vs. clomifene citrate (Placenta previa)											
1 (Legro et al., 2007)	RCT	Very serious [a, b, c]	-	None	Serious [f]	None	0/208 (0%) women	1/209 (<1%) women	RR 0.3 (0.0 to 8.2)	3 fewer per 1000 (from 5 fewer to 34 more)	Very low
							0/18 (0%) pregnancies	1/50 (2%) pregnancies	RR 0.9 (0.0 to 21.0)	2 fewer per 1000 (from 19 fewer to 401 more)	
Metformin vs. clomifene citrate (Postpartum haemorrhage)											
1 (Legro et al., 2007)	RCT	Very serious [a, b, c]	-	None	Serious [f]	None	0/208 (0%) women	2/209 (1%) women	RR 0.2 (0.0 to 4.2)	8 fewer per 1000 (from 9 fewer to 30 more)	Very low
							0/18 (0%) pregnancies	2/50 (4%) pregnancies	RR 0.5 (0.0 to 10.7)	18 fewer per 1000 (from 39 fewer to 387 more)	

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Metformin vs. clomifene citrate (Placental abruption)											
1 (Legro et al., 2007)	RCT	Very serious [a, b, c]	-	None	Serious [f]	None	0/208 (0%) women	2/209 (1%) women	RR 0.2 (0.0 to 4.2)	2 fewer per 1000 (from 19 fewer to 401 more)	Very low
							0/18 (0%) pregnancies	2/50 (4%) pregnancies	RR 0.5 (0.0 to 10.7)	3 fewer per 1000 (from 5 fewer to 34 more)	
Metformin vs. clomifene citrate (Pregnancy loss in second or third trimester)											
1 (Legro et al., 2007)	RCT	Very serious [a, b, c]	-	None	Serious [f]	None	0/208 (0%) women	2/209 (1%) women	RR 0.2 (0.0 to 4.2)	8 fewer per 1000 (from 9 fewer to 30 more)	Very low
							0/18 (0%) pregnancies	2/62 (3%) pregnancies	RR 0.7 (0.0 to 13.2)	11 fewer per 1000 (from 31 fewer to 394 more)	

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Metformin vs. clomifene citrate (Cervical incompetence or preterm labour)											
1 (Legro et al., 2007)	RCT	Very serious [a, b, c]	-	None	Serious [f]	None	0/208 (0%) women	1/209 (<1%) women	RR 0.3 (0.0 to 8.2)	3 fewer per 1000 (from 5 fewer to 34 more)	Very low
							0/18 (0%) pregnancies	1/50 (2%) pregnancies	RR 0.9 (0.0 to 21.0)	2 fewer per 1000 (from 19 fewer to 401 more)	
Metformin vs. clomifene citrate (Severe preeclampsia)											
1 (Legro et al., 2007)	RCT	Very serious [a, b, c]	-	None	-	None	0/208 (0%) women	0/209 (0%) women	Not estimable		Low
							0/18 (0%) pregnancies	0/50 (0%) pregnancies	Not estimable		
Metformin vs. clomifene citrate (HELLP syndrome)											
1 (Legro et al., 2007)	RCT	Very serious [a, b, c]	-	None	Serious [f]	None	0/208 (0%) women	1/209 (<1%) women	RR 0.3 (0.0 to 8.2)	3 fewer per 1000 (from 5 fewer to 34 more)	Very low
							0/18 (0%) pregnancies	1/50 (2%) pregnancies	RR 0.9 (0.0 to 21.0)	2 fewer per 1000 (from 19 fewer to 401 more)	

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Metformin + clomifene citrate vs. clomifene citrate (Death of woman)											
1 (Legro et al., 2007)	RCT	Very serious [a, b, c]	-	None	-	None	0/209 (0%) women	0/209 (0%) women	Not estimable		Low
Metformin + clomifene citrate vs. clomifene citrate (Preterm birth)											
2 (Sahin et al., 2004; Moll et al., 2006)	RCTs	Very serious [a, b, c]	None	None	Serious [f]	None	5/122 (4%) women	3/124 (2%) women	RR 1.6 (0.4 to 5.9)	14 more per 1000 (from 14 fewer to 118 more)	Very low
							5/49 (10%) pregnancies	3/55 (5%) pregnancies	RR 1.7 (0.5 to 6.0)	35 more per 1000 (from 30 fewer to 274 more)	
Metformin + clomifene citrate vs. clomifene citrate (Miscarriage)											
5 (Sahin et al., 2004; Legro et al., 2007; Zain et al., 2009; Johnson et al., 2010; Moll et al., 2006)	RCT	Very serious [a, b, c]	None	None	Serious [f]	Yes [g]	38/404 (9%) women	26/408 (6%) women	RR 1.5 (0.9 to 2.3)	29 more per 1000 (from 6 fewer to 83 more)	Very low
							38/156 (24%) pregnancies	26/137 (19%) pregnancies	RR 1.3 (0.9 to 2.0)	57 more per 1000 (from 28 fewer to 190 more)	

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Metformin + clomifene citrate vs. clomifene citrate (Pregnancy loss in second or third trimester)											
1 (Legro et al., 2007)	RCT	Very serious [a, b, c]	-	None	Serious [f]	None	4/209 (2%) women	2/209 (1%) women	RR 2.0 (0.4 to 10.8)	10 more per 1000 (from 6 fewer to 94 more)	Very low
							4/80 (5%) pregnancies	2/62 (3%) pregnancies	RR 1.6 (0.3 to 8.2)	18 more per 1000 (from 23 fewer to 232 more)	
Metformin + clomifene citrate vs. clomifene citrate (Gestational diabetes)											
3 (Legro et al., 2007; Johnson et al., 2010; Moll et al., 2006)	RCTs	Very serious [a, b, c]	None	None	Serious [f]	Yes [g]	7/355 (2%) women	11/359 (3%) women	RR 0.7 (0.3 to 1.6)	10 fewer per 1000 (from 22 fewer to 19 more)	Very low
							7/128 (5%) pregnancies	11/116 (9%) pregnancies	RR 0.5 (0.2 to 1.3)	45 fewer per 1000 (from 74 fewer to 27 more)	

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Metformin + clomifene citrate vs. clomifene citrate (Gestational hypertension)											
2 (Legro et al., 2007; Moll et al., 2006)	RCTs	Very serious [a, b, c]	None	None	Serious [f]	Yes [g]	5/146 (3%) women	2/150 (1%) women	RR 2.3 (0.5 to 9.9)	17 more per 1000 (from 6 fewer to 119 more)	Very low
							5/63 (8%) pregnancies	2/66 (3%) pregnancies	RR 2.3 (0.5 to 10.1)	41 more per 1000 (from 14 fewer to 275 more)	
Metformin + clomifene citrate vs. clomifene citrate (Pre-eclampsia)											
2 (Legro et al., 2007; Moll et al., 2006)	RCTs	Very serious [a, b, c]	Serious [j]	None	Serious [f]	None	8/320 (3%) women	8/253 (3%) women	RR 0.7 (0.1 to 3.4) [i]	10 fewer per 1000 (from 28 fewer to 74 more)	Very low
			None				8/109 (7%) pregnancies	8/102 (8%) pregnancies	RR 0.8 (0.3 to 2.1)	13 fewer per 1000 (from 53 fewer to 89 more)	

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Metformin + clomifene citrate vs. clomifene citrate (Severe preeclampsia)											
1 (Legro et al., 2007)	RCT	Very serious [a, b, c]	-	None	Serious [f]	None	2/209 (1%) women	0/209 (0%) women	RR 5.0 (0.2 to 103.5)	Not estimable	Very low
							2/65 (3%) pregnancies	0/50 (0%) pregnancies	RR 3.9 (0.2 to 78.7)	Not estimable	
Metformin + clomifene citrate vs. clomifene citrate (HELLP syndrome)											
1 (Legro et al., 2007)	RCT	Very serious [a, b, c]	-	None	Serious [f]	None	1/209 (<1%) women	1/209 (<1%) women	RR 1.0 (0.1 to 15.9)	0 fewer per 1000 (from 4 fewer to 71 more)	Very low
							1/65 (2%) pregnancies	1/50 (2%) pregnancies	RR 0.8 (0.1 to 12.0)	5 fewer per 1000 (from 19 fewer to 220 more)	

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Metformin + clomifene citrate vs. clomifene citrate (Preterm labour or premature rupture of membranes)											
2 (Legro et al., 2007; Johnson et al., 2010)	RCTs	Very serious [a, b, c]	None	None	Serious [f]	Yes [g]	4/244 (2%) women	2/245 (1%) women	RR 2.0 (0.4 to 10.9)	8 more per 1000 (from 5 fewer to 81 more)	Very low
							4/84 (5%) pregnancies	2/64 (3%) pregnancies	RR 0.8 (0.1 to 6.0)	16 more per 1000 (from 22 fewer to 218 more)	
Metformin + clomifene citrate vs. clomifene citrate (Preterm labour or cervical incompetence)											
1 (Legro et al., 2007)	RCT	Very serious [a, b, c]	-	None	Serious [f]	None	1/209 (<1%) women	1/209 (<1%) women	RR 1.0 (0.1 to 15.9)	0 fewer per 1000 (from 4 fewer to 71 more)	Very low
							1/65 (2%) pregnancies	1/50 (2%) pregnancies	RR 3.2 (0.2 to 50.0)	5 fewer per 1000 (from 19 fewer to 220 more)	

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Metformin + clomifene citrate vs. clomifene citrate (Ectopic pregnancy)											
2 (Legro et al., 2007; Johnson et al., 2010)	RCTs	Very serious [a, b, c]	None	None	Serious [f]	Yes [g]	3/244 (1%) women	2/245 (1%) women	RR 1.4 (0.3 to 7.1)	3 more per 1000 (from 6 fewer to 49 more)	Very low
							3/99 (3%) pregnancies	2/76 (3%) pregnancies	RR 2.5 (0.5 to 13.3)	2 more per 1000 (from 21 fewer to 113 more)	
Metformin + clomifene citrate vs. clomifene citrate (Placental abruption)											
1 (Legro et al., 2007)	RCT	Very serious [a, b, c]	-	None	Serious [f]	None	2/209 (1%) women	2/209 (1%) women	RR 1.0 (0.1 to 7.0)	0 fewer per 1000 (from 8 fewer to 58 more)	Very low
							2/65 (3%) pregnancies	2/50 (4%) pregnancies	RR 3.2 (0.5 to 22.3)	9 fewer per 1000 (from 36 fewer to 171 more)	

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Metformin + clomifene citrate vs. clomifene citrate (Placenta previa)											
1 (Legro et al., 2007)	RCT	Very serious [a, b, c]	-	None	Serious [f]	None	1/209 (<1%) women	1/209 (<1%) women	RR 1.0 (0.1 to 15.9)	0 fewer per 1000 (from 4 fewer to 71 more)	Very low
							1/65 (2%) pregnancies	1/50 (2%) pregnancies	RR 3.2 (0.2 to 50.0)	5 fewer per 1000 (from 19 fewer to 220 more)	
Metformin + clomifene citrate vs. clomifene citrate (Postpartum haemorrhage)											
1 (Legro et al., 2007)	RCT	Very serious [a, b, c]	-	None	Serious [f]	None	0/209 (0%) women	2/209 (1%) women	RR 0.2 (0.0 to 4.1)	8 fewer per 1000 (from 9 fewer to 30 more)	Very low
							0/65 (0%) pregnancies	2/50 (4%) pregnancies	RR 0.6 (0.0 to 13.2)	34 fewer per 1000 (from 40 fewer to 86 more)	
Metformin vs. metformin + clomifene citrate (Death of woman)											
1 (Legro et al., 2007)	RCT	Very serious [a, b, c]	-	None	Serious [f]	None	1/208 (1%) women	0/209 (0%) women	RR 3.0 (0.1 to 73.6)	Not estimable	Very low

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Metformin vs. metformin + clomifene citrate (Miscarriage)											
2 (Legro et al., 2007; Johnson et al., 2010)	RCTs	Very serious [a, b, c]	None	None	Serious [f]	Yes [g]	15/281 (5%) women	23/282 (8%) women	RR 0.7 (0.4 to 1.2)	28 fewer per 1000 (from 52 fewer to 19 more)	Very low
							15/47 (32%) pregnancies	23/102 (23%) pregnancies	RR 1.6 (0.9 to 2.8)	142 more per 1000 (from 14 fewer to 413 more)	
Metformin vs. metformin + clomifene citrate (Ectopic pregnancy)											
2 (Legro et al., 2007; Johnson et al., 2010)	RCTs	Very serious [a, b, c]	None	None	Serious [f]	Yes [g]	0/243 (0%) women	3/244 (1%) women	RR 0.3 (0.0 to 2.2)	9 fewer per 1000 (from 12 fewer to 15 more)	Very low
							0/32 (0%) pregnancies	3/99 (3%) pregnancies	RR 0.6 (0.1 to 5.2)	12 fewer per 1000 (from 28 fewer to 128 more)	

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Metformin vs. metformin + clomifene citrate (Pregnancy loss in second or third trimester)											
1 (Legro et al., 2007)	RCT	Very serious [a, b, c]	-	None	Serious [f]	None	0/208 (0%) women	4/209 (2%) women	RR 0.1 (0.0 to 2.1)	17 fewer per 1000 (from 19 fewer to 20 more)	Very low
							0/18 (0%) pregnancies	4/80 (5%) pregnancies	RR 0.5 (0.0 to 8.4)	26 fewer per 1000 (from 49 fewer to 372 more)	
Metformin vs. metformin + clomifene citrate (Cervical incompetence or preterm labour)											
1 (Legro et al., 2007)	RCT	Very serious [a, b, c]	-	None	Serious [f]	None	0/208 (0%) women	1/209 (<1%) women	RR 0.3 (0.0 to 8.2)	3 fewer per 1000 (from 5 fewer to 34 more)	Very low
							0/18 (0%) pregnancies	1/65 (2%) pregnancies	RR 1.2 (0.1 to 27.3)	2 more per 1000 (from 15 fewer to 404 more)	

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Metformin vs. metformin + clomifene citrate (Gestational hypertension)											
1 (Johnson et al., 2010)	RCT	Very serious [a, b, c]	-	None	Serious [f]	Yes [g]	0/35 (0%) pregnancies	1/35 (3%) women	RR 0.3 (0.0 to 7.9)	19 fewer per 1000 (from 28 fewer to 197 more)	Very low
							0/14 (0%) pregnancies	1/19 (5%) pregnancies	RR 0.4 (0.0 to 10.2)	29 fewer per 1000 (from 52 fewer to 482 more)	
Metformin vs. metformin + clomifene citrate (Mild preeclampsia)											
1 (Legro et al., 2007)	RCT	Very serious [a, b, c]	-	None	Serious [f]	None	1/208 (<1%) women	7/209 (3%) women	RR 0.1 (0.0 to 1.2)	29 fewer per 1000 (from 33 fewer to 5 more)	Very low
							1/18 (6%) pregnancies	7/65 (11%) pregnancies	RR 0.5 (0.1 to 3.9)	52 fewer per 1000 (from 100 fewer to 314 more)	

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Metformin vs. metformin + clomifene citrate (Severe preeclampsia)											
1 (Legro et al., 2007)	RCT	Very serious [a, b, c]	-	None	Serious [f]	None	0/208 (0%) women	2/209 (1%) women	RR 0.2 (0.0 to 4.2)	8 fewer per 1000 (from 9 fewer to 30 more)	Very low
							0/18 (0%) pregnancies	2/65 (3%) pregnancies	RR 0.7 (0.0 to 13.9)	10 fewer per 1000 (from 30 fewer to 396 more)	
Metformin vs. metformin + clomifene citrate (HELLP syndrome)											
1 (Legro et al., 2007)	RCT	Very serious [a, b, c]	-	None	Serious [f]	None	0/208 (0%) women	1/209 (<1%) women	RR 0.3 (0.0 to 8.2)	3 fewer per 1000 (from 5 fewer to 34 more)	Very low
							0/18 (0%) pregnancies	1/65 (2%) pregnancies	RR 1.2 (0.1 to 27.3)	2 more per 1000 (from 15 fewer to 404 more)	

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Metformin vs. metformin + clomifene citrate (Gestational diabetes)											
2 (Legro et al., 2007; Johnson et al., 2010)	RCTs	Very serious [a, b, c]	None	None	Serious [f]	Yes [g]	2/244 (1%) women	6/244 (2%) women	RR 0.4 (0.1 to 1.6)	15 fewer per 1000 (from 22 fewer to 15 more)	Very low
							2/32 (6%) pregnancies	6/84 (7%) pregnancies	RR 1.1 (0.3 to 4.2)	5 more per 1000 (from 51 fewer to 226 more)	
Metformin vs. metformin + clomifene citrate (Preterm labour or premature rupture of membranes)											
2 (Legro et al., 2007; Johnson et al., 2010)	RCTs	Very serious [a, b, c]	None	None	Serious [f]	Yes [g]	1/244 (<1%) women	4/244 (2%) women	RR 0.3 (0.1 to 2.1)	11 fewer per 1000 (from 16 fewer to 18 more)	Very low
							1/32 (3%) pregnancies	4/84 (5%) pregnancies	RR 0.8 (0.1 to 4.8)	8 fewer per 1000 (from 41 fewer to 180 more)	

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Metformin vs. metformin + clomifene citrate (Placental abruption)											
1 (Legro et al., 2007)	RCT	Very serious [a, b, c]	-	None	Serious [f]	None	0/208 (0%) women	2/209 (1%) women	RR 0.2 (0.0 to 4.2)	8 fewer per 1000 (from 9 fewer to 30 more)	Very low
							0/18 (0%) pregnancies	2/65 (3%) pregnancies	RR 0.7 (0.0 to 13.9)	10 fewer per 1000 (from 30 fewer to 396 more)	
Metformin vs. metformin + clomifene citrate (Placenta previa)											
1 (Legro et al., 2007)	RCT	Very serious [a, b, c]	-	None	Serious [f]	None	0/208 (0%) women	1/209 (<1%) women	RR 0.3 (0.0 to 8.2)	3 fewer per 1000 (from 5 fewer to 34 more)	Very low
							0/18 (0%) pregnancies	1/65 (2%) pregnancies	RR 1.2 (0.1 to 27.3)	2 more per 1000 (from 15 fewer to 404 more)	
Metformin vs. metformin + clomifene citrate (Postpartum haemorrhage)											
1 (Legro et al., 2007)	RCT	Very serious [a, b, c]	-	None	-	None	0/209 (0%) women	0/208 (0%) women	Not estimable		Low
							0/65 (0%) pregnancies	0/18 (0%) pregnancies	Not estimable		

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Letrozole vs. clomifene citrate (Miscarriage)											
3 (Bayar et al., 2006; Badawy et al., 2009; Dehbashi et al., 2009	RCTs	Very serious [b, c]	None	None	Serious [f]	None	8/306 (3%) women	5/310 (2%) women	RR 1.6 (0.5 to 4.5)	9 more per 1000 (from 7 fewer to 57 more)	Very low
1 (Dehbashi et al., 2009)	RCT	Serious [c]	-	None	Serious [f]	None	3/13 (23%) pregnancies	1/7 (14%) pregnancies	RR 1.6 (0.2 to 12.8)	89 more per 1000 (from 114 fewer to 1683 more)	Very low
rFSH vs. clomifene citrate (Miscarriage)											
1 (Lopez et al., 2004)	RCT	Very serious [b, c]	-	None	Serious [f]	None	5/38 (13%) women	3/38 (9%) women	RR 1.7 (0.4 to 6.5)	53 more per 1000 (from 45 fewer to 433 more)	Very low
							5/16 (31%) pregnancies	3/9 (33%) pregnancies	RR 0.9 (0.3 to 3.0)	20 fewer per 1000 (from 237 fewer to 680 more)	

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Multiple pregnancies (the number of pregnancies with more than one fetus)											
Metformin vs. clomifene citrate											
5 (Johnson et al., 2010; Karimzadeh et al., 2010; Legro et al., 2007; Palomba et al., 2005; Zain et al., 2009)	RCTs	Very serious [a, b, c]	None	None	Serious [f]	Yes [g]	1/421 (<1%) women	6/424 (1%) women	RR 0.3 (0.1 to 1.4)	10 fewer per 1000 (from 13 fewer to 5 more)	Very low
							1/79 (1%) pregnancies	6/97 (6%) pregnancies	RR 0.4 (0.1 to 1.9)	38 fewer per 1000 (from 57 fewer to 53 more)	
Metformin + clomifene citrate vs. clomifene citrate											
5 (Johnson et al., 2010; Karimzadeh et al., 2010; Legro et al., 2007; Moll et al., 2006; Zain et al., 2009)	RCTs	Very serious [a, b, c]	None	None	Serious [f]	Yes [g]	5/481 (1%) women	9/488 (2%) women	RR 0.6 (0.2 to 1.7)	8 fewer per 1000 (from 15 fewer to 12 more)	Very low
							5/149 (3%) pregnancies	9/133 (7%) pregnancies	RR 0.5 (0.2 to 1.4)	35 fewer per 1000 (from 56 fewer to 28 more)	

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Metformin vs. metformin + clomifene citrate											
4 (Johnson et al., 2010; Karimzadeh et al., 2010; Legro et al., 2007; Zain et al., 2009)	RCTs	Very serious [a, b, c]	None	None	Serious [f]	Yes [g]	1/371 (0%) women	4/370 (1%) women	RR 0.7 (0.1 to 3.5)	6 fewer per 1000 (from 10 fewer to 11 more)	Very low
							1/48 (2%) pregnancies	4/105 (4%) pregnancies	RR 0.4 (0.1 to 2.0)	11 fewer per 1000 (from 33 fewer to 97 more)	
Letrozole vs. clomifene citrate											
4 (Atay et al.l 2006; Badawy et al., 2009; Bayar et al., 2006; Dehbashi et al., 2009)	RCTs	Very serious [b, c]	None	None	Serious [f]	None	1/359 (<1%) women	5/365 (1%) women	RR 0.3 (0.1 to 1.7)	9 fewer per 1000 (from 13 fewer to 9 more)	Very low
							1/57 (2%) pregnancies	5/53 (9%) pregnancies	RR 0.3 (0.1 to 1.3)	71 fewer per 1000 (from 90 fewer to 25 more)	

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
rFSH vs. clomifene citrate											
1 (Lopez et al., 1994)	RCT	Very serious [b, c]	-	None	Serious [f]	None	3/38 (8%) women	1/38 (3%) women	RR 3.0 (0.3 to 27.6)	53 more per 1000 (from 18 fewer to 699 more)	Very low
							3/16 (19%) pregnancies	1/9 (11%) pregnancies	RR 1.7 (0.2 to 13.9)	77 more per 1000 (from 89 fewer to 1437 more)	
Multiple births (the number of babies born from a multiple pregnancy)											
No evidence was reported											
Ovarian hyperstimulation syndrome (OHSS)											
Letrozole + hCG vs. clomifene citrate + hCG											
1 (Badawy et al., 2009)	RCT	Very serious [b, c]	-	None	-	None	0/218 (0%) women	0/220 (0%) women	Not estimable		Low
							Number of clinical pregnancies not reported				

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
rFSH + hCG vs. clomifene citrate + hCG											
1 (Lopez et al., 2004)	RCT	Very serious [b, c]	-	None	Serious [f]	None	2/38 (5%) women	0/38 (0%) women	RR 5.0 (0.3 to 100.8)	Not estimable	Very low
							2/16 (13%) pregnancies	0/9 (0%) pregnancies	RR 2.9 (0.2 to 55.3)	Not estimable	
Congenital abnormalities											
Metformin vs. clomifene citrate											
2 (Legro et al., 1997; Johnson et al., 2010)	RCTs	Very serious [a, b, c]	- [l]	None	Serious [f]	Yes [g]	0/243 (0%) women	0/245 (0%) women	RR 0.3 (0.0 to 8.1)	3 fewer per 1000 (from 4 fewer to 29 more)	Very low
							0/32 (0%) pregnancies	1/64 (2%) pregnancies	RR 0.3 (0.0 to 7.6)	10 fewer per 1000 (from 15 fewer to 102 more)	

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Metformin + clomifene citrate vs. clomifene citrate											
3 (Legro et al., 1997; Johnson et al., 2010; Moll et al., 2006)	RCTs	Very serious [a, b, c]	None	None	Serious [f]	Yes [g]	4/355 (1%) women	2/356 (1%) women	RR 1.7 (0.4 to 7.1)	4 more per 1000 (from 3 fewer to 34 more)	Very low
							4/128 (3%) pregnancies	2/116 (2%) pregnancies	RR 1.5 (0.4 to 6.0)	8 more per 1000 (from 11 fewer to 86 more)	
Metformin vs. metformin + clomifene citrate											
2 (Legro et al., 1997; Johnson et al., 2010)	RCTs	Very serious [a, b, c]	- [l]	None	Serious [f]	Yes [g]	0/243 (0%) women	2/244 (1%) women	RR 0.2 (0.0 to 4.2)	7 fewer per 1000 (from 8 fewer to 26 more)	Very low
							0/32 (0%) pregnancies	2/84 (2%) pregnancies	RR 0.7 (0.0 to 13.9)	7 fewer per 1000 (from 23 fewer to 306 more)	

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Letrozole vs. clomifene citrate											
1 (Dehbashi et al., 2009)	RCT	Very serious [a, b, c]	-	None	Serious [f]	None	0/50 (0%) women	1/50 (2%) women	RR 0.3 (0.0 to 8.0)	Not estimable	Very low
							0/13 (0%) pregnancies	1/7 (14%) pregnancies	RR 0.2 (0.0 to 4.2)	Not estimable	
Patient satisfaction											
No evidence was reported											
Health related quality of life											
No evidence was reported											
Anxiety and/or depression											
Metformin vs. clomifene citrate (postpartum depression requiring intervention)											
1 (Legro et al., 2007)	RCT	Very serious [a, b, c]	-	None	Serious [f]	None	0/208 (0%) women	1/209 (<1%) women	RR 0.3 (0.0 to 8.2)	Not estimable	Very low
							0/18 (0%) pregnancies	1/50 (2%) pregnancies	RR 0.9 (0.0 to 21.0)	Not estimable	

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Metformin + clomifene citrate vs. clomifene citrate (postpartum depression requiring intervention)											
1 (Legro et al., 2007)	RCT	Very serious [a, b, c]	-	None	Serious [f]	None	0/209 (0%) women	1/209 (<1%) women	RR 0.3 (0.0 to 8.1)	Not estimable	Very low
							0/65 (0%) pregnancies	1/50 (2%) pregnancies	RR 0.3 (0.0 to 6.2)	Not estimable	
Metformin vs. metformin + clomifene citrate (postpartum depression requiring intervention)											
1 (Legro et al., 2007)	RCT	Very serious [a, b, c]	-	None	-	None	0/208 (0%) women	0/209 (0%) women	Not estimable		Low
							0/18 (0%) pregnancies	0/65 (0%) pregnancies	Not estimable		

Yellow highlight denotes a significant result

[a] The method of randomization was not reported in at least one study

[b] Blinding was not reported in at least one study

[c] Power analysis was not reported in at least one study

[d] I^2 value was greater than 66%

[e] May include births from multiple pregnancies and/or preterm births

[f] 95% confidence intervals hit or cross 0.75 and 1, and/or 1 and 1.25

[g] One study only included women with a BMI $\leq$ 32

[h] One study only included women with a BMI $\leq$ 30

[i] A random effects model was used as I^2 was greater than 33%

[j] I^2 value was greater than 33% but less than 66%

[k] Blinding was not reported. A power analysis was reported and the study did not meet the required sample size.

[l] No I^2 value was reported as the relative risk was only calculable for one study

Table I.8.3 GRADE findings for surgery vs. drugs (first line treatment for PCOS)

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Live full-term singleton birth											
No evidence reported											
Clinical pregnancy											
No evidence reported											
Adverse pregnancy outcome											
No evidence reported											
Multiple pregnancies (the number of pregnancies with more than one fetus)											
No evidence reported											
Multiple births (the number of babies born from a multiple pregnancy)											
No evidence reported											
Ovarian hyperstimulation syndrome (OHSS)											
No evidence reported											
Congenital abnormalities											
No evidence reported											
Patient satisfaction											
No evidence reported											
Health related quality of life											
No evidence reported											
Anxiety and/or depression											
No evidence reported											

Table I.8.4 GRADE findings for comparison of lifestyle modification vs. drugs or surgery (first line treatment for PCOS)

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Live full-term singleton birth											
No evidence reported											
Clinical pregnancy											
Low calorie diet + exercise vs. clomifene citrate											
1 (Karimzadeh et al., 2010)	RCT	Very serious [a, b]	-	None	Serious [c]	Yes [d]	15/75 (20%) women	11/90 (12%) women	RR 1.6 (0.8 to 3.4)	78 more per 1000 (from 24 fewer to 287 more)	Very low
Low calorie diet + exercise vs. metformin											
2 (Karimzadeh et al., 2010; Qublan, 2007)	RCTs	Very serious [a, b]	-	None	Serious [c]	Yes [d, e]	23/99 (23%) women	19/112 (17%) women	RR 1.3 (0.8 to 2.3)	56 more per 1000 (from 39 fewer to 217 more)	Very low
Low calorie diet + exercise vs. clomifene citrate + metformin											
1 (Karimzadeh et al., 2010)	RCT	Very serious [a, b]	-	None	Serious [c]	Yes [d]	15/75 (20%) women	13/88 (14%) women	RR 1.4 (0.7 to 2.7)	55 more per 1000 (from 43 fewer to 248 more)	Very low

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Adverse pregnancy outcome											
1 (Qublan, (2007)	RCT	Serious [b]	-	None	Serious [c]	Yes [e]	1/24 (4%) women	1/22 (5%) women	RR 0.9 (0.1 to 13.8)	4 fewer per 1000 (from 43 fewer to 581 more)	Low
							1/8 (13%) pregnancies	1/6 (17%) pregnancies	RR 0.8 (0.1 to 9.7)	42 fewer per 1000 (from 157 fewer to 1000 more)	
Multiple pregnancies (the number of pregnancies with more than one fetus)											
Low calorie diet + exercise vs. clomifene citrate											
1 (Karimzadeh et al., 2010)	RCT	Serious [a]	-	None	Serious [c]	Yes [d]	0/75 (0%) women	2/90 (2%) women	RR 0.2 (0.0 to 4.9)	17 fewer per 1000 (from 22 fewer to 87 more)	Low
							0/15 (0%) pregnancies	2/11 (18%) pregnancies	RR 0.2 (0.0 to 2.8)	155 fewer per 1000 (from 180 fewer to 335 more)	

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Low calorie diet + exercise vs. metformin											
2 (Karimzadeh et al., 2010; Qublan, 2007)	RCTs	Very serious [a, b]	-	None	Serious [c]	Yes [d, e]	1/99 (1%) women	1/112 (1%) women	RR 0.9 (0.1 to 13.8)	1 fewer per 1000 (from 8 fewer to 114 more)	Very low
							1/23 (4%) pregnancies	1/19 (5%) pregnancies	RR 0.8 (0.1 to 9.7)	13 fewer per 1000 (from 49 fewer to 459 more)	
Low calorie diet + exercise vs. clomifene citrate + metformin											
1 (Karimzadeh et al., 2010)	RCT	Very serious [a, b]	-	None	-	Yes [d]	0/75 (0%) women	0/88 (0%) women	Not estimable		Low
							0/15 (0%) pregnancies	0/13 (0%) pregnancies	Not estimable		
Multiple births (the number of babies born from a multiple pregnancy)											
No evidence reported											
Ovarian hyperstimulation syndrome (OHSS)											
No evidence reported											
Congenital abnormalities											
No evidence reported											
Patient satisfaction											
No evidence reported											

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Health related quality of life											
No evidence reported											
Anxiety and/or depression											
No evidence reported											

Yellow highlight denotes a significant result

[a] Method of randomisation was not clearly reported.

[b] A power calculation was not reported in at least one study

[c] 95% confidence intervals hit or cross 0.75 and 1.0, and/or 1.0 and 1.25

[d] Only women with a BMI of 25 to 29.9 were included. Women were 19 to 35 years old

[e] One study only included women with a BMI > 30

Table I.8.5 GRADE findings for comparison of other drugs vs. clomifene + metformin (clomifene resistant PCOS)

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Live full-term singleton birth											
Clomifene citrate vs. metformin + clomifene citrate											
2 (Vandermolen et al., 2001; Hwu et al., 2005)	RCTs	Very serious [a, b, c]	None	Serious [d]	None	None	1/55 (2%) women	8/52 (15%) women	RR 0.2 (0.0 to 0.9)	129 fewer per 1000 (from 22 fewer to 149 fewer)	Very low

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
hMG vs. metformin + clomifene citrate											
1 (George et al., 2003)	RCT	Very serious [a, b]	-	Serious [d]	Serious [e, f]	Yes [g]	6/30 (20%) women	2/30 (7%) women	RR 3.0 (0.7 to 13.7)	133 more per 1000 (from 23 fewer to 846 more)	Very low
Letrozole + metformin vs. metformin + clomifene citrate											
1 (Sohrabvand et al., 2006)	RCT	Very serious [a, b, c]	-	Serious [d]	None	None	11/30 (37%) women	3/30 (10%) women	RR 3.7 (1.1 to 11.8)	267 more per 1000 (from 14 more to 1084 more)	Very low
Clinical pregnancy											
Clomifene citrate vs. metformin + clomifene citrate											
4 (Hwu et al., 2005; Malkwai et al., 2002; Cheng et al., 2010; Vandermolen et al., 2001)	RCTs	Very serious [a, b, c]	None	None	None	None	9/97 (9%) women	34/98 (35%) women	RR 0.3 (0.2 to 0.5)	246 more per 1000 (from 160 fewer to 295 fewer)	Low

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
hMG vs. metformin + clomifene citrate											
1 (George et al., 2003)	RCT	Very serious [a, b]	-	None	Serious [e, f]	Yes [g]	7/30 (23%) women	5/30 (17%) women	RR 1.4 (0.5 to 3.9)	67 more per 1000 (from 83 fewer to 487 more)	Very low
Letrozole vs. clomifene citrate											
1 (Begum et al., 2009)	RCT	Very serious [a, b, c]	-	None	Serious [e]	None	13/32 (63%) women	6/32 (19%) women	RR 2.2 (0.9 to 5.0)	200 more per 1000 (from 22 fewer to 762 more)	Very low
Letrozole + metformin vs. metformin + clomifene citrate											
1 (Sohrabvand et al., 2006)	RCT	Very serious [b, c]	-	Serious [h]	Serious [e]	None	11/30 (37%) women	5/30 (17%) women	RR 2.2 (0.9 to 5.6)	219 more per 1000 (from 11 fewer to 748 more)	Very low
uFSH vs. metformin + clomifene citrate											
1 (Abu Hashim et al., 2010)	RCT	Serious [i]	-	None	None	None	32/78 (41%) women	18/75 (24%) women	RR 1.7 (1.1 to 2.8)	170 more per 1000 (from 12 more to 425 more)	Moderate

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Adverse pregnancy outcome											
Clomifene citrate vs. metformin + clomifene citrate (miscarriage)											
2 (Vandermolen et al., 2001; Hwu et al.2005	RCTs	Very serious [a, b, c]	- [j]	None	Serious [e]	None	0/55 (0%) women	4/52 (8%) women	RR 0.2 (0.0 to 1.5)	63 fewer per 1000 (from 75 fewer to 37 more)	Very low
							0/1 (0%) pregnancies	4/12 (33%) pregnancies	RR 0.7 (0.1 to 9.4)	100 fewer per 1000 (from 317 fewer to 2803 more)	
Metformin + clomifene citrate vs. hMG (miscarriage)											
1 (George et al., 2003)	RCT	Very serious [a, b]	-	None	Serious [e, f]	Yes [g]	1/30 (3%) women	1/30 (3%) women	RR 1.0 (0.1 to 15.3)	0 fewer per 1000 (from 31 fewer to 475 more)	Very low
							1/7 (14%) pregnancies	1/5 (20%) pregnancies	RR 0.7 (0.1 to 8.9)	58 fewer per 1000 (from 188 fewer to 1580 more)	

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Metformin + clomifene citrate vs. hMG (intrauterine death at 28 weeks)											
1 (George et al., 2003)	RCT	Very serious [a, b]	-	None	Serious [e, f]	Yes [g]	1/30 (3%) women	0/30 (0%) women	RR 3.0 (0.1 to 70.8)	Not estimable	Very low
							1/5 (20%) pregnancies	0/7 (0%) pregnancies	RR 4.0 (0.2 to 82.0)	Not estimable	
Metformin + clomifene citrate vs. hMG (ectopic pregnancy)											
1 (George et al., 2003)	RCT	Very serious [a, b]	-	None	Serious [e, f]	Yes [g]	1/30 (3%) women	0/30 (0%) women	RR 3.0 (0.1 to 70.8)	Not estimable	Very low
							1/5 (20%) pregnancies	0/7 (0%) pregnancies	RR 4.0 (0.2 to 82.0)	Not estimable	
Letrozole vs. clomifene citrate (miscarriage)											
1 (Begum et al., 2009)	RCT	Very serious [a, b, c]	-	Serious [f]	Serious [e]	None	2/32 (6%) women	0/32 (0%) women	RR 5.0 (0.3 to 100)	Not estimable	Very low
							2/13 (15%) pregnancies	0/6 (0%) pregnancies	RR 2.5 (0.1 to 45.3)	Not estimable	

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
hMG vs. clomifene citrate (miscarriage)											
1 (Badawy et al., 2008)	RCT	Very serious [b, c]	-	None	Serious [e]	None	4/158 (3%) women	5/160 (3%) women	RR 0.8 (0.2 to 3.0)	6 fewer per 1000 (from 24 fewer to 61 more)	Very low
							Number of clinical pregnancies not reported				
Letrozole + metformin vs. metformin + clomifene citrate (miscarriage)											
1 (Sohrabvand et al., 2006)	RCT	Very serious [b, c]	-	None	Serious [e]	None	0/30 (0%) women	2/30 (7%) women	RR 0.2 (0.0 to 4.0)	53 fewer per 1000 (from 66 fewer to 200 more)	Very low
							0/11 (0%) pregnancies	2/5 (40%) pregnancies	RR 0.1 (0.0 to 1.8)	360 fewer per 1000 (from 396 fewer to 308 more)	

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
uFSH vs. metformin + clomifene citrate (miscarriage)											
1 (Abu Hashim et al., 2010)	RCT	Serious [i]	-	None	Serious [e]	None	5/78 (6%) women	4/75 (5%) women	RR 1.2 (0.3 to 4.3)	11 more per 1000 (from 35 fewer to 177 more)	Low
							5/32 (16%) pregnancies	4/18 (22%) pregnancies	RR 0.7 (0.2 to 2.3)	67 fewer per 1000 (from 173 fewer to 287 more)	
Multiple pregnancies (the number of pregnancies with more than one fetus)											
Clomifene citrate vs. metformin + clomifene citrate											
1 (Vandermolen et al., 2001)	RCT	Very serious [b, c]	-	None	-	None	0/15 (0%) women	0/12 (0%) women	Not estimable		Low
							0/1 (0%) pregnancies	0/6 (0%) pregnancies	Not estimable		
Letrozole vs. clomifene citrate											
1 (Begum et al., 2009)	RCT	Very serious [a, b, c]	-	None	-	None	0/32 (0%) women	0/32 (0%) women	Not estimable		Low
							0/13 (0%) pregnancies	0/6 (0%) pregnancies	Not estimable		

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
hMG vs. clomifene citrate											
1 (Badawy et al., 2008)	RCT	Very serious [b, c]	-	None	Serious [e]	None	4/158 (3%) women	1/160 (1%) women	RR 4.1 (0.5 to 35.8)	19 more per 1000 (from 3 fewer to 218 more)	Very low
							4/20 (20%) pregnancies	1/28 (4%) pregnancies	RR 5.6 (0.7 to 46.4)	164 more per 1000 (from 11 fewer to 1622 more)	
Letrozole vs. metformin + clomifene citrate											
1 (Abu Hashim et al., 2010)	RCT	Very serious [b, c]	-	None	Serious [e]	None	0/123 (0%) women	3/127 (2%) women	RR 0.2 (0.0 to 2.8)	20 fewer per 1000 (from 23 fewer to 43 more)	Very low
							Number of clinical pregnancies not reported				

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
uFSH vs. metformin + clomifene citrate											
1 (Abu Hashim et al., 2010)	RCT	Serious [i]	-	None	Serious [e]	None	6/78 (8%) women	2/75 (3%) women	RR 2.9 (0.6 to 13.9)	50 more per 1000 (from 11 fewer to 343 more)	Low
							6/32 (19%) pregnancies	2/18 (11%) pregnancies	RR 2.9 (0.6 to 13.9)	209 more per 1000 (from 44 fewer to 1000 more)	
Multiple births (the number of babies born from a multiple pregnancy)											
No evidence reported											
Ovarian hyperstimulation syndrome (OHSS)											
Clomifene citrate vs. metformin + clomifene citrate											
1 (Malkwai et al., 2002)	RCT	Very serious [a, b, c]	-	None	Serious [e]	None	2/12 (17%) women	0/16 (0%) women	RR 6.5 (0.3 to 124.8)	Not estimable	Very low
hMG vs. clomifene citrate											
1 (Badawy et al., 2008)	RCT	Very serious [b, c]	-	None	Serious [e]	None	2/158 (1%) women	0/160 (0%) women	RR 5.1 (0.2 to 105)	Not estimable	Very low
Letrozole vs. metformin + clomifene citrate											
1 (Abu Hashim et al., 2010)	RCT	Very serious [b, c]	-	None	-	None	0/123 (0%) women	0/127 (0%) women	Not estimable		Low

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Congenital abnormalities											
No evidence reported											
Patient satisfaction											
No evidence reported											
Health related quality of life											
No evidence reported											
Anxiety and/or depression											
No evidence reported											

Yellow highlight denotes significant result

[a] Method of randomisation was not reported in at least one study

[b] Blinding was not reported in at least one study

[c] A power analysis was not reported in at least one study

[d] May include births from multiple pregnancies and/or preterm births

[e] 95% confidence intervals hit or cross 0.75 and 1, and/or 1 and 1.25

[f] A power calculation was reported but not enough women were recruited into the study

[g] Only women with a BMI > 35 were included

[h] A definition of clinical pregnancy was not reported

[i] A power analysis was not reported for pregnancy outcomes

[j] I^2 was not reported as the relative risk was only calculable for one study

Table I.8.6 GRADE findings for comparison of surgery vs. drugs (clomifene resistant PCOS)

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Live full-term singleton birth											
Surgery vs. clomifene citrate + tamoxifen											
1 (Zakherah et al., 2010)	RCT	None	-	Serious [a]	Serious [b]	None	33/75 (44%) women	37/75 (49%) women	RR 0.9 (0.6 to 1.3)	54 fewer per 1000 (from 183 fewer to 128 more)	Low
Surgery vs. hMG											
1 (Abdel et al., 1990)	RCT	Serious [c]	-	Very serious [a, d]	Serious [b]	None	11/29 (37%) women	7/30 (23%) women	RR 1.6 (0.7 to 3.6)	147 more per 1000 (from 63 fewer to 609 more)	Very low
Surgery vs. FSH or rFSH											
2 (Abdel et al., 1990; Bayram et al., 2004)	RCTs	Serious [c]	Very serious [e]	Very serious [a, d]	Serious [b]	None	39/112 (35%) women	51/114 (45%) women	RR 1.0 (0.4 to 2.9) [e]	0 fewer per 1000 (from 291 fewer to 832 more)	Very low
Surgery vs. HMG or rFSH											
1 (Farquhar et al., 2002)	RCT	None	-	Very serious [a, d]	Serious [b]	Yes [f]	4/29 (14%) women	4/21 (19%) women	RR 0.7 (0.2 to 2.6)	53 fewer per 1000 (from 152 fewer to 299 more)	Very low

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Clinical pregnancy											
Surgery vs. clomifene citrate + tamoxifen											
1 (Zakherah et al., 2010)	RCT	None	-	None	Serious [b]	None	38/75 (51%) women	40/75 (53%) women	RR 1.0 (0.7 to 1.3)	27 fewer per 1000 (from 160 fewer to 155 more)	Moderate
Surgery vs. metformin + clomifene citrate											
1 (Abu Hashim et al., 2010)	RCT	None	-	None	None	None	95/144 (66%) women	89/138 (65%) women	RR 1.0 (0.9 to 1.2)	13 more per 1000 (from 90 fewer to 135 more)	High
Surgery vs. rFSH											
1 (Bayram et al., 2004)	RCT	None	-	Serious [g]	None	None	31/83 (37%) women	64/85 (75%) women	RR 0.5 (0.4 to 0.7)	376 fewer per 1000 (from 248 fewer to 474 fewer)	Moderate
Surgery vs. hMG or rFSH											
1 (Farquhar et al., 2002)	RCT	None	-	Serious [d]	Serious [b]	Yes [f]	8/29 (28%) women	7/21 (33%) women	RR 0.8 (0.4 to 1.9)	57 fewer per 1000 (from 213 fewer to 310 more)	Low

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Surgery + clomifene citrate vs. FSH											
1 (Kamel et al., 2004)	RCT	Serious [h]	-	Serious [g]	Serious [b]	Yes [i]	2/30 (7%) women	4/25 (16%) women	RR 0.4 (0.1 to 2.1)	93 fewer per 1000 (from 147 fewer to 174 more)	Very low
Adverse pregnancy outcome											
Surgery vs. clomifene citrate + tamoxifen (miscarriage)											
1 (Zakherah et al., 2010)	RCT	None	-	None	Serious [b]	None	5/75 (7%) women	3/75 (4%) women	RR 1.7 (0.4 to 6.7)	27 more per 1000 (from 24 fewer to 229 more)	Moderate
							5/38 (13%) pregnancies	3/40 (8%) pregnancies	RR 1.8 (0.5 to 6.9)	56 more per 1000 (from 41 fewer to 438 more)	

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Surgery vs. hMG or rFSH (miscarriage)											
1 (Farquhar et al., 2002)	RCT	None	-	Very serious [a, d]	Serious [b]	Yes [f]	3/29 (12%) women	3/21 (14%) women	RR 0.7 (0.2 to 3.2)	40 fewer per 1000 (from 120 fewer to 320 more)	Very low
							3/8 (38%) pregnancies	3/7 (43%) pregnancies	RR 0.9 (0.3 to 3.0)	51 fewer per 1000 (from 321 fewer to 866 more)	
Surgery vs. rFSH (miscarriage)											
1 (Bayram et al., 2004)	RCT	None	-	None	Serious [b]	None	3/83 (4%) women	7/85 (8%) women	RR 0.4 (0.1 to 1.6)	46 fewer per 1000 (from 72 fewer to 53 more)	Moderate
							3/31 (10%) pregnancies	7/64 (11%) pregnancies	RR 0.9 (0.3 to 3.2)	13 fewer per 1000 (from 82 fewer to 240 more)	

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Surgery vs. rFSH (premature birth)											
1 (Bayram et al., 2004)	RCT	None	-	None	Serious [b]	None	0/83 (0%) women	6/85 (7%) women	RR 0.1 (0.0 to 1.3)	65 fewer per 1000 (from 71 fewer to 24 more)	Moderate
							0/31 (0%) pregnancies	6/64 (9%) pregnancies	RR 0.2 (0.0 to 2.7)	79 fewer per 1000 (from 93 fewer to 158 more)	
Surgery vs. metformin + clomifene citrate (miscarriage)											
1 (Abu Hashim et al., 2010)	RCT	None	-	None	Serious [b]	None	9/144 (6%) women	8/138 (6%) women	RR 1.1 (0.4 to 2.7)	5 more per 1000 (from 33 fewer to 99 more)	Moderate
							9/95 (10%) pregnancies	8/89 (9%) pregnancies	RR 1.1 (0.4 to 2.6)	4 more per 1000 (from 51 fewer to 145 more)	

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Multiple pregnancies (the number of pregnancies with more than one fetus)											
Surgery vs. hMG											
1 (Abdel et al., 1990)	RCT	Serious [c]	-	Serious [d]	Serious [b]	None	0/29 (0%) women	3/30 (10%) women	RR 0.2 (0.0 to 2.7)	85 fewer per 1000 (from 99 fewer to 174 more)	Very low
							Number of clinical pregnancies not reported				
Surgery vs. FSH or rFSH											
2 Bayram et al., 2004; Abdel et al., 1990)	RCTs	Serious [c]	- [j]	Serious [d]	None	None	0/112 (0%) women	11/114 (10%) women	RR 0.1 (0.0 to 0.6)	89 fewer per 1000 (from 35 fewer to 96 fewer)	Low
							0/31 (0%) pregnancies	9/64 (14%) pregnancies	RR 0.1 (0.0 to 1.8)	125 fewer per 1000 (from 139 fewer to 110 more)	
Surgery vs. hMG or rFSH											
1 (Farquhar et al., 2002)	RCT	None	-	Serious [d]	-	Yes [f]	0/29 (0%) women	0/21 (0%) women	Not estimable		Moderate
							0/8 (0%) pregnancies	0/7 (0%) pregnancies	Not estimable		

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Surgery vs. metformin + clomifene citrate											
1 (Abu Hashim et al., 2010)	RCT	None	-	None	Serious [b]	None	0/144 (0%) women	4/138 (3%) women	RR 0.1 (0.0 to 2.0)	26 fewer per 1000 (from 29 fewer to 28 more)	Moderate
							0/95 (0%) pregnancies	4/89 (5%) pregnancies	RR 0.1 (0.0 to 1.9)	40 fewer per 1000 (from 44 fewer to 41 more)	
Multiple births (the number of babies born from a multiple pregnancy)											
No evidence was reported											
Ovarian hyperstimulation syndrome (OHSS)											
Surgery vs. hMG or rFSH											
1 (Farquhar et al., 2002)	RCT	None	-	Serious [d]	-	Yes [f]	0/29 (0%) women	0/21 (0%) women	Not calculable		Moderate
							0/8 (0%) pregnancies	0/7 (0%) pregnancies	Not calculable		
Congenital abnormalities											
No evidence reported											
Patient satisfaction											
No evidence reported											
Health related quality of life											
No evidence reported											

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Anxiety and/or depression											
No evidence reported											

Yellow highlight denotes significant findings

[a] May also include preterm and/or births from multiple pregnancies

[b] 95% confidence intervals hit or cross 0.75 and 1, and/or 1 and 1.25

[c] Randomisation and allocation were not clearly reported. Power analysis not reported

[d] PCOS was poorly defined

[e] I^2 value was higher than 66%. A random effects model was used

[f] Only included women with a BMI < 33 (if of European descent) or < 35 (Pacific Islander or NZ Maori descent)

[g] Clinical pregnancy not defined

[h] Power calculation was not reported

[i] All women had previously undergone surgery for PCOS

[j] One study did not report the number of pregnancies and therefore the per pregnancy data is derived from only one study

Table I.8.7 GRADE findings for comparison of Lifestyle vs. drugs or surgery (clomifene resistant PCOS)

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Live full-term singleton birth											
No evidence reported											
Clinical pregnancy											
No evidence reported											
Adverse pregnancy outcome											
No evidence reported											

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Multiple pregnancies (the number of pregnancies with more than one fetus)											
No evidence reported											
Multiple births (the number of babies born from a multiple pregnancy)											
No evidence reported											
Ovarian hyperstimulation syndrome (OHSS)											
No evidence reported											
Congenital abnormalities											
No evidence reported											
Patient satisfaction											
No evidence reported											
Health related quality of life											
No evidence reported											
Anxiety and/or depression											
No evidence reported											

Table I.11.1 GRADE findings for comparison of ovarian stimulation agents vs. no ovarian stimulation agents

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Live full-term singleton births											
Clomifene citrate without hCG vs advice only											
1 (Bhattacharya et al., 2008)	RCT	None	-	Serious [c, f]	Serious [e]	None	26/192 women (14%)	32/193 women (17%)	RR 0.8 (0.5 to 1.3)	30 fewer per 1000 (from 81 fewer to 53 more)	Low
Clinical pregnancies											
Clomifene citrate without hCG vs advice only											
1 (Bhattacharya et al., 2008)	RCT	None		Serious [c]	Serious [e]	None	29/192 women (15%)	33/193 women (17%)	RR 0.9 (0.6 to 1.4)	21 fewer per 1000 (from 75 fewer to 68 more)	Low
Ovarian hyperstimulation											
No evidence reported											

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Multiple pregnancies (the number of pregnancies with more than one fetus)											
Clomifene citrate without hCG vs advice only											
1 (Bhattacharya et al., 2008)	RCT	Serious [b]	-	Serious [c]	Serious [e]	None	2/192 women (1%)	2/192 women (1%)	RR 1 (0.1 to 7.0)	0 fewer per 1000 (from 9 fewer to 63 more)	Very low
							2/29 pregnancies (7%)	2/33 pregnancies (6%)	RR 1.1 (0.2 to 7.6)	8 more per 1000 (from 50 fewer to 398 more)	
Multiple births (the number of babies born from a multiple pregnancy)											
No evidence reported											
Adverse pregnancy outcomes											
Clomifene citrate without hCG vs advice only (Miscarriage)											
1 (Bhattacharya et al., 2008)	RCT	Serious [b]	-	Serious [c]	Serious [e]	None	10/129 women (8%)	14/193 women (7%)	RR 1.1 (0.5 to 2.3)	5 more per 1000 (from 37 fewer to 96 more)	Very low
							10/29 pregnancies (35%)	14/33 pregnancies (42%)	RR 0.8 (0.4 to 1.5)	81 fewer per 1000 (from 242 fewer to 229 more)	

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Clomifene citrate without hCG vs advice only (Ectopic pregnancy)											
1 (Bhattacharya et al., 2008)	RCT	Serious [b]	-	Serious [c]	Not calculable	None	0/192 women (0%)	1/193 women (1%)	RR 0.5 (0.0 to 12.1)	3 fewer per 1000 (from 5 fewer to 58 more)	Low
							0/29 pregnancies (0%)	1/33 pregnancies (3%)	RR 0.4 (0.0 to 8.9)	19 fewer per 1000 (from 30 fewer to 240 more)	
Congenital abnormalities											
No evidence reported											
Patient satisfaction											
Clomifene citrate without hCG vs advice only (Process of treatment acceptable)											
1 (Bhattacharya et al., 2008)	RCT	None	-	Serious [c]	None	None	159/192 women (83%)	123/193 women (64%)	RR 1.3 (1.2 to 1.5)	191 more per 1000 (from 96 more to 300 more)	Moderate
Clomifene citrate without hCG vs advice only (Outcome of treatment acceptable)											
1 (Bhattacharya et al., 2008)	RCT	None	-	Serious [c]	Serious [e]	None	100/192 women (52%)	82/193 women (43%)	RR 1.2 (1.0 to 1.5)	98 more per 1000 (from 4 fewer to 221 more)	Low

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Anxiety or depression											
Clomifene citrate without hCG vs advice only (Anxiety)											
1 (Bhattacharya et al., 2008)	RCT	None	-	Serious [c]	Serious [e]	None	34/192 women (18%)	31/193 women (16%)	RR 1.1 (0.7 to 1.7)	16 more per 1000 (from 47 fewer to 116 more)	Low
Clomifene citrate without hCG vs advice only (Depression)											
1 (Bhattacharya et al., 2008)	RCT	None	-	Serious [c]	Serious [e]	None	4/192 women (2%)	4/193 women (2%)	RR 1.0 (0.3 to 4.0)	0 more per 1000 (from 15 fewer to 61 more)	Low

[a] A power analysis was not reported. Blinding was not reported
[b] The number of cycles in the expectant management group was not reported in the paper and was estimated by the reviewer
[c] Between 5 and 9% of the women had mild endometriosis. Between 5 and 7% of the men had male factor infertility
[d] Only the number of deliveries was reported. It is not clear if this includes stillbirths or just live births, and it is not clear how many multiple births there were
[e] The confidence intervals hit or cross 0.75 and 1.0 and/or 1.0 and 1.25
[f] These figures include pre-term births. It was not possible to determine the number of pre-term births separately

Table I.11.2 GRADE findings for comparison of different ovarian stimulation agents

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Live full-term singleton births											
Letrozole + hCG vs. Clomifene citrate + hCG											
1 (Badawy et al., 2009)	RCT	Serious [a]	-	Serious [d]	Serious [e]	None	26/269 (10%) women	63/420 (15%) women	RR 0.6 (0.4 to 1.0)	54 fewer per 1000 (from 1 fewer to 87 fewer)	Very low
Anastrozole + hCG vs. Clomifene citrate + hCG											
1 (Badawy et al., 2009)	RCT	Serious [a]	-	Serious [d]	Serious [e]	None	10/107 (9%) women	63/420 (15%) women	RR 0.6 (0.3 to 1.2)	57 fewer per 1000 (from 101 fewer to 25 more)	Very low
Clinical pregnancies											
Letrozole + hCG vs. Clomifene citrate + hCG											
1 (Badawy et al., 2009)	RCT	Serious a	-	None	Serious [e]	None	36/269 (13%) women	77/420 (18%) women	RR 0.7 (0.5 to 1.1)	49 fewer per 1000 (from 90 fewer to 9 more)	Low
Anastrozole + hCG vs. Clomifene citrate + hCG											
1 (Badawy et al., 2009)	RCT	Serious [a]	-	None	Serious [e]	None	15/107 (14%) women	77/420 (18%) women	RR 0.8 (0.5 to 1.3)	44 fewer per 1000 (from 99 fewer to 49 more)	Low

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Ovarian hyperstimulation											
Letrozole + hCG vs. Clomifene citrate + hCG											
1 (Badawy et al., 2009)	RCT	Serious [a]	-	None	Not calculable	None	0/269 (0%) women	0/420 (0%) women	Not calculable	Not calculable	Moderate
Anastrozole + hCG vs. Clomifene citrate + hCG											
1 (Badawy et al., 2009)	RCT	Serious [a]	-	None	Not calculable	None	0/107 (0%) women	0/420 (0%) women	Not calculable	Not calculable	Moderate
Multiple pregnancies (the number of pregnancies with more than one fetus)											
Letrozole + hCG vs. Clomifene citrate + hCG											
1 (Badawy et al., 2009)	RCT	Serious [a]	-	None	Serious [e]	None	3/269 (1%) women	7/420 (2%) women	RR 0.7 (0.2 to 2.6)	6 fewer per 1000 (from 14 fewer to 26 more)	Low
							3/36 (8%) pregnancies	7/77 (9%) pregnancies	RR 0.9 (0.3 to 3.3)	7 fewer per 1000 (from 68 fewer to 213 more)	

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Anastrozole + hCG vs. Clomifene citrate + hCG											
1 (Badawy et al., 2009)	RCT	Serious [a]	-	None	Serious [e]	None	1/107 (1%) women	7/420 (2%) women	RR 0.6 (0.1 to 4.5)	7 fewer per 1000 (from 16 fewer to 59 more)	Low
							1/15 (7%) pregnancies	7/77 (9%) pregnancies	RR 0.7 (0.1 to 5.5)	25 fewer per 1000 (from 82 fewer to 412 more)	
Multiple births (the number of babies born from a multiple pregnancy)											
No evidence reported											
Adverse pregnancy outcomes											
Letrozole + hCG vs. Clomifene citrate + hCG (miscarriage)											
1 (Badawy et al., 2009)	RCT	Serious [a]	-	None	Serious [e]	None	6/269 (2%) women	11/420 (3%) women	RR 0.9 (0.3 to 2.3)	4 fewer per 1000 (from 18 fewer to 34 more)	Low
							6/36 (17%) pregnancies	11/77 (14%) pregnancies	RR 1.2 (0.5 to 2.9)	24 more per 1000 (from 76 fewer to 273 more)	

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Letrozole + hCG vs. Clomifene citrate + hCG (ectopic)											
1 (Badawy et al., 2009)	RCT	Serious [a]	-	None	Serious [e]	None	0/269 (0%) women	1/420 (<1%) women	RR 0.5 (0.0 to 12.7)	1 fewer per 1000 (from 2 fewer to 28 more)	Low
							0/36 (0%) pregnancies	1/77 (1%) pregnancies	RR 0.7 (0.0 to 16.8)	4 fewer per 1000 (from 13 fewer to 206 more)	
Anastrozole + hCG vs. Clomifene citrate + hCG (miscarriage)											
1 (Badawy et al., 2009)	RCT	Serious [a]	-	None	Serious [e]	None	3/107 (3%) women	11/420 (3%) women	RR 1.1 (0.3 to 3.8)	2 more per 1000 (from 18 fewer to 73 more)	Low
							3/15 (20%) pregnancies	11/77 (14%) pregnancies	RR 1.4 (0.4 to 4.4)	57 more per 1000 (from 80 fewer to 489 more)	
Anastrozole + hCG vs. Clomifene citrate + hCG (ectopic)											
1 (Badawy et al., 2009)	RCT	Serious [a]	-	None	Serious [e]	None	0/107 (0%) women	1/420 (<1%) women	RR 1.3 (0.1 to 31.7)	1 more per 1000 (from 2 fewer to 73 more)	Low
							0/15 (0%) pregnancies	1/77 (1%) pregnancies	RR 1.6 (0.1 to 38.1)	8 more per 1000 (from 12 fewer to 482 more)	

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Congenital abnormalities											
Letrozole + hCG vs. Clomifene citrate + hCG											
1 (Badawy et al., 2009)	RCT	Serious [a]	-	None	Serious [e]	None	2/30 (7%) births	1/65 (2%) births	RR 4.3 (0.4 to 46.0)	51 more per 1000 (from 9 fewer to 692 more)	Low
							2/36 (6%) pregnancies	1/77 (1%) pregnancies	RR 4.3 (0.4 to 45.7)	43 more per 1000 (from 8 fewer to 580 more)	
Anastrozole + hCG vs. Clomifene citrate + hCG											
1 (Badawy et al., 2009)	RCT	Serious [a]	-	None	Not calculable	None	0/11 (0%) births	1/65 (2%) births	RR 1.8 (0.1 to 42.4)	13 more per 1000 (from 14 fewer to 637 more)	Moderate
							0/15 (0%) pregnancies	1/77 (1%) pregnancies	RR 1.6 (0.1 to 38.1)	8 more per 1000 (from 12 fewer to 482 more)	
Patient satisfaction											
No evidence reported											
Anxiety or depression											
No evidence reported											

[a] A power analysis was not reported. Blinding was not reported
[b] The number of cycles in the expectant management group was not reported in the paper and was estimated by the reviewer

[c] Between 5 and 9% of the women had mild endometriosis. Between 5 and 7% of the men had male factor infertility
[d] Only the number of deliveries was reported. It is not clear if this includes stillbirths or just live births, and it is not clear how many multiple births there were
[e] The confidence intervals hit or cross 0.75 and 1.0 and/or 1.0 and 1.25

Table I.12.1 GRADE findings for comparison of IUI without ovarian stimulation versus expectant management

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	IUI without ovarian stimulation	Expectant Management*	Relative (95% CI)	Absolute (95% CI)	
Live full-term singleton birth											
1 (Bhattacharya et al, 2008)	RCT	Serious[1]	None	Serious[2]	Serious[3]	None	43/191 (22.5%)	32/193 (16.6%)	RR 1.36 (0.9 to 2.05)	60 more per 1000 (from 17 fewer to 174 more)	Very low
							38/165 (23%) Unexplained infertility only	26/167 (15.6%)	RR 1.48 (0.94 to 2.32)	75 more per 1000 (from 9 fewer to 206 more)	
Clinical pregnancy											
1 (Bhattacharya et al, 2008)	RCT	Serious [1]	None	None	Serious[3]	None	43/191 (22.5%)	33/193 (17.1%)	RR 1.32 (0.88 to 1.98)	55 more per 1000 (from 21 fewer to 168 more)	Low
Multiple pregnancies											
1 (Bhattacharya et al, 2008)	RCT	Serious [1]	None	None	Serious[3]	None	1/43 (2.3%) per pregnancy	2/33 (6.1%) per pregnancy	RR 0.38 (0.04 to 4.05)	38 fewer per 1000 (from 58 fewer to 185 more)	Low

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	IUI without ovarian stimulation	Expectant Management*	Relative (95% CI)	Absolute (95% CI)	
							1/191 (0.52%) per woman	2/193 (1%) per woman	RR 0.51 (0.05 to 5.53)	5 fewer per 1000 (from 10 fewer to 47 more)	
Multiple births											
No evidence reported											
Miscarriage											
1 (Bhattacharya et al, 2008)	RCT	Serious [1]	None	None	Serious[3]	None	9/55 (16.4%) per pregnancy	14/46 (30.4%) per pregnancy	RR 0.54 (0.26 to 1.13)	140 fewer per 1000 (from 225 fewer to 40 more)	Low
							9/191 (4.7%) per woman	14/193 (7.3%) per woman	RR 0.65 (0.29 to 1.46)	25 fewer per 1000 (from 52 fewer to 33 more)	
Ectopic pregnancy											
1 (Bhattacharya et al, 2008)	RCT	Serious [1]	None	None	Serious[3]	None	2/55 (3.6%) per pregnancy	1/46 (2.2%) per pregnancy	RR 1.67 (0.16 to 17.86)	15 more per 1000 (from 18 fewer to 367 more)	Low
							2/191 (1%) per woman	1/193 (0.52%) per woman	RR 2.02 (0.18 to 22.1)	5 more per 1000 (from 4 fewer to 109 more)	

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	IUI without ovarian stimulation	Expectant Management*	Relative (95% CI)	Absolute (95% CI)	
Pre-term birth											
1 (Bhattacharya et al, 2008)	RCT	Serious [1]	None	None	Serious[3]	None	6/43 (14%) per live birth	5/31 (16.1%) per live birth	RR 0.87 (0.29 to 2.58)	21 fewer per 1000 (from 115 fewer to 255 more)	Low
							6/191 (3.1%) per woman	5/193 (2.6%) per woman	RR 1.21 (0.38 to 3.91)	5 more per 1000 (from 16 fewer to 75 more)	
Treatment related hospital admissions											
1 (Bhattacharya et al, 2008)	RCT	Serious [1]	None	None	Serious[3]	None	0/163 (0%)	2/160 (1.3%)	RR 0.2 (0.01 to 4.06)	10 fewer per 1000 (from 12 fewer to 38 more)	Low
Abdominal pain											
1 (Bhattacharya et al, 2008)	RCT	Serious [1]	None	None	Serious [3]	None	12/164 (7.3%)	5/159 (3.1%)	RR 2.33 (0.84 to 6.45)	42 more per 1000 (from 5 fewer to 171 more)	Low
Vaginal bleeding											
1 (Bhattacharya et al, 2008)	RCT	Serious [1]	None	None	Serious [3]	None	10/164 (6.1%)	4/159 (2.5%)	RR 2.42 (0.78 to 7.57)	36 more per 1000 (from 6 fewer to 165 more)	Low

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	IUI without ovarian stimulation	Expectant Management*	Relative (95% CI)	Absolute (95% CI)	
Nausea											
1 (Bhattacharya et al, 2008)	RCT	Serious [1]	None	None	Serious [3]	None	3/164 (1.8%)	4/159 (2.5%)	RR 0.73 (0.17 to 3.2)	7 fewer per 1000 (from 21 fewer to 55 more)	Low
Vomiting											
1 (Bhattacharya et al, 2008)	RCT	Serious [1]	None	None	Serious [3]	None	0/164 (0%)	0/158 (0%)	Not calculable	Not calculable	Low
Headache											
1 (Bhattacharya et al, 2008)	RCT	Serious [1]	None	None	Serious [3]	None	4/191 (2.1%)	6/193 (3.1%)	RR 0.67 (0.19 to 2.35)	10 fewer per 1000 (from 25 fewer to 42 more)	Low
Hot flushes											
1 (Bhattacharya et al, 2008)	RCT	Serious [1]	None	None	Serious [3]	None	0/164 (0%)	4/159 (2.5%)	RR 0.11 (0.01 to 1.99)	22 fewer per 1000 (from 25 fewer to 25 more)	Low
Bloating											
1 (Bhattacharya et al, 2008)	RCT	Serious [1]	None	None	Serious [3]	None	6/164 (3.7%)	0/158 (0%)	RR 12.53 (0.71 to 220.54)	Not calculable	Low

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	IUI without ovarian stimulation	Expectant Management*	Relative (95% CI)	Absolute (95% CI)	
Process of treatment acceptable											
1 (Bhattacharya et al, 2008)	RCT	Serious [1]	None	None	Serious [3]	None	155/162 (95.7%)	123/153 (80.4%)	RR 1.19 (1.09 to 1.3)	153 more per 1000 (from 72 more to 241 more)	Low
Outcome of treatment acceptable											
1 (Bhattacharya et al, 2008)	RCT	Serious [1]	None	None	Serious [3]	None	117/159 (73.6%)	82/148 (55.4%)	RR 1.33 (1.12 to 1.58)	183 more per 1000 (from 66 more to 321 more)	Low
Anxiety											
1 (Bhattacharya et al, 2008)	RCT	Serious [1]	None	None	Serious [3]	None	22/173 (12.7%)	31/171 (18.1%)	RR 0.7 (0.42 to 1.16)	54 fewer per 1000 (from 105 fewer to 29 more)	Low
Depression											
1 (Bhattacharya et al, 2008)	RCT	Serious [1]	None	None	Serious [3]	None	2/172 (1.2%)	4/170 (2.4%)	RR 0.49 (0.09 to 2.66)	12 fewer per 1000 (from 21 fewer to 39 more)	Low

* expectant management = 6 months during which no clinic or medical interventions were scheduled. Couples were given general advice about the need for regular intercourse, but nothing else.

[1] Blinding not possible.

[2] Live Birth recorded rather than live full-term singleton birth

[3] Imprecise results as results encompass significant negative effect, no effect and positive effect

Table I.12.2 GRADE findings for comparison of IUI with ovarian stimulation versus expectant management

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	IUI with ovarian stimulation	Expectant management	Relative (95% CI)	Absolute (95% CI)	
Live full-term singleton birth (Unexplained infertility)											
1(Steures et al, 2006)	RCT	Serious [1]	None	Very serious [3, 4]	Very serious[5]	None	24/124 (19.4%)	29/122 (23.8%)	RR 0.81 (0.5 to 1.32)	45 fewer per 1000 (from 119 fewer to 76 more)	Very low
Live full-term singleton birth (Endometriosis)											
1(Tummons et al, 1997)	RCT	Serious [1]	None	Serious[4]	Serious [5]	None	11/53 (20.8%)	4/50 (8%)	RR 2.59 (0.88 to 7.62)	127 more per 1000 (from 10 fewer to 530 more)	Low
Live multiple birth (Unexplained infertility)											
1(Steures et al, 2006)	RCT	Serious [1]	None	Serious [3]	Very serious[5]	None	2/124 (1.6%)	1/122 (0.82%)	RR 1.97 (0.18 to 21.42)	8 more per 1000 (from 7 fewer to 167 more)	Very low
Live multiple birth (Endometriosis)											
1(Tummons et al, 1997)	RCT	Serious [1]	None	None	Serious [5]	None	4/53 (7.5%)	0/50 (0%)	RR 8.5 (0.47 to 153.95)	-	Low
Ongoing singleton pregnancy (Unexplained infertility)											
1(Steures et al, 2006)	RCT	Serious [1]	None	Serious [3]	Very serious[5]	None	27/127 (21.3%)	33/126 (26.2%)	RR 0.81 (0.52 to 1.27)	50 fewer per 1000 (from 126 fewer to 71 more)	Very low

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	IUI with ovarian stimulation	Expectant management	Relative (95% CI)	Absolute (95% CI)	
Multiple pregnancies (Unexplained infertility)											
1(Steures et al, 2006)	RCT	Serious [1]	None	Serious [3]	Very serious [5]	None	2/127 (1.6%)	1/126 (0.79%)	RR 1.98 (0.18 to 21.61)	8 more per 1000 (from 7 fewer to 164 more)	Very low
Clinical pregnancy (Unexplained infertility)											
1(Steures et al, 2006)	RCT	Serious [1]	None	Serious [3]	Very serious [5]	None	42/127 (33.1%)	40/126 (31.7%)	RR 1.04 (0.73 to 1.49)	13 more per 1000 (from 86 fewer to 156 more)	Very low
Miscarriage per clinical pregnancy (Unexplained infertility)											
1(Steures et al, 2006)	RCT	Serious [1]	None	Serious [3]	Serious [5]	None	13/42 (31%) per pregnancy	6/40 (15%) per pregnancy	RR 2.06 (0.87 to 4.9)	159 more per 1000 (from 20 fewer to 585 more)	Very low
							13/127 (10.2%) per woman	6/126 (4.8%) per woman	RR 2.15 (0.84 to 5.48)	55 more per 1000 (from 8 fewer to 213 more)	
OHSS (Endometriosis)											
1(Tummons et al, 1997)	RCT	Serious [1]	None	None	Serious [5]	None	0/53 (0%)	0/50 (0%)	-	-	Low

[1] Blinding of treatment not possible

[2] Mixed populations

[3] Steures: Only include couples with 30 to 40% chance of naturally conceiving within 1 year.

[4] Live birth reported instead of live full-term singleton birth

[5] Wide confidence intervals

Table I.12.3 GRADE findings for comparison of IUI with ovarian stimulation versus IUI without ovarian stimulation for all types of infertility (unless otherwise stated)

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	IUI with ovarian stimulation	IUI without stimulation	Relative (95% CI)	Absolute (95% CI)	
Live full-term singleton birth											
2 (Goverde et al, 2005; Guzick et al, 1999)	RCT	Very serious[1,2,3,4]	None	Serious[9]	None	None	72/315 (22.9%)	53/318 (16.7%)	RR 1.37 (1 to 1.88)	62 more per 1000 (from 0 more to 147 more)	Very low
Live full-term singleton birth (Unexplained infertility based on sub-group from main studies)											
1 (Veltman-Verhulst et al, 2006)	Meta-analysis of 2 studies	Very serious[1,2,3,4]	None	Serious[9]	None	None	47/172 (27.3%)	24/159 (15.1%)	RR 1.83 (1.18 to 2.84)	125 more per 1000 (from 27 more to 278 more)	Very low
Live full-term singleton birth (Male factor infertility based on sub-group from main studies)											
1 (Bensdorp et al, 2007)	Meta-analysis of 2 studies	Very serious[1,2,3,4]	None	Serious[9]	Serious[5]	None	9/25 (36%)	11/28 (39.3%)	RR 0.92 (0.46 to 1.83)	31 fewer per 1000 (from 212 fewer to 326 more)	Very low
Pregnancy rates											
2 (Goverde et al, 2005; Guzick et al, 1999)	RCT	Very serious[1,2,3,4]	None	Serious[6]	None	None	110/317 (34.7%)	70/317 (22.1%)	RR 1.57 (1.22 to 2.03)	126 more per 1000 (from 49 more to 227 more)	Very low

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	IUI with ovarian stimulation	IUI without stimulation	Relative (95% CI)	Absolute (95% CI)	
Pregnancy rates (Unexplained infertility based on sub-group from main studies)											
2(Veltman-Verhulst et al, 2006)	Meta-analysis of 2 studies	Very serious[1,2,3,4]	None	Serious[6]	None	None	47/172 (27.3%)	24/159 (15.1%)	RR 1.83 (1.18 to 2.84)	125 more per 1000 (from 27 more to 278 more)	Very low
Pregnancy rates (Male factor infertility based on sub-group from main studies)											
1 (Bensdorp et al, 2007)	Meta-analysis of 3 studies	Very serious[1,2,3,4]	None	Serious[6]	Serious[5]	None	49/180 (27.2%)	42/199 (21.1%)	RR 1.3 (0.91 to 1.85)	63 more per 1000 (from 19 fewer to 179 more)	Very low
Multiple births											
2 (Goverde et al, 2005; Guzick et al, 1999)	RCT	Very serious[1,2,3,4]	Serious	Very serious[10]	None	None	33/154 (21.4%) per pregnancy	2/93 (2.2%) per pregnancy	RR 10.51 (2.53 to 43.7)	205 more per 1000 (from 33 more to 918 more)	Very low
							33/550 (6%) per woman	2/553 (0.36%) per woman	RR 16.62 (4.01 to 68.85)	56 more per 1000 (from 11 more to 245 more)	

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	IUI with ovarian stimulation	IUI without stimulation	Relative (95% CI)	Absolute (95% CI)	
IUI with stimulation vs. IUI natural cycle											
1 (Goverde et al, 2005)	RCT	Very serious[1,2,3]	None	Serious[10]	None	None	9/33 (27.3%) per pregnancy	1/28 (3.6%) per pregnancy	RR 7.64 (1.03 to 56.63)	237 more per 1000 (from 1 more to 1000 more)	Very low
							9/85 (10.6%) per woman	1/86 (1.2%) per woman	RR 9.11 (1.18 to 70.32)	94 more per 1000 (from 2 more to 806 more)	
Superovulation vs. no superovulation (IUI or ICSI)											
1 (Guzick et al, 1999)	RCT	Very serious[1,2,3]	None	Serious[10]	None	None	24/121 (19.8%) per pregnancy	1/65 (1.5%) per pregnancy	RR 12.89 (1.78 to 93.15)	183 more per 1000 (from 12 more to 1000 more)	Very low
							24/465 (5.2%) per woman	1/467 (0.21%) per woman	RR 24.1 (3.27 to 177.43)	49 more per 1000 (from 5 more to 378 more)	

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	IUI with ovarian stimulation	IUI without stimulation	Relative (95% CI)	Absolute (95% CI)	
Pre-term birth per livebirth											
1(Guzick et al, 1999)	RCT	Serious[1,3]	None	None	Serious[5]	None	9/50 (18%) per livebirth	2/30 (6.7%) per livebirth	RR 2.7 (0.62 to 11.67)	113 more per 1000 (from 25 fewer to 711 more)	Low
							9/231 (3.9%) per woman	2/234 (0.85%) per woman	RR 4.56 (1 to 20.87)	30 more per 1000 (from 0 more to 170 more)	
Stillbirth per pregnancy											
1 (Guzick et al, 1999)	RCT	Serious[1,3]	None	None [6]	Serious[5]	None	0/76 (0%)	1/40 (2.5%)	RR 0.18 (0.01 to 4.26)	21 fewer per 1000 (from 25 fewer to 82 more)	Low
Miscarriage per pregnancy											
1 (Guzick et al, 1999)	RCT	Serious[1,3]	None	None[6]	Serious[5]	None	22/77 (28.6%) per pregnancy	6/42 (14.3%) per pregnancy	RR 2 (0.88 to 4.54)	143 more per 1000 (from 17 fewer to 506 more)	Low
							22/230 (9.6%) per woman	6/232 (2.6%) per woman	RR 3.7 (1.53 to 8.95)	70 more per 1000 (from 14 more to 206 more)	

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	IUI with ovarian stimulation	IUI without stimulation	Relative (95% CI)	Absolute (95% CI)	
Miscarriage per woman (Male factor infertility sub-group from main studies)											
1 (Cohlen et al, 1999)	RCT	Very serious[1]	None	None	Serious[5]	None	3/36 (8.3%)	3/38 (7.9%)	RR 1.06 (0.23 to 4.89)	5 more per 1000 (from 61 fewer to 307 more)	Very low
Ectopic pregnancy per pregnancy											
1 (Guzick et al, 1999)	RCT	Serious[1,3]	None	None	Serious[5]	None	4/77 (5.2%) per pregnancy	2/42 (4.8%) per pregnancy	RR 1.09 (0.21 to 5.71)	4 more per 1000 (from 38 fewer to 224 more)	Low
							4/230 (1.7%) per woman	2/232 (0.86%) per woman	RR 2.02 (0.37 to 10.91)	9 more per 1000 (from 5 fewer to 85 more)	
Ectopic pregnancy per woman (Unexplained infertility sub-group from main studies)											
1 (Guzick et al, 1999)	RCT	Very serious[1,8]	None	None	Serious[5]	None	3/111 (2.7%)	0/100 (0%)	RR 6.31 (0.33 to 120.72)	-	Very low

[1] Blinding of women or practitioners was not possible.

[2] High drop-out rate and not feasible to undertake ITT analysis

[3] In Guzick et al., 1999 no power analysis reported

[4] In Goverde et al., 2005 power calculation for pregnancy rate per cycle

[5] Wide confidence intervals due to low event rate

[6] In Guzick et al., 1999 the outcome 'pregnancy' reported does not match a GDG/technical team agreed definition

[7] Combined IUI and ICI group used.

[8] Sub-group analysis so not powered to examine outcome

[9] Live birth recorded rather than live full-term singleton birth

[10] Multiple pregnancy reported rather than multiple births

Table I.15.1 GRADE findings for pre-treatment vs. no pre-treatment in women receiving IVF treatment for the first time

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Live full-term singleton birth											
Combined oral contraceptive (antagonist protocol) vs. no pre-treatment (antagonist protocol)											
1 (Smulders et al., 2010)	Cochrane review of 1 RCT	Serious [a]	-	Serious [b]	Serious [c]	No	3/21 (14%) women	7/24 (29%) women	Peto OR 0.4 (0.1 to 1.7)	141 fewer per 1000 (from 248 fewer to 126 more)	Very low
Progesterone (agonist) vs. placebo or no treatment (agonist)											
1 (Smulders et al., 2010)	Cochrane review of 2 RCTs	Serious [a]	None	Serious [b]	Serious [c]	No	24/110 (22%) women	19/112 (17%) women	Peto OR 1.4 (0.7 to 2.6)	47 more per 1000 (from 46 fewer to 179 more)	Very low
Progesterone (antagonist) vs. placebo or no treatment (antagonist)											
1 (Smulders et al., 2010)	Cochrane review of 1 RCT	Serious [a]	-	Serious [b]	Serious [c]	No	5/23 (22%) women	7/24 (29%) women	Peto OR 0.7 (0.2 to 2.5)	73 fewer per 1000 (from 219 fewer to 216 more)	Very low
Oestrogen (antagonist) vs. no treatment (antagonist)											
1 (Smulders et al., 2010)	Cochrane review of 1 RCT	Serious [a]	-	Serious [b]	Serious [c]	No	3/25 (12%) women	7/24 (29%) women	Peto OR 0.4 (0.1 to 1.4	163 fewer per 1000 (from 256 fewer to 76 more)	Very low

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Clinical pregnancy											
Combined oral contraceptive (agonist protocol) vs. no pre-treatment (agonist protocol)											
1 (Smulders et al., 2010)	Cochrane review of 1 RCT	Serious [a]	-	Serious [d]	Serious [c]	No	19/51 (37%) women	17/51 (33%) women	Peto OR 1.2 (0.5 to 2.7)	40 more per 1000 (from 124 fewer to 237 more)	Very low
Combined oral contraceptive (antagonist protocol) vs. no pre-treatment (antagonist protocol)											
2 (Nyboe Andersen et al., 2011 and Smulders et al., 2010)	1 RCT and a Cochrane review of 4 RCTs	Serious [a]	None	Serious [d]	Serious [c]	No	142/629 (23%) women	195/626 (31%) women	RR 0.7 (0.6 to 0.9)	87 fewer per 1000 (from 40 fewer to 125 fewer)	Very low
Progesterone (agonist) vs. placebo or no treatment (agonist)											
1 (Smulders et al., 2010)	Cochrane review of 3 RCTs	Serious [a]	None	None	None	No	53/187 (28%) women	31/187 (17%) women	Peto OR 2.0 (1.2 to 3.2)	114 more per 1000 (from 27 more to 221 more)	Moderate
Progesterone (antagonist) vs. placebo or no treatment (antagonist)											
1 (Smulders et al., 2010)	Cochrane review of 1 RCT	Serious [a]	-	None	Serious [c]	No	7/23 (30%) women	11/24 (46%) women	Peto OR 0.5 (0.2 to 1.7)	149 fewer per 1000 (from 333 fewer to 130 more)	Low

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Progesterone (no down-regulation) vs. placebo or no treatment (no down-regulation)											
1 (Smulders et al., 2010)	Cochrane review of 1 RCT	Serious [a]	-	None	Serious [c]	No	3/21 (14%) women	4/21 (19%) women	Peto OR 0.7 (0.1 to 3.6)	46 fewer per 1000 (from 159 fewer to 265 more)	Low
Oestrogen (antagonist) vs. no treatment (antagonist)											
1 (Smulders et al., 2010)	Cochrane review of 2 RCTs	Serious [a]	Very serious [e]	None	Serious [c]	No	20/72 (28%) women	22/67 (33%) women	Peto OR 0.8 (0.4 to 1.6)	50 fewer per 1000 (from 172 fewer to 114 more)	Very low
Adverse pregnancy outcome											
Combined oral contraceptive (antagonist protocol) vs. no pre-treatment (antagonist protocol) (miscarriages and/or stillbirths)											
1 (Smulders et al., 2010)	Cochrane review of 4 RCTs	Serious [a]	Serious [f]	None	Serious [c]	No	35/420 (8%) women	29/427 (7%) women	Peto OR 1.3 (0.8 to 2.1)	16 more per 1000 (from 15 fewer to 66 more)	Very low
							Not reported per clinical pregnancy				
Progesterone (agonist) vs. placebo or no treatment (agonist) (miscarriages and/or stillbirths)											
1 (Smulders et al., 2010)	Cochrane review of 2 RCTs	Serious [a]	None	None	Serious [c]	No	9/110 (8%) women	4/112 (4%) women	Peto OR 2.2 (0.7 to 6.7)	39 more per 1000 (from 10 fewer to 163 more)	Low
							Not reported per clinical pregnancy				

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Progesterone (antagonist) vs. placebo or no treatment (antagonist) (miscarriages and/or stillbirths)											
1 (Smulders et al., 2010)	Cochrane review of 1 RCT	Serious [a]	-	None	Serious [c]	No	2/23 (9%) women	5/24 (21%) women	Peto OR 0.4 (0.1 to 1.9)	115 fewer per 1000 (from 188 fewer to 127 more)	Low
							2/7 (29%) pregnancies	5/11 (46%) pregnancies	Peto OR 0.5 (0.1 to 3.4)	156 fewer per 1000 (from 392 fewer to 283 more)	
Progesterone (no down-regulation) vs. placebo or no treatment (no down-regulation) (miscarriages and/or stillbirths)											
1 (Smulders et al., 2010)	Cochrane review of 1 RCT	Serious [a]	-	None	Serious [c]	No	1/21 (5%) women	1/21 (5%) women	Peto OR 1.0 (0.1 to 16.6)	0 fewer per 1000 (from 45 fewer to 405 more)	Low
							1/3 (33%) pregnancies	1/4 (25%) pregnancies	Peto OR 1.4 (0.1 to 30.5)	71 more per 1000 (from 227 fewer to 660 more)	
Oestrogen (antagonist) vs. no treatment (antagonist) (miscarriages and/or stillbirths)											
1 (Smulders et al., 2010)	Cochrane review of 1 RCT	Serious [a]	-	None	Serious [c]	No	1/25 (4%) women	5/24 (21%) women	Peto OR 0.2 (0.0 to 1.2)	154 fewer per 1000 (from 198 fewer to 27 more)	Low
							Not reported per clinical pregnancy				

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Multiple pregnancies (the number of pregnancies with more than one fetus)											
Combined oral contraceptive (antagonist protocol) vs. no pre-treatment (antagonist protocol)											
1 (Smulders et al., 2010)	Cochrane review of 1 RCT	Serious [a]	-	None	Serious [c]	No	2/21 (10%) women	1/24 (4%) women	Peto OR 2.3 (0.2 to 23.7)	50 more per 1000 (from 32 fewer to 465 more)	Low
							Not reported per clinical pregnancy				
Progesterone (antagonist) vs. placebo or no treatment (antagonist)											
1 (Smulders et al., 2010)	Cochrane review of 1 RCT	Serious [a]	-	None	Serious [c]	No	1/23 (4%) women	1/24 (4%) women	Peto OR 1.0 (0.1 to 17.2)	2 more per 1000 (from 39 fewer to 387 more)	Low
							1/7 (14%) pregnancies	1/11 (9%) pregnancies	Peto OR 1.6 (0.1 to 30.8)	50 more per 1000 (from 82 fewer to 664 more)	
Oestrogen (antagonist) vs. no treatment (antagonist)											
1 (Smulders et al., 2010)	Cochrane review of 1 RCT	Serious [a]	-	None	Serious [c]	No	0/25 (0%) women	1/24 (4%) women	Peto OR 0.1 (0.0 to 6.6)	36 fewer per 1000 (from 42 fewer to 180 more)	Low
							0/4 (0%) pregnancies	1/11 (9%) pregnancies	Peto OR 0.3 (0 to 21.5)	Not calculable	

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Multiple births (the number of babies born from a multiple pregnancy)											
No evidence was reported											
Ovarian hyperstimulation syndrome (OHSS)											
Combined oral contraceptive (antagonist protocol) vs. no pre-treatment (antagonist protocol)											
1 (Smulders et al., 2010)	Cochrane review of 1 RCT	Serious [a]	-	None	Serious [c]	No	3/117 (3%) women	2/117 (2%) women	Peto OR 1.5 (0.3 to 8.8)	8 more per 1000 (from 13 fewer to 116 more)	Low
Oestrogen (antagonist protocol) vs. no pre-treatment (antagonist protocol)											
1 (Smulders et al., 2010)	Cochrane review of 1 RCT	Serious [a]	-	None	-	No	0/16 (0%) women	0/6 (0%) women	Not calculable		Moderate
Congenital abnormalities											
No evidence reported											
Patient satisfaction											
No evidence reported											
Health related quality of life											
No evidence reported											
Anxiety and/or depression											
No evidence reported											

[a] 12/23 studies did not report the method of randomisation used. Seven studies did not adhere to a power calculation, and in five other studies adherence to a power calculation was not clear

[b] May include pre-term births and births from multiple pregnancies – births from multiple pregnancies were counted as one live birth event per multiple pregnancy, regardless of the number of babies born

[c] 95% confidence intervals hit or cross 0.75 and 1, and/or 1 and 1.25

[d] This data includes ongoing pregnancy data when clinical pregnancy data was not reported in a study

[e] I^2 value is greater than 66%

[f] I^2 value is greater than 33% but less than 66%

Table I. 15.2 GRADE findings for pre-treatment vs. no pre-treatment in women with a previous low response to IVF treatment

Quality assessment							**Summary of findings**				
							No. of patients/women		**Effect**		**Quality**
No. of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Intervention**	**Comparator**	**Relative (95% CI)**	**Absolute (95% CI)**	
Live full-term singleton birth											
Combined oral contraceptive (antagonist protocol) vs. no pre-treatment (antagonist protocol)											
1 (Smulders et al., 2010)	Cochrane review of 1 RCT	Serious [a]	-	Serious [b]	Serious [c]	No	8/27 (30%) women	5/27 (19%) women	Peto OR 1.8 (0.5 to 6.3)	107 more per 1000 (from 78 fewer to 402 more)	Very low
Clinical pregnancy											
Combined oral contraceptive (antagonist protocol) vs. no pre-treatment (antagonist protocol)											
1 (Smulders et al., 2010)	Cochrane review of 1 RCT	Serious [a]	-	Serious [d]	Serious [c]	No	9/27 (33%) women	6/27 (22%) women	Peto OR 1.7 (0.5 to 5.6)	107 more per 1000 (from 91 fewer to 393 more)	Very low

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Adverse pregnancy outcome											
Combined oral contraceptive (antagonist protocol) vs. no pre-treatment (antagonist protocol) (miscarriages and/or stillbirths)											
1 (Smulders et al., 2010)	Cochrane review of 1 RCT	Serious [a]	-	None	Serious [c]	No	1/27 (4%) women	1/27 (4%) women	Peto OR 1.0 (0.1 to 16.4)	0 fewer per 1000 (from 35 fewer to 350 more)	Low
							1/9 (11%) pregnancies	1/6 (17%) pregnancies	Peto OR 0.6 (0.0 to 12.0)	53 fewer per 1000 (from 161 fewer to 540 more)	
Multiple pregnancies (the number of pregnancies with more than one fetus)											
Combined oral contraceptive (antagonist protocol) vs. no pre-treatment (antagonist protocol)											
1 (Smulders et al., 2010)	Cochrane review of 1 RCT	Serious [a]	-	None	Serious [c]	No	2/27 (7%) women	1/27 (4%) women	Peto OR 2.0 (0.2 to 20.1)	34 more per 1000 (from 29 fewer to 399 more)	Low
							2/9 (22%) pregnancies	1/6 (17%) pregnancies	Peto OR 1.4 (0.1 to 16.8)	50 more per 1000 (from 145 fewer to 604 more)	
Multiple births (the number of babies born from a multiple pregnancy)											
No evidence reported											
Ovarian hyperstimulation syndrome (OHSS)											
No evidence reported											

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Congenital abnormalities											
No evidence reported											
Patient satisfaction											
No evidence reported											
Health related quality of life											
No evidence reported											
Anxiety and/or depression											
No evidence reported											

[a] 12/23 studies did not report the method of randomisation used. Seven studies did not adhere to a power calculation, and in five other studies adherence to a power calculation was not clear

[b] May include pre-term births and births from multiple pregnancies – births from multiple pregnancies were counted as one live birth event per multiple pregnancy, regardless of the number of babies born

[c] 95% confidence intervals hit or cross 0.75 and 1, and/or 1 and 1.25

[d] This data includes ongoing pregnancy data when clinical pregnancy data was not reported in a study

Table I.15.3 GRADE findings for comparison of different types of pre-treatment

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Live full-term singleton birth											
Combined oral contraceptive (antagonist) vs. progesterone (antagonist) (first treatment)											
1 (Smulders et al., 2010)	Cochrane review of 1 RCT	Serious [a]	-	Serious [b]	Serious [c]	No	3/21 (14%) women	5/23 (22%) women	Peto OR 0.6 (0.1 to 2.8)	72 fewer per 1000 (from 183 fewer to 219 more)	Very low
Combined oral contraceptive (antagonist) vs. oestrogen (antagonist) (first treatment)											
1 (Smulders et al., 2010)	Cochrane review of 1 RCT	Serious [a]	-	Serious [b]	Serious [c]	No	3/21 (14%) women	3/25 (12%) women	Peto OR 1.2 (0.2 to 6.7)	23 more per 1000 (from 91 fewer to 357 more)	Very low
Progestogen (antagonist) vs. oestrogen (antagonist) (first treatment)											
1 (Smulders et al., 2010)	Cochrane review of 1 RCT	Serious [a]	-	Serious [b]	Serious [c]	No	5/23 (22%) women	3/25 (12%) women	Peto OR 2.0 (0.4 to 8.9)	93 more per 1000 (from 63 fewer to 429 more)	Very low
Clinical pregnancy											
Combined oral contraceptive (antagonist) vs. progesterone (antagonist) (first treatment)											
1 (Smulders et al., 2010)	Cochrane review of 1 RCT	Serious [a]	-	None	Serious [c]	No	5/21 (24%) women	7/23 (30%) women	Peto OR 0.7 (0.2 to 2.7)	65 fewer per 1000 (from 228 fewer to 235 more)	Low

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Combined oral contraceptive (antagonist) vs. oestrogen (antagonist) (first treatment)											
1 (Smulders et al., 2010)	Cochrane review of 1 RCT	Serious [a]	-	None	Serious [c]	No	5/21 (24%) women	4/25 (16%) women	Peto OR 1.6 (0.4 to 6.9)	76 more per 1000 (from 93 fewer to 408 more)	Low
Progestogen (antagonist) vs. oestrogen (antagonist) (first treatment)											
1 (Smulders et al., 2010)	Cochrane review of 1 RCT	Serious [a]	-	None	Serious [c]	No	7/23 (30%) women	4/25 (16%) women	Peto OR 2.2 (0.6 to 8.4)	138 more per 1000 (from 59 fewer to 457 more)	Low
Adverse pregnancy outcome											
Combined oral contraceptive (antagonist) vs. progesterone (antagonist) (miscarriages and/or stillbirths) (first treatment)											
1 (Smulders et al., 2010)	Cochrane review of 1 RCT	Serious [a]	-	None	Serious [c]	No	2/21 (10%) women	2/23 (9%) women	Peto OR 1.1 (0.1 to 8.4)	8 more per 1000 (from 74 fewer to 358 more)	Low
							2/5 (40%) pregnancies	2/7 (29%) pregnancies	Peto OR 1.6 (0.2 to 16.5)	105 more per 1000 (from 226 fewer to 583 more)	

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Combined oral contraceptive (antagonist) vs. oestrogen (antagonist) (miscarriages and/or stillbirths) (first treatment)											
1 (Smulders et al., 2010) (Smulders et al., 2010)	Cochrane review of 1 RCT	Serious [a]	-	None	Serious [c]	No	2/21 (10%) women	1/25 (4%) women	Peto OR 2.4 (0.2 to 24.8)	52 more per 1000 (from 30 fewer to 468 more)	Low
							2/5 (40%) pregnancies	1/4 (25%) pregnancies	Peto OR 1.8 (0.1 to 25.3)	128 more per 1000 (from 208 fewer to 644 more)	
Progestogen (antagonist) vs. oestrogen (antagonist) (miscarriages and/or stillbirths) (first treatment)											
1 (Smulders et al., 2010)	Cochrane review of 1 RCT	Serious [a]	-	None	Serious [c]	No	2/23 (9%) women	1/25 (4%) women	Peto OR 2.2 (0.2 to 22.2)	44 more per 1000 (from 31 fewer to 440 more)	Low
							2/7 (29%) pregnancies	1/4 (25%) pregnancies	Peto OR 1.2 (0.1 to 16.3)	32 more per 1000 (from 224 fewer to 595 more)	

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Multiple pregnancies (the number of pregnancies with more than one fetus)											
Combined oral contraceptive (antagonist) vs. progesterone (antagonist) (first treatment)											
1 (Smulders et al., 2010)	Cochrane review of 1 RCT	Serious [a]	-	None	Serious [c]	No	2/21 (10%) women	1/23 (4%) women	Peto OR 2.2 (0.2 to 22.6)	48 more per 1000 (from 34 fewer to 463 more)	Low
							2/5 (40%) pregnancies	1/7 (14%) pregnancies	Peto OR 3.5 (0.3 to 44.5)	227 more per 1000 (from 98 fewer to 738 more)	
Combined oral contraceptive (antagonist) vs. oestrogen (antagonist) (first treatment)											
1 (Smulders et al., 2010)	Cochrane review of 1 RCT	Serious [a]	-	None	Serious [c]	No	2/21 (10%) women	0/25 (0%) women	Peto OR 9.4 (0.6 to 156.7)	Not calculable	Low
							2/5 (40%) pregnancies	0/4 (0%) pregnancies	Peto OR 7.8 (0.4 to 154.3)	Not calculable	

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Progestogen (antagonist) vs. oestrogen (antagonist) (first treatment)											
1 (Smulders et al., 2010)	Cochrane review of 1 RCT	Serious [a]	-	None	Serious [c]	No	1/23 (4%) women	0/25 (0%) women	Peto OR 8.1 (0.2 to 407.6)	Not calculable	Low
							1/7 (14%) pregnancies	0/4 (0%) pregnancies	Peto OR 4.8 (0.1 to 283)	Not calculable	
Multiple births (the number of babies born from a multiple pregnancy)											
No evidence was reported											
Ovarian hyperstimulation syndrome (OHSS)											
No evidence was reported											
Congenital abnormalities											
No evidence was reported											
Patient satisfaction											
No evidence was reported											
Health related quality of life											
No evidence was reported											
Anxiety and/or depression											
No evidence was reported											

[a] 12/23 studies did not report the method of randomisation used. Seven studies did not adhere to a power calculation, and in five other studies adherence to a power calculation was not clear

[b] May include pre-term births and births from multiple pregnancies – births from multiple pregnancies were counted as one live birth event per multiple pregnancy, regardless of the number of babies born

[c] 95% confidence intervals hit or cross 0.75 and 1, and/or 1 and 1.25

Table I.15.4 GRADE findings for comparison of down regulated vs. non down regulated cycles (with or without clomifene citrate)

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Live full-term singleton birth											
Down-regulation (with clomifene citrate) vs. no down-regulation (with clomifene citrate)											
1 (Long et al., 1995)	RCT	Very serious [a, b, c]	-	None	Serious [d]	No	1/36 (3%) women	4/36 (11%) women	RR 0.3 (0.0 to 2.1)	83 fewer per 1000 (from 108 fewer to 126 more)	Very low
Clinical pregnancy											
Down-regulation (without clomifene citrate) vs. no down-regulation (without clomifene citrate)											
4 (Antoine et al., 1990; Neveu et al., 1987; Polson et al., 1991; van de Helder et al., 1990)	RCTs	Very serious [a, b, c]	None	Serious [e]	None	No	59/270 (22%) women	20/178 (11%) women	RR 2.0 (1.2 to 3.2)	116 more per 1000 (from 29 more to 255 more)	Very low
Down-regulation (with clomifene citrate) vs. no down-regulation (with clomifene citrate)											

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
4 (Dhont et al., 1995; Grochowski et al., 1999, Long et al., 1995; Weigert et al., 2002)	RCTs	Very serious [a, b, c]	Serious [f]	Serious [e]	Serious [d]	No	128/455 (28%) women	128/471 (27%) women	RR 1.1 (0.8 to 1.5) [g]	14 more per 1000 (from 65 fewer to 122 more)	Very low
Adverse pregnancy outcome											
Down-regulation (with clomifene citrate) vs. no down-regulation (with clomifene citrate) (miscarriage)											
1 (Long et al., 1995)	RCT	Very serious [a, b, c]	-	None	Serious [d]	No	2/36 (6%) women	0/36 (0%) women	RR 5.0 (0.3 to 100.6)	Not calculable	Very low
							2/5 (40%) pregnancies	0/5 (0%) pregnancies	RR 5.0 (0.3 to 83.7)	Not calculable	
Down-regulation (with clomifene citrate) vs. no down-regulation (with clomifene citrate) (ectopic pregnancy)											
1 (Long et al., 1995)	RCT	Very serious [a, b, c]	-	None	Serious [d]	No	0/36 (0%) women	1/36 (3%) women	RR 0.3 (0.0 to 7.9)	19 fewer per 1000 (from 28 fewer to 192 more)	Very low

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
							0/5 (0%) pregnancies	1/5 (20%) pregnancies	RR 0.3 (0.0 to 6.7)	134 fewer per 1000 (from 196 fewer to 1000 more)	
Down-regulation (with clomifene citrate) vs. no down-regulation (with clomifene citrate) (early pregnancy loss)											
2 (Harrison et al., 1994 and Weigert et al., 2002)	RCTs	Very serious [a, b, c]	None	None	Serious [d]	Yes [h]	10/190 (5%) women	14/204 (7%) women	RR 0.8 (0.4 to 1.7)	16 fewer per 1000 (from 45 fewer to 47 more)	Very low
							7/41 (17%) pregnancies [i]	10/54 (19%) pregnancies [i]	RR 0.9 (0.4 to 2.2) [i]	15 fewer per 1000 (from 115 fewer to 224 more) [i]	
Multiple pregnancies (the number of pregnancies with more than one fetus)											
Down-regulation (without clomifene citrate) vs. no down-regulation (without clomifene citrate)											
1 (Antoine et al., 1990)	RCT	Very serious [a, b, c]	None	None	Serious [d]	No	5/90 (6%) Women	0/90 (0%) women	RR 11.0 (0.6 to 196.0)	Not calculable	Very low

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
							5/19 pregnancies	0/11 pregnancies	RR 6.6 (0.4 to 109.1)	Not calculable	
Down-regulation (with clomifene citrate) vs. no down-regulation (with clomifene citrate)											
2 (Harrison et al., 1994; Grochowski et al., 1999)	RCTs	Very serious [a, b, c]	Serious [f]	None	Serious [d]	Yes [h]	8/210 (4%) women	10/214 (5%) women	RR 0.9 (0.2 to 3.1) [g]	7 fewer per 1000 (from 36 fewer to 100 more)	Very low
			-				3/38 pregnancies [j]	7/41 pregnancies [j]	RR 0.5 (0.1 to 1.7) [j]	92 fewer per 1000 (from 149 fewer to 113 more) [j]	
Multiple births (the number of babies born from a multiple pregnancy)											
Down-regulation (with clomifene citrate) vs. no down-regulation (with clomifene citrate)											
1 (Long et al., 1995)	RCT	Very serious [a, b, c]	-	None	Serious [d]	No	2/3 (67%) babies	0/4 (0%) babies	RR 6.3 (0.4 to 96.5)	Not calculable	Very low
Ovarian hyperstimulation syndrome (OHSS)											
Down-regulation (with clomifene citrate) vs. no down-regulation (with clomifene citrate)											

Quality assessment							Summary of findings				
							No. of patients/women		Effect		
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	Quality
2 Grochowski et al., 1999; Weigert et al., 2002)	RCTs	Very serious [a, b, c]	None	None	None	No	17/300 (6%) women	4/318 (1%) women	RR 4.2 (1.5 to 11.7)	41 more per 1000 (from 6 more to 135 more)	Low
Congenital abnormalities											
No evidence reported											
Patient satisfaction											
Down-regulation (without clomifene citrate) vs. no down-regulation (with clomifene citrate)											
1 (Hojgaard et al., (2001)	Questionnaire	Serious [k]	-	None	None	Yes [l]	60/64 (94%) women	139/141 (99%) women	RR 1.0 (0.9 to 1.0)	49 fewer per 1000 (from 108 fewer to 20 more)	Moderate
Live full-term singleton birth											
GnRH antagonist vs. long course GnRH agonist											
Live full-term singleton birth											
GnRH antagonist vs. long course GnRH agonist											

[a] Blinding was not reported
[b] Allocation concealment not reported or inadequate
[c] A power calculation was not reported
[d] 95% confidence intervals hit or cross 0.75 and 1, and/or 1 and 1.25
[e] Definition of clinical pregnancy was not reported
[f] I^2 value is greater than 33% but less than 66%

[g] Random effects model reported as I^2 value is greater than 33%
[h] The Harrison (1994) study had three arms – one received triptoerlin (GnRH agonist), the second buserelin (GnRH agonist), and the third clomifene citrate. The multiple pregnancy and pregnancy loss results were the same for both of the GnRH agonist groups
[i] This is based on the Weigert et al. (2002) study only, as the Harrison et al. (1994) study did not report data per pregnancy
[j] This is based on the Grochowski et al. (1999) study only, as the Harrison et al. (1994) study did not report data per pregnancy
[k] Response rate was significantly higher in the clomifene citrate group
[l] This study was done as a follow up to a study by Ingerslev (2001) (comparison with unstimulated cycles) and unpublished data (comparison with CC cycles)

Table I.15.5 GRADE findings for comparison of antagonist and agonist down-regulated protocols

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Live full-term singleton birth											
GnRH antagonist vs. long course GnRH agonist											
2 (Al-Inany et al., 2011 and DiLuigi et al., 2011)	1 RCT and a Cochrane review of 9 RCTs	Very serious [a, b, c]	None	Serious [d]	None	No	228/850 (27%) women	224/719 (31%) women	RR 0.9 (0.8 to 1.0)	31 fewer per 1000 (from 69 fewer to 16 more)	Very low
GnRH antagonist + OCP vs. long course GnRH agonist											
1 (Garcia-Velasco, 2011)	RCT	None	-	Serious [d]	Very serious [e, f]	No	51/115 (44%) women	53/113 (47%) women	RR 1.0 (0.7 to 1.3)	23 fewer per 1000 (from 136 fewer to 122 more)	Very low
Clinical pregnancy											
GnRH antagonist vs. long course GnRH agonist (including low response)											

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
3 (Al-Inany et al., 2011; DiLuigi et al., 2011; Devesa et al., 2010; and Tehraninejad et al., 2011)	3 RCTs and a Cochrane review of 41 RCTs	Very serious [a, b, c]	None	None	None	No	1091/4035 (27%) women	963/3111 (31%) women	RR 0.9 (0.8 to 1.0)	31 fewer per 1000 (from 9 fewer to 50 fewer)	Low
GnRH antagonist vs. long course GnRH agonist (low response only)											
1 (Al-Inany et al., 2011)	Cochrane review of 6 RCTs	Very serious [a, b, c]	None	None	Serious [e]	No	67/473 (14%) women	80/446 (18%) women	OR 0.7 (0.5 to 1.0)	45 fewer per 1000 (from 83 fewer to 3 more)	Very low
GnRH antagonist + OCP vs. long course GnRH agonist											
2 (Al-Inany et al., 2011, Garcia-Velasco, 2011)	1 RCT and Cochrane review of 12 RCTs	Very serious [a, b, c]	None	None	Serious [f]	No	293/761 (39%) women	312/703 (44%) women	RR 0.9 (0.8 to 1.0)	49 fewer per 1000 (from 93 fewer to 4 more)	Very low
Adverse pregnancy outcome											
GnRH antagonist vs. long course GnRH agonist (miscarriage)											
1 (Al-Inany et al., 2011)	Cochrane review of 26 RCTs	Very serious [a, b, c]	None	None	Serious [e]	No	92/2861 (3%) women	88/2040 (4%) women	OR 0.8 (0.6 to 1.0)	10 fewer per 1000 (from 19 fewer to 2 more)	Very low

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
	Cochrane review of 27 RCTs						98/873 (11%) pregnancies	91/774 (12%) pregnancies	OR 1.0 (0.7 to 1.3)	4 fewer per 1000 (from 32 fewer to 31 more)	
GnRH antagonist + OCP vs. long course GnRH agonist (miscarriage)											
1 (Garcia-Velasco, 2011)	RCT	None	-	None	Very serious [e, f]	No	5/115 (4%) women	11/113 (10%) women	RR 0.5 (0.2 to 1.2)	54 fewer per 1000 (from 82 fewer to 23 more)	Low
							5/56 (9%) pregnancies	11/64 (17%) pregnancies	RR 0.5 (0.2 to 1.4)	83 fewer per 1000 (from 139 fewer to 69 more)	
GnRH antagonist vs. GnRH agonist (abortion)											
1 (Tehraninejad et al., 2011)	RCT	Very serious [a, b]	-	None	Serious [e]	No	18/150 (12%) women	9/150 (6%) women	RR 2.0 (0.9 to 4.3)	60 more per 1000 (from 4 fewer to 199 more)	Very low
							18/51 (35%) pregnancies	9/53 (17%) pregnancies	RR 2.1 (1.0 to 4.2)	183 more per 1000 (from 5 fewer to 542 more)	

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Multiple pregnancies (the number of pregnancies with more than one fetus)											
GnRH antagonist + OCP vs. long course GnRH agonist											
1 (Garcia-Velasco, 2011)	RCT	None	-	None	Very serious [e, f]	No	15/115 (13%) women	18/113 (16%) women	RR 0.8 (0.4 to 1.5)	29 fewer per 1000 (from 91 fewer to 86 more)	Low
							15/56 (27%) pregnancies	18/64 (28%) pregnancies	RR 1.0 (0.5 to 1.7)	14 fewer per 1000 (from 132 fewer to 200 more)	
Multiple births (the number of babies born from a multiple pregnancy)											
No evidence was reported											
Ovarian hyperstimulation syndrome (OHSS)											
GnRH antagonist vs. long course GnRH agonist											
1 (Al-Inany et al., 2011 and Tehraninejad et al., 2011)	1 RCT and Cochrane review of 29 RCTs	Very serious [a, b, c]	Very serious [g]	None	-	No	110/3315 (3%) women	168/2402 (7%) women	RR 0.6 (0.4 to 0.8) [h]	31 fewer per 1000 (from 15 fewer to 43 fewer)	Very low
Congenital abnormalities											
No evidence was reported											

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Intervention**	**Comparator**	**Relative (95% CI)**	**Absolute (95% CI)**	
Patient satisfaction											
No evidence was reported											
Health related quality of life											
No evidence was reported											
Anxiety and/or depression											
No evidence was reported											

[a] Blinding was not clearly reported in all studies

[b] Allocation concealment was not clearly reported in all studies

[c] Method of randomisation was not clearly reported in all studies

[d] May include births from multiple pregnancies and/or pre-term births

[e] 95% confidence intervals hit or cross 0.75 and 1.0, and/or 1.0 and 1.25

[f] A power calculation was performed, but not enough couples were recruited into the study

[g] I^2 value is greater 66%

[h] A random effects model is reported as the I^2 value is greater than 33%

Table I.15.6 GRADE finding for comparison of different types of down-regulation protocol (including long, short, ultra-short, and stop protocols)

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Live full-term singleton birth											
Long vs. short protocol											
1 (Maheshwari et al., 2011)	Cochrane review of 3 RCTs	Very serious [a, b, c]	None	Serious [d]	Serious [e]	No	27/124 (22%) women	17/127 (13%) women	OR 1.8 (0.9 to 3.5)	84 more per 1000 (from 8 fewer to 217 more)	Very low
Long vs. ultra-short protocol											
1 (Maheshwari et al., 2011)	Cochrane review of 1 RCTs	Serious [a]	-	Serious [d]	Serious [e]	No	15/76 (20%) women	9/74 (12%) women	OR 1.8 (0.7 to 4.4)	76 more per 1000 (from 31 fewer to 255 more)	Very low
Long (luteal) vs. long (follicular)											
1 (Maheshwari et al., 2011)	Cochrane review of 1 RCTs	Very serious [a, b]	-	Serious [d]	Serious [e]	No	17/96 (18%) women	13/127 (10%) women	OR 1.9 (0.9 to 4.1)	75 more per 1000 (from 12 fewer to 216 more)	Very low
Clinical pregnancy											
Long vs. short protocol											
1 (Maheshwari et al., 2011)	Cochrane review of 17 RCTs	Very serious [a, b, c]	Serious [f]	None	None	No	176/725 (24%) women	126/712 (18%) women	OR 1.5 (1.2 to 1.9) [g]	66 more per 1000 (from 21 more to 116 more)	Very low

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Long vs. ultra-short protocol											
1 (Maheshwari et al., 2011)	Cochrane review of 2 RCTs	Very serious [a, b, c]	None	None	Serious [e]	No	25/113 (22%) women	18/117 (15%) women	OR 1.6 (0.8 to 3.0)	67 more per 1000 (from 27 fewer to 203 more)	Very low
Long (luteal) vs. long (follicular)											
1 (Maheshwari et al., 2011)	Cochrane review of 4 RCTs	Very serious [a, b, c]	Serious [f]	None	Serious [e]	No	66/281 (23%) women	64/288 (31%) women	OR 1.1 (0.7 to 1.6) [g]	12 more per 1000 (from 50 fewer to 90 more)	Very low
Long (continued GnRHa) vs. long (stop GnRHa)											
1 (Maheshwari et al., 2011)	Cochrane review of 3 RCTs	Very serious [a, b]	None	None	Serious [e]	No	21/132 (16%) women	26/132 (20%) women	OR 0.8 (0.4 to 1.4)	38 fewer per 1000 (from 106 fewer to 65 more)	Very low
Long (continued GnRHa) vs. long (reduced dose GnRHa)											
1 (Maheshwari et al., 2011)	Cochrane review of 3 RCTs	Very serious [a, b]	None	None	Serious [e]	No	58/156 (37%) women	57/155 (37%) women	OR 1.0 (0.6 to 1.6)	5 more per 1000 (from 96 fewer to 116 more)	Very low
Adverse pregnancy outcomes											
No evidence was reported											
Multiple pregnancies (the number of pregnancies with more than one fetus)											
No evidence was reported											

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Multiple births (the number of babies born from a multiple pregnancy)											
No evidence was reported											
Ovarian hyperstimulation syndrome (OHSS)											
No evidence was reported											
Congenital abnormalities											
No evidence was reported											
Patient satisfaction											
No evidence was reported											
Health related quality of life											
No evidence was reported											
Anxiety and/or depression											
No evidence was reported											

[a] Blinding was not clearly reported in all studies

[b] Allocation concealment was not clearly reported in all studies

[c] Method of randomisation was not clearly reported in all studies

[d] May include births from multiple pregnancies and/or pre-term births

[e] 95% confidence intervals hit or cross 0.75 and 1.0, and/or 1.0 and 1.25

[f] I^2 value is greater than 33% but less than 66%

[g] A fixed effects model is reported in the Cochrane review as a Peto Odds Ratio was used. When recalculated as a random effects statistic, no difference in the odds ratio or absolute effect was found

Table I.15.7 GRADE findings for comparison of unstimulated IVF vs. stimulated IVF

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Live full-term singleton birth											
CC + hCG vs. natural cycle IVF + hCG											
1 (MacDougall et al., 1994)	RCT	Very serious [a, b, c]	-	Serious [d]	Serious [e]	No	2/16 (13%) women	0/14 (0%) women	RR 4.4 (0.2 to 84.8)	Not calculable	Very low
Clinical pregnancy											
CC + hCG vs. natural cycle IVF + hCG											
2 (Ingerslev et al., 2001, MacDougall et al., 1994)	RCTs	Very serious [a, b, c]	None	Serious [f]	None	No	22/84 (26%) women	4/78 (5%) women	RR 4.7 (1.8 to 12.2)	188 more per 1000 (from 40 more to 576 more)	Very low
GnRH agonist + FSH vs. natural cycle IVF + hCG (low response)											
2 (Morgia et al., 2004; Ragni et al., 2000)	RCT	Very serious [a, b, c]	None	Serious [g]	Serious [e]	No	9/77 (12%) women	9/66 (14%) women	RR 0.9 (0.4 to 2.1)	16 fewer per 1000 (from 86 fewer to 143 more)	Very low
Adverse pregnancy outcome											
No evidence reported											

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Multiple pregnancies (the number of pregnancies with more than one fetus)											
CC + hCG vs. natural cycle IVF + hCG											
1 (Ingerslev et al., 2001)	RCT	Serious [c]	-	None	Serious [e]	No	2/68 (3%) women	0/64 (0%) women	RR 4.7 (0.2 to 96.3)	Not calculable	Low
							2/20 (10%) pregnancies	0/4 (0%) pregnancies	RR 1.2 (0.07 to 21.1)	Not calculable	
Multiple births (the number of babies born from a multiple pregnancy)											
No evidence reported											
Ovarian hyperstimulation syndrome (OHSS)											
No evidence reported											
Congenital abnormalities											
No evidence reported											
Patient satisfaction											
GnRH agonist + FSH/hMG + hCG vs. natural cycle or CC stimulated IVF + hCG											
1 (Hojgaard et al., 2001)	Questionnaire	Serious [h]	-	None	None	Yes [i]	60/64 (94%) women	139/141 (99%) women	RR 1.0 (0.9 to 1.0)	49 fewer per 1000 (from 108 fewer to 20 more)	Moderate
Health related quality of life											
No evidence reported											

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Anxiety and/or depression											
No evidence reported											

[a] Blinding was not reported
[b] Allocation concealment was not reported
[c] Power analysis was not reported
[d] May include pre-term births
[e] 95% confidence intervals hit or cross 0.75 and 1, and/or 1 and 1.25
[f] Clinical pregnancy defined in one study as 'live intrauterine pregnancy' and in the other it was not defined
[g] Clinical pregnancy defined in one study as 'ultrasound demonstration of the gerstational sac 4 weeks after embryo transfer'
[h] Response rate was significantly higher in the clomifene citrate group
[i] This study was done as a follow up to a study by Ingerslev (2001) (comparison with unstimulated cycles) and unpublished data (comparison with CC cycles)

Table I.15.8 GRADE findings for comparison of urinary vs. recombinant gonadotrophins

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Live full-term singleton birth											
rFSH vs. urinary gonadotrophins											
1 (Van Wely et al., 2011)	Cochrane review of 29 RCTs	Very serious [a]	None	Serious [b]	None	No	894/3796 (24%) women	868/3543 (24%) women	OR 1.0 (0.9 to 1.1)	9 fewer per 1000 (from 29 fewer to 11 more)	Very low

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Clinical pregnancy											
rFSH vs. urinary gonadotrophins											
1 (Van Wely et al., 2011)	Cochrane review of 42 RCTs	Very serious [a]	Very serious [c]	None	None	No	1353/4864 (28%) women	1301/4618 (28%) women	OR 1.0 (0.9 to 1.1) [d]	4 fewer per 1000 (from 21 fewer to 14 more)	Very low
Adverse pregnancy outcome											
rFSH vs. urinary gonadotrophins (miscarriage)											
1 (Van Wely et al., 2011)	Cochrane review of 30 RCTs	Very serious [a]	None	None	Serious [e]	No	192/3329 (6%) women	166/3334 (5%) women	OR 1.2 (0.9 to 1.4)	8 fewer per 1000 (from 20 fewer to 5 more)	Very low
							Not reported per clinical pregnancy				

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Multiple pregnancies (the number of pregnancies with more than one fetus)											
rFSH vs. urinary gonadotrophins											
1 (Van Wely et al., 2011)	Cochrane review of 25 RCTs	Very serious [a]	None	None	None	No	232/3150 (7%) women	260/3179 (8%) women	OR 0.9 (0.8 to 1.1)	8 fewer per 1000 (from 20 fewer to 5 more)	Low
							232/906 (26%) pregnancies	260/989 (26%) pregnancies	OR 1.0 (0.8 to 1.2)	6 fewer per 1000 (from 43 fewer to 35 more)	
Multiple births (the number of babies born from a multiple pregnancy)											
No evidence was reported											
Ovarian hyperstimulation syndrome (OHSS)											
rFSH vs. urinary gonadotrophins											
1 (Van Wely et al., 2011)	Cochrane review of 33 RCTs	Very serious [a]	None	None	Serious [e]	No	92/3994 (2%) women	73/3746 (2%) women	OR 1.2 (0.9 to 1.6)	4 more per 1000 (from 2 fewer to 12 more)	Very low
Congenital abnormalities											
No evidence was reported											

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Patient satisfaction											
No evidence was reported											
Health related quality of life											
No evidence was reported											
Anxiety and/or depression											
No evidence was reported											

[a] No studies were double blinded. Method of randomisation was unclear for some studies. Method of allocation concealment was unclear for some studies

[b] For some studies in the review, this was reported as ongoing pregnancy (>20 weeks). This may include preterm births and births from multiple pregnancies

[c] I^2 value was higher than 66%

[d] Despite a high I^2 value, this is not reported as a random effects statistic in the Cochrane review. A fixed effects Peto odds ratio analysis was used

[e] 95% confidence intervals hit or cross 0.75 and 1, and/or 1 and 1.25

Table I.15.9 GRADE findings for comparison of specific recombinant vs. specific urinary gonadotrophins

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Live full-term singleton birth											
rFSH vs. hMG/hp-hMG											
1 (Van Wely et al., 2011)	Cochrane Review of 11 trials	Very serious [a, b, c]	None	Serious [d]	Serious [e]	No	359/1604 (22%) women	406/1593 (25%) women	OR 0.8 (0.7 to 1.0)[aa]	32 fewer per 1000 (from 2 fewer to 57 fewer)	Very low

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
rFSH vs. pFSH											
1 (Van Wely et al., 2011)	Cochrane Review of 5 trials	Very serious [a, b, c]	None	Serious [d]	Serious [e]	No	171/825 (21%) women	103/605 (17%) women	OR 1.3 (1.0 to 1.7)	36 more per 1000 (from 4 fewer to 85 more)	Very low
rFSH vs. hp-FSH											
1 (Van Wely et al., 2011)	Cochrane Review of 13 trials	Very serious [a, b, c]	None	Serious [d]	None	No	364/1367 (27%) women	359/1345 (27%) women	OR 1.0 (0.9 to 1.2)	4 more per 1000 (from 20 fewer to 28 more)	Very low
rFSH vs. uFSH											
1 (Kahn et al., 1999)	RCT	Very serious [f, g]	-	Serious [h]	Serious [e]	No	49/147 (33%) women	38/115 (33%) women	RR 1.0 (0.7 to 1.4)	3 more per 1000 (from 96 fewer to 142 more)	Very low
rFSH vs rFSH + hCG											
2 (Blockell et al., 2009; Check et al., 2008)	RCTs	Very serious [f, g, i]	None	None	Very serious [e, j]	Yes [k]	14/57 (24.6%)	17/55 (30.9%)	RR 0.8 (0.4 to 1.5)	65 fewer per 1000 (from 176 fewer to 139 more)	Very low

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
rFSH vs. rFSH + hMG											
1 (Sohrabvand et al., 2010)	RCT	Very serious [f, g, i, l]	-	Serious [h]	Serious [e]	Yes [m]	6/32 (19%) women	6/32 (19%) women	RR 1 (0.4 to 2.8)	0 fewer per 1000 (from 120 fewer to 332 more)	Very low
Clinical pregnancy											
rFSH vs. hMG/hp-hMG											
2 (Gomes et al., 2007; and Van Wely et al., 2011)	1 RCT and Cochrane Review of 12 trials	Very serious [a, b, c, g]	None	Serious [n]	None	No	507/1917 (26%) women	563/1892 (30%) women	RR 0.9 (0.8 to 1.0)[ab]	33 fewer per 1000 (from 6 fewer to 57 fewer)	Very low
rFSH vs. hCG											
1 (Gomes et al., (2007)	RCT	Very serious [g, l]	-	Serious [n]	Serious [e]	Yes [o]	3/17 (18%) women	6/17 (35%) women	RR 0.5 (0.2 to 1.7)	176 fewer per 1000 (from 300 fewer to 240 more)	Very low
rFSH + rLH vs. uhMG											
1 (Pacchiarotti et al., 2010)	RCT	Very serious [g, l]	-	Serious [n]	Serious [e]	No	15/62 (24%) women	17/60 (28%) women	RR 0.9 (0.5 to 1.6)	42 fewer per 1000 (from 150 fewer to 156 more)	Very low

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
rFSH + hCG vs. rFSH + rLH											
1 (Drakakis et al., 2009)	RCT	Very serious [f, g, l]	-	Serious [p]	None	Yes [q]	16/60 (27%) women	6/60 (10%) women	RR 2.7 (1.1 to 6.4)	167 more per 1000 (from 12 more to 535 more)	Very low
rFSH vs. pFSH											
1 (Van Wely et al., 2011)	Cochrane Review of 7 trials	Very serious [a, b, c]	None	None	Serious [e]	No	244/891 (27%) women	150/669 (22%) women	OR 1.3 (1.0 to 1.7)	49 more per 1000 (from 5 more to 99 more)	Very low
rFSH vs. hp-FSH											
2 (Aboulghar et al., 2010 and Van Wely et al., 2011)	1 RCT and Cochrane Review of 23 trials	Very serious [a, b, c]	None	Serious [n]	None	No	627/2115 (30%) women	615/2116 (29%) women	RR 1.0 (0.9 to 1.1)	9 more per 1000 (from 17 fewer to 38 more)	Very low
rFSH vs. uFSH											
4 (Coelingh Bennink et al., 1998; Kahn et al., 1999; Raga et al., 1999; Tanbo et al., 2001)	RCTs	Very serious [f, g, i, j]	None	Serious [n]	Serious [e]	Yes [r]	105/292 (36%)	74/219 (33.8%)	RR 1.1 (0.8 to 1.4)	24 more per 1000 (from 54 fewer to 118 more)	Very low

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
rFSH vs. hFSH											
2 (Gholami et al., 2010; Selman et al., 2010)	RCTs	Very serious [g, i, j]	None	Serious [s]	Serious [e]	Yes [t]	42/118 (35.6%)	47/122 (38.5%)	RR 0.9 (0.7 to 1.3)	27 fewer per 1000 (from 127 fewer to 112 more)	Very low
rFSH vs. rFSH + hFSH											
1 (Selman et al., 2010)	RCT	Serious [g]	-	Serious [n]	Serious [e]	Yes [u]	21/65 (32%) women	27/63 (43%) women	RR 0.8 (0.5 to 1.2)	107 fewer per 1000 (from 223 fewer to 81 more)	Very low
rFSH + hFSH vs. hFSH											
1 (Selman et al., 2010)	RCT	Serious [g]	-	Serious [n]	Serious [e]	Yes [u]	27/63 (43%) women	23/60 (38%) women	RR 1.1 (0.7 to 1.7)	46 more per 1000 (from 103 fewer to 276 more)	Very low
rFSH + hp-FSH vs. hp-FSH											
1 (Battaglia et al., 2000)	RCT	Very serious [f, g]	-	None	Serious [e]	Yes [v]	5/20 (25%) women	2/18 (11%) women	RR 2.3 (0.5 to 10.2)	139 more per 1000 (from 56 fewer to 1000 more)	Very low

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
rFSH vs. rFSH + hMG											
6 (Check et al., 2008; De Placido et al., 2001; Devesa et al., 2010; Drakakis et al., 2005; Loutradis et al., 2003; Sohrabvand et al., 2010)	RCTs	Very serious [f, g, i, j]	None	Serious [w]	Serious [e]	Yes [x]	146/496 (29%) women	66/253 (26%) women	RR 1.0 (0.8 to 1.3)	5 fewer per 1000 (from 65 fewer to 73 more)	Very low
rFSH vs. rFSH + hCG											
1 (Ashrafi et al., 2011)	RCT	Serious [l]	-	None	None	No	14/27 (52%) women	26/51 (51%) women	RR 1.0 (0.7 to 1.6)	10 more per 1000 (from 178 fewer to 306 more)	Moderate

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Adverse pregnancy outcome											
rFSH vs. uFSH (abortions before 12 weeks after hCG administration)											
1 (Coelingh Bennink et al., 1998)	RCT	Serious [f]	-	None	Serious [e]	Yes [r]	10/105 (10%) women	6/67 (9%) women	RR 1.1 (0.4 to 2.8)	5 more per 1000 (from 53 fewer to 160 more)	Low
							10/32 (31%) pregnancies	6/19 (32%) pregnancies	RR 1.0 (0.4 to 2.3)	3 fewer per 1000 (from 180 fewer to 407 more)	
rFSH vs. hFSH (miscarriage)											
2 (Gholami et al., 2010; Selman et al., 2010)	RCTs	Very serious [f, g, i]	None	None	Serious [e]	Yes [t]	5/118 (4%) women	6/122 (5%) women	RR 0.9 (0.3 to 2.7)	7 fewer per 1000 (from 36 fewer to 86 more)	Very low
							5/42 (12%) pregnancies	6/47 (13%) pregnancies	RR 0.9 (0.3 to 2.8)	9 fewer per 1000 (from 88 fewer to 234 more)	

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
rFSH vs. rFSH + hFSH (abortion)											
1 (Selman et al., 2010)	RCT	Serious [g]	-	None	Serious [e]	Yes [u]	3/65 (5%) women	4/63 (6%) women	RR 0.7 (0.2 to 3.1)	17 fewer per 1000 (from 53 fewer to 135 more)	Low
							3/21 (14%) pregnancies	4/27 (15%) pregnancies	RR 1.0 (0.2 to 3.9)	6 fewer per 1000 (from 113 fewer to 422 more)	
rFSH + hFSH vs. hFSH (abortion)											
1 (Selman et al., 2010)	RCT	Serious [g]	-	None	Serious [e]	Yes u	4/63 (6%) women	3/60 (5%) women	RR 1.3 (0.3 to 5.4)	13 more per 1000 (from 35 fewer to 222 more)	Low
							4/27 (15%) pregnancies	3/23 (13%) pregnancies	RR 1.1 (0.3 to 4.6)	18 more per 1000 (from 94 fewer to 464 more)	

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
rFSH vs rFSH + hCG (miscarriage)											
1 (Blockeel et al., 2009)	RCT	Serious [g]	-	None	Serious [e, j]	Yes [k]	3/35 (9%) women	3/35 (9%) women	RR 1 (0.2 to 4.6)	0 fewer per 1000 (from 67 fewer to 310 more)	Very low
							Not reported per clinical pregnancy				
rFSH vs rFSH + hCG (ectopic pregnancy)											
1 (Blockeel et al., 2009)	RCT	Serious [g]	-	None	Serious [e, j]	Yes [k]	1/35 (3%) women	0/35 (0%) women	RR 3 (0.1 to 71.2)	Not calculable	Very low
							Not reported per clinical pregnancy				
rFSH vs. rFSH + hMG (abortion)											
1 (De Placido et al., 2001)	RCT	Very serious [f, g, l]	-	None	Serious [e]	Yes [y]	2/23 (8%) women	1/20 (5%) women	RR 1.7 (0.2 to 17.8)	37 more per 1000 (from 42 fewer to 839 more)	Very low
							2/8 (25%) pregnancies	1/10 (10%) pregnancies	RR 2.5 (0.3 to 22.9)	150 more per 1000 (from 73 fewer to 1000 more)	

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
rFSH vs. hCG (miscarriage)											
1 (Gomes et al., 2007)	RCT	Very serious [g, l]	-	None	Serious [e]	Yes [o]	1/17 (6%) women	3/17 (18%) women	RR 0.3 (0.0 to 2.9)	118 fewer per 1000 (from 169 fewer to 334 more)	Very low
							1/3 (33%) pregnancies	3/6 (50%) pregnancies	RR 0.7 (0.1 to 4.0)	165 fewer per 1000 (from 445 fewer to 1000 more)	
Multiple pregnancies (the number of pregnancies with more than one fetus)											
rFSH vs. rFSH + hMG											
1 (Check et al., 2008)	RCT	Very serious [f, g, i]	-	None	Serious [e]	No	2/22 (9%) women	2/20 (10%) women	RR 0.9 (0.1 to 5.9)	9 fewer per 1000 (from 86 fewer to 486 more)	Very low
							2/7 (29%) pregnancies	2/10 (20%) pregnancies	RR 1.4 (0.3 to 7.9)	86 more per 1000 (from 148 fewer to 1000 more)	

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
rFSH vs. rFSH + hCG											
1 (Ashrafi et al., 2011)	RCT	Serious [l]	-	None	None	No	4/27 (15%) women	3/51 (6%) women	RR 2.5 (0.6 to 10.4)	89 more per 1000 (from 23 fewer to 555 more)	Moderate
							4/14 (29%) pregnancies	3/26 (12%) pregnancies	RR 2.5 (0.6 to 9.5)	171 more per 1000 (from 42 fewer to 985 more)	
Multiple births (the number of babies born from a multiple pregnancy)											
No evidence reported											
Ovarian hyperstimulation syndrome (OHSS)											
rFSH vs. hMG/hp-hMG											
1 (Van Wely et al., 2011)	Cochrane Review of 11 trials	Very serious [a, b, c]	None	None	Serious [e]	No	27/1604 (2%) women	27/1593 (2%) women	OR 1.0 (0.6 to 1.7)	0 fewer per 1000 (from 7 fewer to 12 more)	Very low
rFSH vs. pFSH											
1 (Van Wely et al., 2011)	Cochrane Review of 6 trials	Very serious [a, b, c]	None	None	Serious [e]	No	24/855 (3%) women	9/635 (1%) women	OR 1.8 (0.9 to 3.6) [z]	11 more per 1000 (from 1 fewer to 35 more)	Very low

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
rFSH vs. hp-FSH											
1 (Van Wely et al., 2011)	Cochrane Review of 16 trials	Very serious [a, b, c]	None	None	Serious [e]	No	41/1535 (3%) women	37/1518 (2%) women	OR 1.1 (0.7 to 1.8)	3 more per 1000 (from 7 fewer to 18 more)	Very low
rFSH vs. rFSH + hCG											
1 (Ashrafi et al., 2011)	RCT	Serious [l]	-	None	None	No	4/27 (15%) women	0/54 (0%) women	RR 17.7 (0.9 to 316.9)	Not calculable	
Congenital abnormalities											
No evidence reported											
Patient satisfaction											
No evidence reported											
Health related quality of life											
No evidence reported											
Anxiety and/or depression											
No evidence reported											

[a] Not all studies clearly reported blinding

[b] Not all studies clearly reported allocation concealment

[c] Not all studies clearly reported the method of randomisation used

[d] Also includes ongoing pregnancies (beyond 20 weeks) where live birth rate was not reported

[e] 95% confidence intervals hit or cross 0.75 and 1, and/or 1 and 1.25

[f] A power calculation was not reported

[g] Blinding was not reported in at least one study

[h] May include preterm births and births from multiple pregnancies
[i] Method of randomisation was not reported
[j] A power calculation was performed but not enough women were recruited
[k] One study only included women less than 36 years old
[l] Allocation concealment not reported
[m] Only included women aged 20 to 35 and with a BMI of 18 to 30
[n] Clinical pregnancy not defined in at least one study
[o] Only included women aged 25 to 35
[p] Clinical pregnancy defined as endometrial gestational sac with a transvaginal ultrasound scan
[q] Only included women aged 36 to 42 years old with a BMI =< 32
[r] One study only included women with a BMI of 19 to 32
[s] Clinical pregnancy not defined in one study. Defined as 'cardiac activity after 7 weeks' in the other study.
[t] One study only included women aged 27 to 38 and BMI between 20 and 26. The other study only included women under 37 years.
[u] Only included women aged 27 to 38 and BMI between 20 and 26
[v] Excluded women with a BMI > 30
[w] Clinical pregnancy not defined in two studies. Confirmed at 8 weeks in one study. Confirmed at 4 weeks with ultrasound in one study.
[x] One study only included women aged 20 to 35 and with a BMI of 18 to 30. Other study excluded women with BMI > 29
[y] Excluded women with BMI > 29
[z] Calculated in RevMan as OR 2.0 (0.9 to 4.4) with an absolute effect of 14 more per 1000 (from 1 fewer to 45 more)
[aa] this result was significantly in favour of hMG at 2 decimal places
[ab] this result was significantly in favour of hMG at 2 decimal places

Table I.15.10 GRADE findings for comparisons of a) urinary vs. urinary gonadotrophins and b) recombinant vs. recombinant gonadotrophins

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Live full-term singleton birth											
rhFSH vs. rhFSH + rhLH											
2 (Matorras et al., 2009; Tarlatzis et al., 2006)	RCTs	Serious [a, b]	Very serious [c]	Serious [d]	Serious [e]	Yes [f]	15/125 (12%) women	18/118 (15%) women	RR 0.8 (0.2 to 3.2) [g]	32 fewer per 1000 (from 122 fewer to 339 more)	Very low
rhFSH vs. hMG											
1 (Quigley et al., 1988)	RCT	None	-	Serious [d]	Serious [e]	No	4/48 (8%) women	2/50 (4%) women	RR 2.1 (0.4 to 10.9)	43 more per 1000 (from 24 fewer to 394 more)	Low
Clinical pregnancy											
pFSH vs. pFSH + hMG											
1 (Balasch et al., 1996)	RCT	Very serious [b, h, i]	-	Serious [j]	Serious [e]	No	13/92 (14%) women	11/96 (12%) women	RR 1.2 (0.6 to 2.6)	26 more per 1000 (from 48 fewer to 184 more)	Very low

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
hp-FSH vs. hp-FSH + hMG											
2 (Balasch et al., 1996; and Ku et al., 2003)	RCTs	Very serious [a, b, h, i]	Serious [k]	Serious [j]	Serious [e]	No	22/149 (15%) women	23/148 (16%) women	RR 1.0 (0.4 to 2.5) [g]	6 more per 1000 (from 87 fewer to 233 more)	Very low
rhFSH vs. rhFSH + rhLH											
6 (Balasch et al., 2001; Barrenetxea et al., 2008; Fabregues et al., (2011); Marrs et al., 2004; Matorras et al., 2009; Tarlatzis et al., 2006)	RCTs	Very serious [a, b, i]	Serious [k]	Serious [l]	Serious [e]	No	148/462 (32%) women	157/513 (31%) women	RR 1.1 (0.8 to 1.4) [g]	15 more per 1000 (from 67 fewer to 125 more)	Very low
rhFSH + rhLH vs. rhLH											
1 (Dunerin et al., 2008)	RCT	Very serious [b, h, i]	-	Serious [j]	Serious [e]	Yes [m]	24/75 (32%) women	23/71 (32%) women	RR 1.0 (0.6 to 1.6)	3 fewer per 1000 (from 123 fewer to 188 more)	Very low

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
rFSH vs. rFSH + rLH											
7 (Caserta et al., 2011; Ferraretti et al., (2004; Griesinger et al., 2005; Kovacs et al., 2010; Levi-Setti et al., 2006; NyboeAndersen et al., 2008; Pezzuto et al., 2010)	RCTs	Very serious [a, b, h, i]	Serious [k]	Serious [n]	Very serious [e, o]	Yes [p]	183/957 (19%) women	221/951 (23%) women	RR 0.8 (0.6 to 1.1)	49 fewer per 1000 (from 100 fewer to 28 more)	Very low
hCG vs. hMG											
1 (Gomes et al., 2007)	RCT	Very serious [h, i]	-	Serious [j]	Serious [e]	Yes [q]	6/17 (35%) women	6/17 (35%) women	RR 1 (0.4 to 2.5)	0 fewer per 1000 (from 212 fewer to 522 more)	Very low

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Adverse pregnancy outcome											
pFSH vs. pFSH + hMG (clinical abortion)											
1 (Balasch et al., 1996)	RCT	Very serious [b, h, i]	-	None	Serious [e]	No	2/92 (2%) women	2/96 (2%) women	RR 1.0 (0.2 to 7.3)	1 more per 1000 (from 18 fewer to 130 more)	Very low
							2/13 (15%) pregnancies	2/11 (18%) pregnancies	RR 0.9 (0.1 to 5.1)	27 fewer per 1000 (from 156 fewer to 738 more)	
Hp-FSH vs. hp-FSH + hMG (clinical abortion)											
1 (Balasch et al., 1996)	RCT	Very serious [b, h, i]	-	None	Serious [e]	No	2/123 (2%) women	4/129 (3%) women	RR 0.5 (0.1 to 2.8)	15 fewer per 1000 (from 28 fewer to 56 more)	Very low
							2/16 (13%) pregnancies	4/21 (19%) pregnancies	RR 0.7 (0.1 to 3.2)	65 fewer per 1000 (from 164 fewer to 410 more)	

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
rFSH vs. rFSH + rLH (abortion)											
1 (Ferraretti et al., 2004)	RCT	Very serious [b, h, i]	-	None	Serious [e]	Yes [r]	1/45 (2%) women	2/41 (5%) women	RR 0.5 (0.0 to 4.8)	26 fewer per 1000 (from 47 fewer to 187 more)	Very low
							1/11 (9%) women	2/22 (9%) women	RR 1 (0.1 to 9.9)	0 fewer per 1000 (from 82 fewer to 805 more)	
rFSH vs. rFSH + rLH (miscarriage before 12 weeks)											
1 (Griesinger et al., 2005)	RCT	Very serious [b, h, i]	-	None	Serious [e]	Yes [s]	3/65 (5%) women	8/62 (13%) women	RR 0.4 (0.1 to 1.3)	83 fewer per 1000 (from 116 fewer to 37 more)	Very low
							Not reported per clinical pregnancy				

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
rhFSH vs. rhFSH + rhLH (miscarriage)											
1 (Fabregues et al., 2011)	RCT	Serious [i]	-	None	Serious [e]	No	4/62 (7%) women	6/125 (5%) women	RR 1.3 (0.4 to 4.6)	16 more per 1000 (from 29 fewer to 172 more)	Low
							4/22 (18%) pregnancies	6/31 (19%) pregnancies	RR 0.9 (0.3 to 2.9)	12 fewer per 1000 (from 135 fewer to 375 more)	
rhFSH + rhLH vs. rhLH (miscarriage)											
1 (Tarlatzis et al., 2006)	RCT	Serious [b]	-	None	Serious [e]	No	4/57 (7%) women	3/55 (5%) women	RR 1.29 (0.3 to 5.5)	16 more per 1000 (from 38 fewer to 245 more)	Low
							4/14 (29%) pregnancies	3/9 (33%) pregnancies	RR 0.9 (0.3 to 3.0)	47 fewer per 1000 (from 250 fewer to 653 more)	

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
hCG vs. hMG (miscarriage)											
1 (Gomes et al., 2007)	RCT	Very serious [h, i]	-	None	Serious [e]	Yes [q]	3/17 (18%) women	0/17 (0%) women	RR 7 (0.4 to 126.0)	Not calculable	Very low
							3/6 (50%) pregnancies	0/6 (0%) pregnancies	RR 7 (0.4 to 111.9)	Not calculable	
Multiple pregnancies (the number of pregnancies with more than one fetus)											
rhFSH vs. rhFSH + rhLH											
1 (Fabruegues et al., 2011)	RCT	Serious [i]	-	None	Serious [e]	No	6/62 (10%) women	6/125 (5%) women	RR 2.0 (0.7to 6.0)	49 more per 1000 (from 15 fewer to 240 more)	Low
							6/22 (27%) pregnancies	6/31 (19%) pregnancies	RR 1.41 (0.52 to 3.8)	79 more per 1000 (from 93 fewer to 542 more)	

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
rFSH vs. rFSH + rLH											
1 (NyboeAndersen et al., 2008)	RCT	Serious [i]	-	None	Very serious [e, n]	No	16/261 (6%) women	20/265 (8%) women	RR 0.8 (0.4 to 1.5)	14 fewer per 1000 (from 43 fewer to 40 more)	Very low
							16/88 (18%) pregnancies	20/83 (24%) pregnancies	RR 0.8 (0.4 to 1.4)	60 fewer per 1000 (from 140 fewer to 84 more)	
Multiple births (the number of babies born from a multiple pregnancy)											
No evidence reported											
Ovarian hyperstimulation syndrome (OHSS)											
pFSH vs. pFSH + hMG											
1 (Balasch et al., 1996)	RCT	Very serious [b, h, i]	-	None	Serious [e]	No	1/92 (1%) women	2/96 (2%) women	RR 0.5 (0.1 to 5.7)	10 fewer per 1000 (from 20 fewer to 97 more)	Very low

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Hp-FSH vs. hp-FSH + hMG											
1 (Balasch et al., 1996)	RCT	Very serious [b, h, i]	-	None	Serious [e]	No	2/123 (2%) women	3/129 (2%) women	RR 0.7 (0.1 to 4.1)	7 fewer per 1000 (from 20 fewer to 72 more)	Very low
rFSH vs. rFSH + rLH											
1 (Caserta et al., 2011)	RCT	Serious [b]	-	None	Serious [e]	No	6/521 (1%) women	1/518 (0.2%) women	RR 6.0 (0.7 to 49.4)	10 more per 1000 (from 1 fewer to 93 more)	Low
Congenital abnormalities											
No evidence reported											
Patient satisfaction											
No evidence reported											
Health related quality of life											
No evidence reported											
Anxiety and/or depression											
No evidence reported											

[a] Randomisation was poorly conducted in at least one study

[b] A power calculation was not clearly reported in at least one study

[c] The I^2 value is greater than 66%

[d] May include preterm births and births from multiple pregnancies

[e] 95% confidence intervals hit or cross 0.75 and 1, and/or 1 and 1.25

[f] One study was restricted to those of a BMI of 18 to 30
[g] Random effects model is reported as I^2 value > 33%
[h] Allocation concealment was not clearly reported in at least one study
[i] Blinding was not clearly reported in at least one study
[j] Definition of clinical pregnancy not reported
[k] The I^2 value is greater than 33% but less than 66%
[l] One study reported pregnancy confirmed by presence of fetal sac and heart beat on day 35 after oocyte retrieval. One study only included women over 40 years old
[m] This was a multi-centre trial – authors report that luteal phase support may have varied across centres
[n] Clinical pregnancy was not defined in one study. Defined as ongoing gestation > 12 weeks in two studies
[o] One study reported a power calculation but did not recruit enough women
[p] One study only included women with a BMI =< 27, one 18 to 35, one 20 to 25
[q] Women were only included if they were 25-35 years old
[r] Only included women with a BMI =<27
[s] Only included women with a BMI of 18 to 35

Table I.15.11 GRADE findings for comparison of dosages of FSH/rFSH for ovarian stimulation

Quality assessment							**Summary of findings**				
							No. of patients/women		**Effect**		**Quality**
No. of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Intervention**	**Comparator**	**Relative (95% CI)**	**Absolute (95% CI)**	
Live full-term singleton birth											
Low dose step-up FSH (75 IU/day for 6 days, increased by 37.5 IU/day thereafter) vs. step-down FSH (225 IU/day for 3 days then decreased to 150 IU/day for three days) (low response)											
1 (Koundouros et al., 2008)	RCT	Very serious [a, b, c]	-	Serious [d, e]	Serious [f]	No	13/75 (17%) women	11/75 (15%) women	RR 1.2 (0.6 to 2.5)	26 more per 1000 (from 63 fewer to 216 more)	Very low

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
150 IU rFSH vs. 225 IU rFSH											
1 (Yong et al., 2003)	RCT	Very serious [a, b]	-	Serious [d]	Serious [f]	Yes [g]	7/60 (12%) women	9/63 (14%) women	RR 0.8 (0.3 to 2.1)	26 fewer per 1000 (from 97 fewer to 150 more)	Very low
Clinical pregnancy											
150 IU rFSH vs. 200 IU rFSH											
3 (Cavagna et al., 2006; Harrison et al., 2001; Out et al., 2004)	RCTs	Very serious [a, b, c]	None	Serious [h]	Serious [f]	Yes [i]	79/318 (24.8%)	73/319 (22.9%)	RR 1.1 (0.8 to 1.4)	18 more per 1000 (from 41 fewer to 98 more)	Very low
100 IU rFSH vs. 200 IU rFSH											
5 (De Jong et al., 2000; Hoomans et al., 2002; Out et al., 1999; Out et al, 2001; Tan et al., 2005)	RCTs	Very serious [a, b, c]	None	Serious [h, j]	Serious [f]	Yes [k]	93/460 (20%) women	92/455 (20%) women	RR 1 (0.8 to 1.3)	0 fewer per 1000 (from 47 fewer to 59 more)	Very low

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Low dose step-up FSH (75 IU/day for 6 days, increased by 37.5 IU/day thereafter) vs. step-down FSH (225 IU/day for 3 days then decreased to 150 IU/day for three days) (low response)											
1 (Koundouros et al., 2008)	RCT	Very serious [a, b, c]	-	Serious [f]	Serious [f]	No	18/75 (24%) women	20/75 (27%) women	RR 0.9 (0.5 to 1.6)	27 fewer per 1000 (from 128 fewer to 149 more)	Very low
300 IU rFSH vs. 400 IU rFSH											
1 (Harrison et al., 2001)	RCT	Very serious [a, b]	-	None	Serious [f]	No	2/24 (8%) women	2/24 (8%) women	RR 1 (0.2 to 6.5)	0 fewer per 1000 (from 71 fewer to 461 more)	Very low
150 IU rFSH vs. 300 IU rFSH											
1 (Klinkert et al., 2005)	RCT	Very serious [b, c]	-	Very serious [h, l]	Very serious [f, m]	No	3/26 (11.5%)	1/26 (3.8%)	RR 3.0 (0.3 to 27.0)	77 more per 1000 (from 26 fewer to 1000 more)	Very low
150 IU rFSH vs. 250 rFSH											
2 (Latin-American, 2001; Out et al., 2000)	RCTs	Serious [a]	None	None	Serious [f]	Yes [n]	44/268 (16%) women	42/276 (15%) women	RR 1.1 (0.7 to 1.6)	12 more per 1000 (from 41 fewer to 90 more)	Low

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Individual dose (100 to 250 IU) rFSH vs. 150 IU rFSH											
1 (Popovic-Todorovic et al., 2003)	RCT	Very serious [a, b]	-	Serious [h]	Serious [f]	No	48/131 (37%) women	32/131 (24%) women	RR 1.5 (1.0 to 2.2)	122 more per 1000 (from 7 more to 288 more)	Very low
150 IU rFSH vs. 225 IU rFSH											
1 (Wikland et al., (2001)	RCT	Very serious [a, b, c]	-	Serious [h]	Serious [f]	No	21/60 (35%) women	24/60 (40%) women	RR 0.9 (0.6 to 1.4)	48 fewer per 1000 (from 180 fewer to 156 more)	Very low
Low dose FSH (between 37.5 IU and 75 IU) vs. standard dose FSH (between 112.5 IU and 225 IU)											
1 (Zhu et al., 2009)	RCT	Very serious [a, b]	-	None	Serious [f]	Yes [o]	33/60 (57%) women	31/60 (60%) women	RR 1.1 (0.8 to 1.5)	31 more per 1000 (from 124 fewer to 253 more)	Very low

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Adverse pregnancy outcome											
Low dose step-up FSH (75 IU/day for 6 days, increased by 37.5 IU/day thereafter) vs. step-down FSH (225 IU/day for 3 days then decrease of 150 IU/day for three days) (low response) (miscarriage)											
1 (Koundouros et al., 2008)	RCT	Very serious [a, b, c]	-	Serious [e]	Serious [f]	No	7/75 (9%) women	9/75 (12%) women	RR 0.8 (0.3 to 2.0)	26 fewer per 1000 (from 83 fewer to 118 more)	Very low
							7/18 (39%) pregnancies	9/20 (45%) pregnancies	RR 0.9 (0.4 to 1.8)	63 fewer per 1000 (from 266 fewer to 378 more)	
100 IU rFSH vs. 200 IU rFSH (miscarriage)											
2 (Hoomans et al., 2002; Out et al., 2001)	RCTs	Very serious [a, b, c]	None	None	Serious [f]	Yes [k]	3/254 (1%) women	10/255 (4%) women	RR 0.3 (0.1 to 1.1)	27 fewer per 1000 (from 36 fewer to 2 more)	Very low Low
					None		3/49 (6%) pregnancies	10/45 (22%) pregnancies	RR 0.3 (0.1 to 0.9)	162 fewer per 1000 (from 18 fewer to 204 fewer)	

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
150 IU rFSH vs. 250 rFSH (extra-uterine pregnancy)											
1 (Latin-American Puregon IVF study group, 2001)	RCT	None	-	None	Serious [f]	Yes [n]	1/201 (1%) women	0/203 (0%) women	RR 3.0 (0.1 to 73.9)	Not calculable	Moderate
							1/34 (3%) pregnancies	0/33 (0%) pregnancies	RR 2.9 (0.1 to 69.1)	Not calculable	
100 IU rFSH vs. 200 IU rFSH (ectopic pregnancy and/or miscarriage)											
2 (Out et al., 1999; Tan et al., 2005)	RCTs	Serious [a]	Serious [q]	None	Serious [f]	Yes [k]	13/198 (7%) women	5/193 (3%) women	RR 2.2 (0.5 to 10.8) [r]	32 more per 1000 (from 14 fewer to 254 more)	Very low
1 (Out et al., 1999)			-		None		10/16 (63%) pregnancies	2/23 (9%) pregnancies	RR 7.2 (1.8 to 28.5)	538 more per 1000 (from 70 more to 1000 more)	Moderate

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
150 IU rFSH vs 200 rFSH (miscarriage and/or ectopic pregnancy)											
1 (Out et al., 1999)	RCT	Serious [a]	-	None	Serious [f]	Yes [k]	8/132 (6%) women	9/132 (7%) women	RR 0.9 (0.4 to 2.2)	8 fewer per 1000 (from 44 fewer to 84 more)	Low
							8/41 (20%) pregnancies	9/32 (28%) pregnancies	RR 0.7 (0.3 to 1.6)	87 fewer per 1000 (from 197 fewer to 169 more)	
Individual dose (100 to 250 IU) rFSH vs. 150 IU rFSH (biochemical pregnancy, abortion, or extrauterine pregnancy)											
1 (Popovic-Todorovic et al., 2003)	RCT	Very serious [a, b, c]	-	None	Serious [f]	No	11/131 (8%) women	15/131 (11%) women	RR 0.7 (0.4 to 1.5)	31 fewer per 1000 (from 74 fewer to 62 more)	Very low
					None		11/48 (23%) pregnancies	15/32 (47%) pregnancies	RR 0.5 (0.3 to 0.9)	239 fewer per 1000 (from 37 fewer to 347 fewer)	

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
150 IU rFSH vs. 225 IU rFSH (miscarriage or extrauterine pregnancies)											
1 (Wikland et al., 2001)	RCT	Very serious [a, b, c]	-	None	Serious [f]	No	6/60 (10%) women	9/60 (15%) women	RR 0.7 (0.3 to 1.8)	49 fewer per 1000 (from 113 fewer to 114 more)	Very low
							6/21 (28.6%) pregnancies	9/24 (37.5%) pregnancies	RR 0.8 (0.3 to 1.8)	90 fewer per 1000 (from 251 fewer to 292 more)	
150 IU rFSH vs. 225 IU rFSH (miscarriage)											
1 (Yong et al., 2003)	RCT	Very serious [a, b]	-	None	Serious [f]	Yes [p]	1/60 (2%) women	1/63 (2%) women	RR 1.1 (0.1 to 16.4)	1 more per 1000 (from 15 fewer to 245 more)	Very low
							Not reported per clinical pregnancy				

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Multiple pregnancies (the number of pregnancies with more than one fetus)											
Low dose step-up FSH (75 IU/day for 6 days, increased by 37.5 IU/day thereafter) vs. step-down FSH (225 IU/day for 3 days then decrease of 150 IU/day for three days) (low response)											
1 (Koundouros et al., 2008)	RCT	Very serious [a, b, c]	-	Serious [e]	Serious [f]	No	4/74 (5%) women	5/75 (7%) women	RR 0.8 (0.2 to 2.9)	13 fewer per 1000 (from 51 fewer to 127 more)	Very low
							4/18 (22%) pregnancies	5/20 (20%) pregnancies	RR 0.9 (0.3 to 2.8)	28 fewer per 1000 (from 180 fewer to 452 more)	
100 IU rFSH vs. 200 IU rFSH											
1 (Hoomans et al., 2002)	RCT	Very serious [a, b]	-	None	Serious [f]	Yes [k]	9/163 (6%) women	9/167 (5%) women	RR 1.0 (0.4 to 2.5)	1 more per 1000 (from 31 fewer to 82 more)	Very low
							9/32 (28%) pregnancies	9/30 (30%) pregnancies	RR 0.9 (0.4 to 2.0)	18 fewer per 1000 (from 171 fewer to 312 more)	

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
150 IU rFSH vs. 300 IU rFSH											
1 (Klinkert et al., 2005)	RCT	Very serious [b, c]	-	Serious [l]	Serious [m]	No	0/26 (0%) women	0/26 (0%) women	Not calculable	Not calculable	Very low
							0/3 (0%) pregnancies	0/1 (0%) pregnancies	Not calculable	Not calculable	
150 IU rFSH vs. 250 rFSH											
1 (Latin-American Puregon IVF study group, 2001)	RCT	None	-	None	Serious [f]	Yes [n, s]	16/201 (8%) women	9/203 (4%) women	RR 1.8 (0.8 to 4.0)	35 more per 1000 (from 8 fewer to 132 more)	Moderate
							16/34 (47%) pregnancies	9/33 (27%) pregnancies	RR 1.7 (0.9 to 3.3)	199 more per 1000 (from 30 fewer to 638 more)	

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
150 IU rFSH vs. 225 IU rFSH											
2 (WIkland et al., 2001; Yong et al., 2003)	RCTs	Very serious [a, b, c]	None	None	Serious [f]	Yes [p]	5/120 (4.2%)	8/123 (6.5%)	RR 0.6 (0.2 to 1.9)	23 fewer per 1000 (from 51 fewer to 58 more)	Very low
							5/28 (17.9%)	8/33 (24.2%)	RR 0.8 (0.3 to 2)	61 fewer per 1000 (from 175 fewer to 242 more)	
Multiple births (the number of babies born from a multiple pregnancy out of the total number of babies born)											
Low dose step-up FSH (75 IU/day for 6 days, increased by 37.5 IU/day thereafter) vs. step-down FSH (225 IU/day for 3 days then decreased to 150 IU/day for three days) (low response)											
1 (Koundouros et al., 2008)	RCT	Very serious [a, b, c]	-	Serious [e]	Serious [f]	No	8/21 (38%) babies	10/21 (48%) babies	RR 0.8 (0.4 to 1.6)	95 fewer per 1000 (from 290 fewer to 295 more)	Very low
Ovarian hyperstimulation syndrome (OHSS)											
150 IU FSH vs. 200 IU FSH											
2 (Cavagna et al., 2006; and Out et al., 2004)	RCTs	Very serious [a, b, c]	NA	None	Serious [f]	Yes [i]	8/172 (5%) women	10/168 (6%) women	RR 0.8 (0.3 to 2.0)	12 fewer per 1000 (from 40 fewer to 57 more)	Very low

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Low dose step-up FSH (75 IU/day for 6 days, increased by 37.5 IU/day thereafter) vs. step-down FSH (225 IU/day for 3 days then decreased to 150 IU/day for three days) (low response)											
1 (Koundouros et al., 2008)	RCT	Very serious [a, b, c]	-	Serious [e]	Serious [f]	No	3/75 (4%) women	8/75 (11%) women	RR 0.4 (0.1 to 1.4)	66 fewer per 1000 (from 96 fewer to 38 more)	Very low
100 IU rFSH vs. 200 IU rFSH											
3 (Hoomans et al. 2002; Out et al., 2001; Tan et al. 2005)	RCTs	Very serious [a, b, c]		None	Serious [f]	Yes [k]	8/351 (2%) women	9/350 (3%) women	RR 1.0 (0.3 to 4.0)	0 fewer per 1000 (from 19 fewer to 76 more)	Very low
150 IU rFSH vs. 300 IU rFSH											
1 (Klinkert et al., 2005)	RCT	Very serious [a, b, c]	-	Serious [l]	Serious [m]	No	0/26 (0%) women	0/26 (0%) women	Not calculable	Not calculable	Very low
150 IU rFSH vs. 250 rFSH											
1 (Latin-American Puregon IVF study group, 2001)	RCT	None	-	None	Serious [f]	Yes [n]	5/201 (3%) women	8/203 (4%) women	RR 0.6 (0.2 to 2.0)	15 fewer per 1000 (from 31 fewer to 35 more)	Moderate

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
150 IU rFSH vs. 225 IU rFSH											
1 (Yong et al., 2003)	RCT	Very serious [a, b]	-	None	Serious [f]	Yes [p]	0/60 (0%) women)	4/63 (6%) women	RR 0.1 (0.0 to 2.1)	56 fewer per 1000 (from 63 fewer to 71 more)	Very low
Low dose FSH (between 37.5 IU and 75 IU) vs. standard dose FSH (between 112.5 IU and 225 IU)											
1 (Zhu et al., 2009)	RCT	Very serious [a, b]	-	None	Serious [f]	Yes [o]	4/60 (7%) women	12/60 (20%) women	RR 0.3 (0.1 to 1.0)	134 fewer per 1000 (from 4 fewer to 178 fewer)	Very low
Congenital abnormalities											
No evidence reported											
Patient satisfaction											
No evidence reported											
Health related quality of life											
No evidence reported											
Anxiety and/or depression											
No evidence reported											

[a] Power calculation not reported

[b] blinding not reported

[c] Method of randomisation not reported

[d] May include preterm births and/or births from multiple pregnancies

[e] Women were under the age of 30, had PCOS
[f] 95% confidence intervals hit or cross 0.75 and 1, and/or 1 and 1.25
[g] Women were only included if aged 23 to 41 with a BMI < 34
[h] Pregnancy not defined in at least one study
[i] One study only included women under 35 years with a BMI between 19 and 29. The other study only included women with a BMI between 18 and 29.
[j] Pregnancy defined in one study as 'ongoing pregnancy' (>12 weeks gestation)
[k] Studies only included women with a BMI between 18 and 29
[l] Women were aged 41 to 46 years
[m] A power calculation was reported but not enough women were recruited
[n] Women were only recruited if aged 30 to 39 years with a BMI of 18 to 29 (in both studies)
[o] Only women under 35 years were included
[p] Only included women aged 23 to 41 years with a BMI < 34
[q] I^2 value is greater than 33% but less than 66%
[r] Random effects model reported as I^2 > 33%
[s] Included 17 twins, 5 triplets, and 4 quadruplet pregnancies

Table I.15.12 GRADE findings for comparison of Unstimulated IVF vs. stimulation with clomifene citrate and/or gonadotrophins (no IVF/ICSI)

Quality assessment							**Summary of findings**				
							No. of patients/women		**Effect**		**Quality**
No. of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Intervention**	**Comparator**	**Relative (95% CI)**	**Absolute (95% CI)**	
Live full-term singleton birth											
No evidence reported											
Clinical pregnancy											
No evidence reported											
Adverse pregnancy outcome											
No evidence reported											
Multiple pregnancies (the number of pregnancies with more than one fetus)											
No evidence reported											

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Multiple births (the number of babies born from a multiple pregnancy)											
No evidence reported											
Ovarian hyperstimulation syndrome (OHSS)											
No evidence reported											
Congenital abnormalities											
No evidence reported											
Patient satisfaction											
No evidence reported											
Health related quality of life											
No evidence reported											
Anxiety and/or depression											
No evidence reported											

Table I.15.13 GRADE findings for comparison of GnRH agonist + gonadotrophins IVF/ICSI cycles vs. clomifene citrate + gonadotrophins (+ GnRH antagonist) IVF/ICSI cycles

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Live full-term singleton birth											
GnRH agonist + hMG vs. CC + hMG											
1 (Long et al., 1995)	RCT	Very serious [a, b, c]	-	None	Serious [d]	No	1/36 (3%) women	4/36 (11%) women	RR 0.3 (0.0 to 2.1)	83 fewer per 1000 (from 108 fewer to 126 more)	Very low
GnRH agonist + hMG/FSH vs. CC + hMG + GnRH antagonist											
1 (Lin et al., 2006)	RCT	Serious [a]	-	Serious [e]	Serious [d]	No	21/60 (35%) women	22/60 (37%) women	RR 1.0 (0.6 to 1.5)	18 fewer per 1000 (from 150 fewer to 198 more)	Very low
Clinical pregnancy											
GnRH agonist + hMG vs. CC + hMG											
3 (Dhont et al., 1995; Grochowski et al., 1999; Long et al., 1995)	RCTs	Very serious [a, b, c]	Serious [f]	Serious [g]	Serious [d]	No	87/315 (27.6%)	74/317 (23.3%)	RR 1.2 (0.8 to 1.7) [h]	44 more per 1000 (from 44 fewer to 173 more)	Very low

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
GnRH agonist + gonadotrophins vs. CC + hMG + GnRH antagonist											
2 (Karimzadeh and Lin, 2006)	RCTs	Very serious [a, c]	None	None	Serious [d]	No	55/160 (34%) women	62/160 (39%) women	RR 0.9 (0.7 to 1.2)	43 fewer per 1000 (from 132 fewer to 70 more)	Very low
GnRH agonist + rFSH vs. CC + rFSH + rLH + corticosteroid											
1 Weigert et al., 2002)	RCT	Very serious [a, b, c]	-	None	Serious [d]	No	41/140 (29%) women	54/154 (35%) women	RR 0.8 (0.6 to 1.2)	56 fewer per 1000 (from 140 fewer to 60 more)	Very low
Adverse pregnancy outcome											
GnRH agonist + hMG vs. CC + hMG (miscarriage)											
1 (Long et al., 1995)	RCT	Very serious [a, b, c]	-	None	Serious [d]	No	2/36 (6%) women	0/36 (0%) women	RR 5.0 (0.3 to 100.6)	Not calculable	Very low
							2/5 (40%) pregnancies	0/5 (0%) pregnancies	RR 5.0 (0.3 to 83.7)	Not calculable	

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
GnRH agonist + hMG vs. CC + hMG (ectopic)											
1 (Long et al., 1995)	RCT	Very serious [a, b, c]	-	None	Serious [d]	No	0/36 (0%) women	1/36 (3%) women	RR 0.3 (0.0 to 7.9)	19 fewer per 1000 (from 28 fewer to 192 more)	Very low
							0/5 (0%) pregnancies	1/5 (20%) pregnancies	RR 0.3 (0.0 to 6.7)	134 fewer per 1000 (from 196 fewer to 1000 more)	
GnRH agonist (triptorelin) + hMG vs. CC + hMG (pregnancy loss)											
1 (Harrison et al., 1994)	RCT	Serious [c]	-	None	Serious [d]	Yes [i]	3/50 (6%) women	4/50 (8%) women	RR 0.8 0.2 to 3.2)	20 fewer per 1000 (from 66 fewer to 174 more)	Low
							Not reported per clinical pregnancy				
GnRH agonist (buserelin) + hMG vs. CC + hMG (pregnancy loss)											
1 (Harrison et al., 1994)	RCT	Serious [c]	-	None	Serious [d]	Yes [i]	3/50 (6%) women	4/50 (8%) women	RR 0.8 (0.2 to 3.2)	20 fewer per 1000 (from 66 fewer to 174 more)	Low
							Not reported per clinical pregnancy				

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
GnRH agonist + hMG/FSH vs. CC + hMG + GnRH antagonist (abortion or stillbirth)											
1 (Lin et al., 2006)	RCT	Serious [a]	-	None	Serious [d]	No	3/60 (5%) women	3/60 (5%) women	RR 1 (0.2 to 4.8)	0 fewer per 1000 (from 40 fewer to 188 more)	Low
							3/24 (13%) pregnancies	3/25 (12%) pregnancies	RR 1.0 (0.2 to 4.7)	5 more per 1000 (from 92 fewer to 439 more)	
GnRH agonist + rFSH vs. CC + rFSH + rLH + corticosteroid (early pregnancy losses)											
1 (Weigert et al., 2002)	RCT	Very serious [a, b, c]	-	None	Serious [d]	No	7/140 (5%) women	10/154 (6%) women	RR 0.8 (0.3 to 2.0)	15 fewer per 1000 (from 45 fewer to 63 more)	Very low
							7/41 (17%) pregnancies	10/54 (19%) pregnancies	RR 0.9 (0.4 to 2.2)	15 fewer per 1000 (from 115 fewer to 224 more)	

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Multiple pregnancies (the number of pregnancies with more than one fetus)											
GnRH agonist + hMG vs. CC + hMG											
1 (Grochowski et al., 1999)	RCT	Very serious [a, b]	-	None	Serious [d]	Yes [j]	7/164 (4%) women	3/160 (2%) women	RR 2.3 (0.6 to 8.7)	24 more per 1000 (from 7 fewer to 143 more)	Very low
							7/41 (17%) pregnancies	3/38 (8%) pregnancies	RR 2.2 (0.6 to 7.8)	92 more per 1000 (from 32 fewer to 534 more)	
GnRH agonist (triptorelin) + hMG vs. CC + hMG											
1 (Harrison et al., 1994)	RCT	Serious [c]	-	None	Serious [d]	Yes [i]	5/50 (10%) women	3/50 (6%) women	RR 1.7 (0.4 to 6.6)	40 more per 1000 (from 35 fewer to 336 more)	Low
							Not reported per clinical pregnancy				
GnRH agonist (buserelin) + hMG vs. CC + hMG											
1 (Harrison et al., 1994)	RCT	Serious [c]	-	None	Serious [d]	Yes [i]	5/50 (10%) women	3/50 (6%) women	RR 1.7 (0.4 to 6.6)	40 more per 1000 (from 35 fewer to 336 more)	Low
							Not reported per clinical pregnancy				

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Multiple births (the number of babies born from a multiple pregnancy)											
GnRH agonist + hMG vs. CC + hMG											
1 (Long et al., 1995)	RCT	Very serious [a, b, c]	-	None	Serious [d]	No	2/3 (67%) babies	0/4 (0%) babies	RR 6.3 (0.4 to 96.5)	Not calculable	Very low
Ovarian hyperstimulation syndrome (OHSS)											
GnRH agonist + hMG vs. CC + hMG											
1 (Grochowski et al., 1999)	RCT	Very serious [a, b]	-	None	None	No	5/160 (3%) women	41/164 (25%) women	RR 0.1 (0.1 to 0.3)	220 fewer per 1000 (from 172 fewer to 237 fewer)	Low
GnRH agonist + gonadotrophins vs. CC + hMG + GnRH antagonist											
2 (Karimzadeh and Lin, 2006)	RCTs	Very serious [a, c]	None	None	None	No	9/160 (6%) women	1/160 (1%) women	RR 6.3 (1.2 to 35)	33 more per 1000 (from 1 more to 212 more)	Low
GnRH agonist + rFSH vs. CC + rFSH + rLH + corticosteroids											
1 (Weigert et al., 2002)	RCT	Very serious [a, b, c]	-	None	None	No	12/140 (9%) women	4/154 (3%) women	RR 3.3 (1.1 to 10.0)	60 more per 1000 (from 2 more to 234 more)	Low

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Congenital abnormalities											
No evidence reported											
Patient satisfaction											
GnRH agonist + FSH/hMG vs. natural cycle or CC stimulated IVF											
1 (Hojgaard et al., 2001)	Questionnaire	Serious [k]	-	None	None	Yes [l]	60/64 (94%) women	139/141 (99%) women	RR 1.0 (0.9 to 1.0)	49 fewer per 1000 (from 108 fewer to 20 more)	Moderate
Health related quality of life											
No evidence reported											
Anxiety and/or depression											
No evidence reported											

[a] Blinding was not reported

[b] Allocation concealment not reported or inadequate

[c] A power calculation was not reported

[d] 95% confidence intervals hit or cross 0.75 and 1, and/or 1 and 1.25

[e] May include pre-term and multiple births

[f] I^2 value is greater than 33% but less than 66%

[g] Definition of clinical pregnancy was not reported

[h] Random effects model reported as I^2 value is greater than 33%

[i] This study had three arms – one received triptoerlin (GnRH agonist), the second buserelin (GnRH agonist), and the third clomifene citrate. The multiple pregnancy and pregnancy loss results were the same for both of the GnRH agonist groups

[j] All multiple pregnancies were twin pregnancies

[k] Response rate was significantly higher in the clomifene citrate group

[l] This study was done as a follow up to a study by Ingerslev (2001) (comparison with unstimulated cycles) and unpublished data (comparison with CC cycles)

Table I.15.14 GRADE findings for comparison of adjuvant growth hormone for women with a previous low response

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Live full-term singleton birth											
Growth hormone + GnRH agonist + FSH and/or hMG + hCG vs. GnRH agonist + FSH and/or hMG + hCG											
1 (Duffy et al., 2010)	Cochrane review (2 RCTs)	None	None	Serious [a]	Serious [b]	Yes [c]	6/23 (26%) women	0/15 (0%) women	OR 5.8 (0.7 to 50.4) [d]	Not estimable	Low
Clinical pregnancy											
Growth hormone + GnRH agonist + FSH and/or hMG + hCG vs. GnRH agonist + FSH and/or hMG + hCG											
1 (Duffy et al., 2010)	Cochrane review (4 RCTs)	None	None	Serious [e]	Serious [b]	Yes [c]	19/62 (31%) women	8/54 (15%) women	OR 2.6 (1.0 to 6.5)	163 more per 1000 (from 0 more to 728 more)	Low
Adverse pregnancy outcome											
No evidence reported											
Multiple pregnancies (the number of pregnancies with more than one fetus)											
Growth hormone + GnRH agonist + FSH + hCG vs. placebo + GnRH agonist + FSH + hCG (using 4 IU GH group only)											
1 (Suikkari et al., 1996)	RCT	Very serious [f, g]	-	None	Serious [b]	Yes [h]	1/10 (10%) women	0/6 (0%) women	RR 1.9 (0.1 to 40.6)	Not estimable	Very low
							1/2 (50%) pregnancies	0/0 (0%) pregnancies	Not estimable		

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Growth hormone + GnRH agonist + FSH + hCG vs. placebo + GnRH agonist + FSH + hCG (using 12 IU GH group only)											
1 (Suikkari et al., 1996)	RCT	Very serious [f, g]	-	None	NA	No	0/6 (0%) women	0/6 (0%) women	Not estimable		Low
							0/0 (0%) pregnancies	0/0 (0%) pregnancies	Not estimable		
Growth hormone + hMG + GnRH agonist + hCG + hCG vs. placebo + hMG + GnRH agonist + hCG + hCG											
1 (Owen et al., 1991)	RCT	Very serious [f, g, i]	-	None	Serious [b]	Yes [j]	2/13 (15%) women	0/12 (0%) women	RR 4.6 (0.3 to 87.9)	Not estimable	Very low
							2/4 (50%) pregnancies	0/1 (0%) pregnancies	RR 2 (0.2 to 25.8)	Not estimable	
Multiple births (the number of babies born from a multiple pregnancy)											
Growth hormone + GnRH agonist + FSH + hCG vs. placebo + GnRH agonist + FSH + hCG (using 4 IU GH group only)											
1 (Suikkari et al., 1996)	RCT	Very serious [f, g]	-	None	NA	Yes [k]	1/2 (50%) babies	0/0 (0%) babies	Not estimable		Low
Growth hormone + hMG + GnRH agonist + hCG + hCG vs. placebo + hMG + GnRH agonist + hCG + hCG											
1 (Owen et al., 1991)	RCT	Very serious [f, g, i]	-	None	Serious [b]	Yes [l]	4/6 (67%) babies	0/1 (0%) babies	RR 2.6 (0.2 to 30.2)	Not estimable	Very low
Ovarian hyperstimulation syndrome (OHSS)											
No evidence was reported											

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Congenital abnormalities											
No evidence was reported											
Patient satisfaction											
No evidence was reported											
Health related quality of life											
No evidence was reported											
Anxiety and/or depression											
No evidence was reported											

[a] Live birth was not defined and may include preterm and/or births from multiple pregnancies

[b] 95% confidence intervals hit or cross 0.75 and 1, and/or 1 and 1.25

[c] Some studies in the review may have given drugs for pretreatment or luteal support but details were not reported

[d] The analysis in the Cochrane review shows the odds ratio was weighted 60/40 in favour of the Suikkari study, despite the Owen study including more women and being of better quality. No reason was given for this weighting. When considered separately, neither study had a significant result. With weighting based on sample size alone, the OR is 11.51 (CI 0.6 to 221.4)

[e] Clinical pregnancy was not defined

[f] Blinding was not reported

[g] A power calculation was not reported

[h] The one multiple pregnancy was a triplet pregnancy

[i] Allocation concealment was not reported

[j] the two multiple pregnancies were both twin pregnancies

[k] One of the babies born was from a triplet pregnancy. It is not reported what happened to the other two triplets

[l] Four of the six babies born were from twin pregnancies (two sets of twins)

Table I.15.15 GRADE findings for comparison of adjuvant DHEA for women with a previous low response

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Live full-term singleton birth											
DHEA + GnRH agonist + rFSH + rhCG + progesterone vs. GnRH agonist + rFSH + rhCG + progesterone											
1 (Wiser et al., 2010)	RCT	Very serious [a]	-	Serious [b]	Serious [c]	Yes [d]	6/17 (35%) women	1/16 (6%) women	RR 5.7 (0.8 to 41.9)	291 more per 1000 (from 15 fewer to 1000 more)	Very low
Clinical pregnancy											
DHEA + GnRH agonist + rFSH + rhCG + progesterone vs. GnRH agonist + rFSH + rhCG + progesterone											
1 (Wiser et al., 2010)	RCT	Very serious [a]	-	None	Serious [c]	Yes [d]	7/17 (41%) women	3/16 (19%) women	RR 2.2 (0.7 to 7.1)	225 more per 1000 (from 60 fewer to 1000 more)	Very low
Adverse pregnancy outcome											
DHEA + GnRH agonist + rFSH + rhCG + progesterone vs. GnRH agonist + rFSH + rhCG + progesterone (abortion)											
1 (Wiser et al., 2010)	RCT	Very serious [a]	-	None	Serious [c]	Yes [d]	1/17 (6%) women	2/16 (13%) women	RR 0.5 (0.1 to 4.7)	66 fewer per 1000 (from 119 fewer to 462 more)	Very low
							1/7 (14%) pregnancies	2/3 (67%) pregnancies	RR 0.2 (0.0 to 1.6)	527 fewer per 1000 (from 647 fewer to 373 more)	
Multiple pregnancies (the number of pregnancies with more than one fetus)											
No evidence reported											

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Multiple births (the number of babies born from a multiple pregnancy)											
No evidence reported											
Ovarian hyperstimulation syndrome (OHSS)											
No evidence reported											
Congenital abnormalities											
No evidence reported											
Patient satisfaction											
No evidence reported											
Health related quality of life											
No evidence reported											
Anxiety and/or depression											
No evidence reported											

[a] Blinding not reported. Power analysis not conducted

[b] May include pre-term births

[c] 95% confidence intervals hit or cross 0.75 and 1.0, and/or 1.0 and 1.25

[d] One woman conceived spontaneously 45 days after DHEA exposure, but before starting IVF treatment, and was included in the study group pregnancies

Table I.15.16 GRADE findings for comparison of different types of trigger

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Live full-term singleton birth											
rhCG vs uhCG											
2 (Youssef et al., 2011a; Papanikolaou et al., 2010)	1 RCT and a Cochrane review of 6 RCTs	Very serious [a, b, c, d]	None	Serious [e, f]	Serious [g]	No	205/565 (36%) women	221/573 (39%) women	RR 1.1 (0.9 to 1.3)	31 more per 1000 (from 27 fewer to 96 more)	Very low
rhLH vs uhCG											
1 (Youssef et al., 2011a)	Cochrane review of 2 RCTs	Very serious [a, b, c]	None	Serious [e, f]	Serious [g]	No	27/144 (19%) women	27/136 (20%) women	OR 0.9 (0.5 to 1.8)	11 fewer per 1000 (from 86 fewer to 97 more)	Very low
GnRH agonist vs. hCG											
2 (Youssef et al., 2011b; Papanikolaou et al., 2010)	1 RCT and a Cochrane review of 4 RCTs	Very serious [a, d, h]	Serious [i]	Serious [f]	None	Yes [j]	51/270 (19%) women	85/262 (32%) women	RR 0.5 (0.3 to 0.9) [k]	162 fewer per 1000 (from 23 fewer to 237 fewer)	Very low

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Clinical pregnancy											
rhCG vs uhCG											
2 (Youssef et al., 2011a; Papanikolaou et al., 2010)	1 RCT and a Cochrane review of 7 RCTs	Very serious [a, b, c, d]	None	Serious [l, m]	Serious [g]	No	263/708 (37%) women	192/617 (31%) women	RR 1.2 (1.0 to 1.4)	62 more per 1000 (from 12 more to 121 more)	Very low
rhLH vs uhCG											
1 (Youssef et al., 2011a)	Cochrane review of 2 RCTs	Very serious [a, b, c]	None	Serious [l]	Serious [g]	No	36/144 (25%) women	36/136 (27%) women	OR 0.9 (0.5 to 1.6)	14 fewer per 1000 (from 102 fewer to 98 more)	Very low
GnRH agonist vs. hCG											
3 (Youssef et al., 2011; Papanikolaou et al., 2010; and Segal et al. (1992)	2 RCTs and a Cochrane review of 8 RCTs	Very serious [a, b, d, h]	Serious [i]	Serious [m, n]	Serious [g]	Yes [j]	108/482 (22%) women	138/480 (29%) women	RR 0.7 (0.5 to 1.0) [k]	80 fewer per 1000 (from 138 fewer to 3 fewer)	Very low

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Adverse pregnancy outcome											
rhCG vs uhCG (miscarriage)											
1 (Youssef et al., 2011a)	Cochrane review of 7 RCTs	Very serious [a, b, c]	None	None	Serious [g]	No	26/599 (4%) women	32/507 (6%) women	OR 0.7 (0.4 to 1.2)	20 fewer per 1000 (from 37 fewer to 9 more)	Very low
							Not reported per clinical pregnancy				
rhCG vs uhCG (abortion)											
1 (Papanikolaou et al., 2010)	RCT	Serious [d]	-	None	Serious [g]	No	1/59 (2%) women	2/60 (3%) women	RR 0.5 (0.1 to 5.5)	16 fewer per 1000 (from 32 fewer to 149 more)	Low
							1/27 (4%) pregnancies	2/18 (11%) pregnancies	RR 0.3 (0.0 to 3.4)	74 fewer per 1000 (from 108 fewer to 268 more)	
rhLH vs uhCG (miscarriage)											
1 (Youssef et al., 2011a)	Cochrane review of 2 RCTs	Very serious [a, b, c]	None	None	Serious [g]	No	9/144 (6%) women	9/136 (7%) women	OR 0.9 (0.4 to 2.4)	4 fewer per 1000 (from 41 fewer to 82 more)	Very low
							Not reported per clinical pregnancy				

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
GnRH agonist vs. hCG (miscarriage)											
1 (Youssef et al., 2011b)	Cochrane review of 8 RCTs	Very serious [a, b]	None	None	None	No	44/368 (12%) women	22/345 (6%) women	OR 1.9 (1.1 to 3.2)	56 more per 1000 (from 10 more to 124 more)	Low
							Not reported per clinical pregnancy				
GnRH agonist vs hCG (pregnancy loss)											
1 (Papanikolaou et al., 2011 b)	RCT	Very serious [d, h]	-	Serious [p]	Serious [g]	Yes [j]	1/18 (6%) women	2/17 (12%) women	RR 0.5 (0.1 to 4.7)	62 fewer per 1000 (from 112 fewer to 440 more)	Very low
							1/4 (25%) pregnancies	2/4 (50%) pregnancies	RR 0.5 (0.1 to 3.6)	250 fewer per 1000 (from 465 fewer to 1000 more)	
Multiple pregnancies (the number of pregnancies with more than one fetus)											
No evidence reported											
Multiple births (the number of babies born from a multiple pregnancy)											
No evidence reported											

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Ovarian hyperstimulation syndrome (OHSS)											
rhCG vs uhCG											
1 (Youssef et al., 2011a)	Cochrane review of 3 RCTs	Serious [a]	None	None	Serious [g]	No	11/324 (3%) women	6/225 (3%) women	OR 1.3 (0.5 to 4.1)	7 more per 1000 (from 14 fewer to 61 more)	Low
rhLH vs uhCG											
1 (Youssef et al., 2011a)	Cochrane review of 2 RCTs	Very serious [a, b, c]	None	None	Serious [g]	No	15/144 (10%) women	17/136 (13%) women	OR 0.8 (0.4 to 1.7)	21 fewer per 1000 (from 72 fewer to 70 more)	Very low
GnRH agonist vs. hCG											
1 (Youssef et al., 2011b)	Cochrane review of 5 RCTs	Very serious [a, b]	None	None	None	No	0/266 (0%) women	7/238 (3%) women	OR 0.1 (0.0 to 0.8)	28 fewer per 1000 (from 29 fewer to 1 fewer)	Low
Congenital abnormalities											
No evidence reported											
Patient satisfaction											
No evidence reported											

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Health related quality of life											
No evidence reported											
Anxiety and/or depression											
No evidence reported											

[a] Not all studies clearly reported blinding

[b] Not all studies clearly reported allocation concealment

[c] Not all studies clearly reported the method of randomisation

[d] A power calculation was not reported in all studies

[e] If live birth rates were not reported then ongoing pregnancy was used, defined as the number of women who were pregnant for more than 12 weeks

[f] May include pre-term births and/or births from multiple pregnancies

[g] 95% confidence intervals hit or cross 0.75 and 1.0, and/or 1.0 and 1.25

[h] Clinicians were blind to group allocation until day of treatment

[i] I^2 value is greater than 33% but less than 66%

[j] The GnRH agonist group in one study received LH in addition to progesterone for luteal phase support. One of these births was from a multiple pregnancy that was reduced to a singleton pregnancy

[k] Random effects model reported here as $I^2 > 33\%$

[l] Clinical pregnancy defined as fetal heart activity on ultrasound assessment, trophoblastic tissue on pathologic examination at time of miscarriage or surgery for ectopic pregnancy in the Cochrane review

[m] Clinical pregnancy defined as cardiac activity present at 7 weeks gestation in the RCT

[n] Clinical pregnancy not defined

Table I.15.19 GRADE findings for comparison of numbers of embryos transferred

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention (SET)	Comparator (DET)	Relative (95% CI)	Absolute (95% CI)	
Live full-term singleton birth - Cumulative (fresh +frozen-thawed)											
1 (Martikainen et al, 2001)	randomised trial	Very serious[a]	-	None	Serious[b]	Yes[c]	29/74 (39.2%)	36/70% (51.4%)	OR 0.61 (0.31 to 1.18)	122 fewer per 1000 (from 267 fewer to 41 more)	Very low
Live full-term singleton birth – Cumulative (fresh + frozen-thawed) – Blastocyst stage											
No evidence reported											
Live full-term singleton birth - Fresh cycle - Cleavage stage											
5 (Lukassen et al, 2005; Thurin et al, 2004; Martikainen et al, 2001; Gerris et al, 1999; Fiddelers et al, 2006)	randomised trials	Very serious[d]	Serious[e]	Serious[f]	none	Yes[g]	169/638 (26.5%)	282/635 (44.4%)	OR 0.44 (0.31 to 0.62)	184 fewer per 1000 (113 fewer to 246 fewer)	Very low
Live full-term singleton birth - Fresh cycle – Blastocyst stage											
No evidence reported											

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention (SET)	Comparator (DET)	Relative (95% CI)	Absolute (95% CI)	
Live full-term singleton birth - Frozen cycle – Cleavage stage											
1 (Martikainen et al, 2001)	randomised trials	Very serious[a]	-	None	Serious[b]	Yes[c]	7/54 (13%)	8/38 (21.1%)	OR 0.56 (0.18 to 1.70)	81 fewer per 1000 (from 165 fewer to 101 more)	Very low
Live full-term singleton birth (any live birth)– Cleavage or blastocyst											
1 (McLernon et al, 2011)	Meta-analysis of 8 RCTs	Serious[h]	Serious[i]	None	None	None	181/683 (26.5%)	285/683 (41.7%)	OR 0.50 (0.40 to 0.63)	-	Low
Live full-term singleton birth – Cleavage or blastocyst											
1 (McLernon et al, 2011)	Meta-analysis of 8 RCTs	None	Serious[i]	None	None	None	158/181 (87.3%)	169/284 (59.5%)	OR 4.93 (2.98 to 8.18)	-	Moderate

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention (SET)	Comparator (DET)	Relative (95% CI)	Absolute (95% CI)	
Clinical pregnancy											
Clinical pregnancy –Cleavage stage											
5 (Lukassen et al, 2005; Thurin et al, 2004; Martikainen et al, 2001; Gerris et al, 1999; van Montfoort et al, 2006)	randomised trials	Very serious[d]	None	Serious[b]	None	Yesp	202/638 (31.7%)	315/635 (50%)	OR 0.46 [0.37, 0.58]	184 fewer per 1000 (from 133 fewer to 229 fewer)	Very low
Clinical pregnancy - Blastocyst stage											
1 (Gardner et al, 1998)	randomised trials	Very serious[j]	-	None	Serious[b]	None	14/23 (60.9%)	19/25 (76%)	OR 0.49 (0.14 to 1.70)	152 fewer per 1000 (from 453 fewer to 83 more)	Very low

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention (SET)	Comparator (DET)	Relative (95% CI)	Absolute (95% CI)	
Multiple pregnancies (the number of pregnancies with more than one fetus)											
Cleavage stage											
5 (Lukassen et al, 2005; Thurin et al, 2004; Martikainen et al, 2001; Gerris et al, 1999; van Montfoort et al, 2006)	randomised trials	Very serious[d]	None	Serious[b]	None	Yeso	3/638 (0.5%)	82/635 (12.9%)	OR 0.04 [0.01 to 0.11]	123 fewer per 1000 (from 113 fewer to 128 fewer)	Very low
Blastocyst stage											
1 (Gardner et al, 1998)	randomised trials	Very serious[j]	-	None	None	Yes[k]	0/23 (0%)	9/25 (36%)	OR 0.04 (0.00 to 0.68)	338 fewer per 1000 (from 83 fewer to 360 fewer)	Low
Cleavage or blastocyst											
1 (McLernon et al, 2011)	Meta-analysis of 8 RCTs	None	Seriousi	None	None	None	3/181	84/285	OR 0.07 (0.03 to 0.17)	-	Moderate
Multiple births											
No evidence reported											

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention (SET)	Comparator (DET)	Relative (95% CI)	Absolute (95% CI)	
Preterm delivery – Cleavage stage											
3 (Lukassen et al, 2005; Thurin et al, 2004; Martikainen et al, 2001)	randomised trials	Very serious[l]	None	None	None	Yes[m]	18/458 (3.9%)	66/454 (14.5%)	OR 0.24 (0.14 to 0.41)	106 fewer per 1000 (from 80 fewer to 122 fewer)	Low
Preterm delivery – Blastocyst stage											
No evidence reported											
Preterm delivery – Cleavage or blastocyst stages											
1 (McLeron et al, 2011)	Meta-analysis of 8 RCTs	None	Serious[i]	None	None	None	14/181 (7.7%)	69/284 (24.3%)	OR 0.26 (0.14 to 0.48)	-	Moderate
Adverse pregnancy outcome (miscarriage, ectopic pregnancy, extra uterine pregnancy) – Cleavage stage											
4 (Lukassen et al, 2005 ;Thurin et al, 2004; Martikainen et al, 2001; van Montfoort et al, 2006)	randomised trials	Very serious[n]	None	None	Serious[b]	None	46/612 (7.5%)	54/608 (8.9%)	OR 0.84 (0.55 to 1.26)	13 fewer per 1000 (from 38 fewer to 21 more)	Very low
Adverse pregnancy outcome – Blastocyst stage											
No evidence reported											

a. Lack of blinding. Power calculation not reported. Allocation concealment not reported. It is not clear how many embryos were transferred for the frozen cycles. Live birth used rather than live full term singletonbirth (Martikainen 2001).

b. Wide confidence interval.
c. Figures may include preterm births (Martikainen 2001).
d. Method of randomisation was not clearly reported (Gerris 1999). Blinding not reported (Gerris 1999, Martikainen 2001, Lukkassen 2004, Van Monfoort 2006). Allocation concealment not reported (Gerris 1999, Martikainen 2001, Thurin 2004). Power calculation not reported (Gerris 1999, Martikainen 2001, Lukkassen 2004). Live birth used rather than live full term singleton birth (Martikainen 2001; Van Monfoort 2006; Gerris 1999; Lukkassen 2004).
e. I2 = 38% (Random effects model).
f. Indirect outcome: Figures reflect number of 'ongoing pregnancies' and may include some miscarriages, preterm, still-births (Gerris 1999).
g. Figures may include preterm births (Martikainen 20016, van Montfoort 2006, Lukassen 2004, Thurin 2004). Figures reflect number of 'ongoing pregnancies' and may include some miscarriages, preterm, still-births (Gerris 1999)
h. Live birth not live full term birth
i. Different IVF protocols combined
j. Power calculation not reported. Allocation concealment not reported (Gardner 2004).
k. Figures reflect number of twin pregnancies. Other types of multiples were not reported (Gardner 2004).
l. Blinding not reported. Power calculation not reported (Martikainen 2001, Lukkassen 2004). Allocation concealment not reported (Martikainen 2001, Thurin 2004).
m.9/10 preterm births were from the multiple pregnancies (Lukassen 2005). The preterm births were not attributed to any cause (Martikainen 2001, Thurin 2004)
n. Blinding not reported (Martikainen 2001, Lukkassen 2004, Van Monfoort 2006). Allocation concealment not reported (Martikainen 2001, Thurin 2004). Power calculation not reported (Martikainen 2001, Lukkassen 2004).
o. Figures reflect number of twin pregnancies. Other types of multiples were not reported (van Montfoort 2006)
p. Clinical pregnancy was not defined (Gerris 1999, Martikainen 2001). Figures reflect number of 'pregnancy' reported (Thurin 2004). Figures reflect number of ongoing pregnancy (van Montfoort 2006)

Table I.15.27 GRADE findings for comparison of timing of embryo transfer

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention (Day 2 – 3)	Comparator (Day 5 – 6)	Relative (95% CI)	Absolute (95% CI)	
Live full-term singleton birth – Cumulative											
No evidence reported											
Live full-term singleton birth – Fresh cycle											
Live full-term singleton birth - Fresh cycle – DET											
4 (Van,der Auwera et al , 2002; Rienzi et al , 2002; Emiliani et al, 2003; Papanikolaou et al , 2005)	randomised trials	Very serious[a]	None	None	Very serious[b]	Yes[c]	121/287 (42.2%)	140/282 (49.6%)	OR 0.74 (0.53 to 1.04)	75 fewer per 1000 (from 153 fewer to 10 more)	Very low
Live full-term singleton birth - Fresh cycle – SET											
1 (Papanikolaou et al, 2006)	randomised trial	Serious[d]	-	None	None	Yes[e]	38/176 (21.6%)	56/175 (32%)	OR 0.59 (0.36 to 0.95)	103 fewer per 1000 (from 11 fewer to 175 fewer)	Moderate
Live full-term singleton birth - Frozen cycle											
No evidence reported											

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention (Day 2 – 3)	Comparator (Day 5 – 6)	Relative (95% CI)	Absolute (95% CI)	
Clinical pregnancy											
Clinical pregnancy – DET											
7 (Van,der Auwera et al, 2002; Rienzi et al , 2002; Emiliani et al , 2003; Papanikolaou et al, 2005; Hreinsson et al, 2004; Bungum et al, 2003; Coskun et al, 2000)	randomised trials	Very serious[f]	None	None	Very serious[g]	Yes[h]	219/525 (41.7%)	232/507 (45.8%)	OR 0.86 (0.67 to 1.1)	37 fewer per 1000 (from 96 fewer to 24 more)	Very low
Clinical pregnancy – SET											
2 (Papanikolaou et al, 2006; Zech et al, 2007)	randomised trials	Serious[d, o]	None	None	None	Yes[i]	64/275 (23.3%)	100/303 (33%)	OR 0.62 (0.43 to 0.89)	96 fewer per 1000 (from 25 fewer to 155 fewer)	Moderate

Quality assessment							Summary of findings				
							No. of patients/women		Effect		
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention (Day 2 – 3)	Comparator (Day 5 – 6)	Relative (95% CI)	Absolute (95% CI)	Quality
Multiple pregnancies (the number of pregnancies with more than one fetus)											
DET											
7 (Kolibianakis et al , 2004; Van,der Auwera et al , 2002; Rienzi et al , 2002; Emiliani et al, 2003; Papanikolaou et al , 2005; Hreinsson et al , 2004; Bungum et al , 2003)	randomised trials	Very serious[j]	None	None	Very serious[k]	Yes[l]	72/658 (10.9%)	78/633 (12.3%)	OR 0.9 (0.64 to 1.27)	11 fewer per 1000 (from 41 fewer to 28 more)	Very low
SET											
1 (Papanikolaou et al , 2006)	randomised trials	Serious[d]		None	Serious[m]	None	2/176 (1.1%)	0/175 (0%)	OR 5.03 (0.24 to 105.5)	Not calculable	Low
Multiple births (the number of babies born from a multiple pregnancy)											
No evidence reported											
Preterm delivery											
No evidence reported											

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention (Day 2 – 3)	Comparator (Day 5 – 6)	Relative (95% CI)	Absolute (95% CI)	
Adverse pregnancy outcome (ectopic pregnancy, extrauterine pregnancy, miscarriage)											
DET											
7 (Kolibianakis et al , 2004; Van,der Auwera et al , 2002; Rienzi et al , 2002; Emiliani et al, 2003; Papanikolaou et al , 2005; Hreinsson et al , 2004; Bungum et al , 2003)	randomised trials	Very serious[j]	None	None	Serious[m]	Yes[n]	51/658 (7.8%)	67/633 (10.6%)	OR 0.72 (0.49 to 1.05)	27 fewer per 1000 (from 51 fewer to 5 more)	Very low
SET											
2 (Papanikolaou et al, 2006; Zech et al, 2007)	randomised trials	Serious[d, o]	-	None	Serious[m]	None	29/275 (10.5%)	26/303 (8.6%)	OR 1.23 (0.7 to 2.15)	18 more per 1000 (from 24 fewer to 82 more)	Low

a. It is not clear whether the allocation concealment was adequate. Method of randomisation was not reported in details (Van der Auwera 2002). Allocation concealment not reported. Power calculation not reported (Rienzi 2002). Blinding not reported (Rienzi 2002, Van der Auwera 2002). Allocation concealment not reported (Papanikolaou 2005). Full term birth not reported (Van der Auwera 2002; Emiliani, 2003; Rienzi 2002; Papanikolaou, 2005)

b.The sample size did not meet power calculation (Van der Auwera 2002). Wide confidence interval. Sample size did not meet power calculation (Papanikolaou 2005)

c.Figures reflect number of 'births' and may include preterm and still-births (Rienzi 2002; Van der Auwera 2002)
d.Allocation concealment not reported (Papanikolaou 2006).
e.Figures reflect number of 'births' and may include preterm and still-births (Papanikolaou 2006).
f. It is not clear whether the allocation concealment was adequate (Bungum 2003, Hreinsson 2004 and Van der Auwera 2002). Method of randomisation was not reported in details (Van der Auwera 2002) Allocation concealment not reported. Power calculation not reported (Rienzi 2002). Blinding not reported (Hreinsson 2004, Rienzi 2002, and Van der Auwera 2002). In 6/61 patients in the blastocyst group, the protocol was not adhered to in terms of timing and numbers of embryo transferred and it was not reported whether they were excluded from the analysis (Bungum 2003). Allocation concealment not reported (Coskun 2000, Emiliani 2003 and Papanikolaou 2005). Power calculation not reported (Coskun 2000 and Emiliani 2003). Blinding not reported (Coskun 2000, Emiliani 2003 and Papanikolaou 2005)
g.The sample size did not meet power calculation (Bungum 2003, Hreinsson 2004). Wide confidence interval

Table I.15.31 GRADE findings for comparison luteal phase support vs. no luteal phase support

Quality assessment							**Summary of findings**				
							No. of patients/women		**Effect**		**Quality**
No. of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Intervention**	**Comparator**	**Relative (95% CI)**	**Absolute (95% CI)**	
Live full-term singleton birth											
Any type of support vs. placebo/no support											
1 (van der Linden et al., 2011)	Cochrane review of 2 RCTs	Very serious [a, b, c]	None	Serious [d]	None	No	18/117 (15%) women	5/77 (7%) women	OR 2.8 (1.1 to 6.9)	95 more per 1000 (from 6 more to 259 more)	Very low
Progesterone vs. placebo/no support											
1 (van der Linden et al., 2011)	Cochrane review of 1 RCT	Very serious [a, b, c]	-	Serious [d]	None	No	15/104 (14%) women	2/52 (4%) women	OR 3.0 (1.0 to 8.6)	67 more per 1000 (from 1 more to 217 more)	Very low

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
hCG vs. placebo											
1 (van der Linden et al., 2011)	Cochrane review of 1 RCT	Very serious [a, b, c]	-	Serious [d]	Serious [e]	No	3/13 (23%) women	3/25 (12%) women	OR 2.3 (0.4 to 14)	115 more per 1000 (from 72 fewer to 533 more)	Very low
Clinical pregnancy											
Any type of support vs. placebo/no support											
1 (van der Linden et al., 2011)	Cochrane review of 12 RCTs	Very serious [a, b, c]	None	None	None	No	181/831 (22%) women	117/756 (16%) women	OR 1.6 (1.2 to 2.0)	66 more per 1000 (from 25 more to 114 more)	Low
Progesterone vs. placebo/no support											
1 (van der Linden et al., 2011)	Cochrane review of 7 RCTs	Very serious [a, b, c]	None	None	None	No	106/470 (23%) women	52/371 (14%) women	OR 1.8 (1.3 to 2.6)	90 more per 1000 (from 34 more to 158 more)	Low
Support with hCG vs. placebo support											
1 (van der Linden et al., 2011)	Cochrane review of 5 RCTs	Very serious [a, b, c]	None	None	Serious [e]	No	75/361 (21%) women	65/385 (17%) women	OR 1.3 (0.9 to 1.9)	40 more per 1000 (from 14 fewer to 108 more)	Very low

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Adverse pregnancy outcome											
Any type of support vs. placebo/no support (miscarriage)											
1 (van der Linden et al., 2011)	Cochrane review of 5 RCTs	Very serious [a, b, c]	None	None	Serious [e]	No	14/271 (5%) women	12/294 (4%) women	OR 1.3 (0.6 to 2.8)	10 more per 1000 (from 17 fewer to 65 more)	Very low
	Cochrane review of 4 RCTs						14/59 (24%) pregnancies	10/51 (20%) pregnancies	OR 1.27 (0.5 to 3.1)	40 more per 1000 (from 84 fewer to 235 more)	
Support with progesterone vs. placebo (miscarriage)											
1 (van der Linden et al., 2011)	Cochrane review of 3 RCTs	Very serious [a, b, c]	None	None	Serious [e]	No	10/207 (5%) women	9/218 (4%) women	OR 1.2 (0.5 to 3.0)	7 more per 1000 (from 21 fewer to 73 more)	Very low
	Cochrane review of 2 RCTs						10/43 (23%) pregnancies	7/34 (21%) pregnancies	OR 1.2 (0.4 to 3.4)	24 more per 1000 (from 112 fewer to 260 more)	

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Support with hCG vs. placebo (miscarriage)											
1 (van der Linden et al., 2011)	Cochrane review of 2 RCTs	Very serious [a, b, c]	Serious [f]	None	Serious [e]	No	4/64 (6%) women	3/76 (4%) women	OR 1.5 (0.3 to 6.9)	18 more per 1000 (from 26 fewer to 180 more)	Very low
							4/16 (25%) pregnancies	3/17 (18%) pregnancies	OR 1.6 (0.3 to 8.1)	76 more per 1000 (from 114 fewer to 458 more)	
Multiple pregnancies (the number of pregnancies with more than one fetus)											
Support with progesterone vs. placebo support											
1 (van der Linden et al., 2011)	Cochrane review of 1 RCT	Very serious [a, b]	-	None	Serious [e]	No	1/12 (8%) women	0/22 (0%) women	OR 17 (0.3 to 1027.3)	Not calculable	Very low
							Not reported by clinical pregnancy				
Multiple births (the number of babies born from a multiple pregnancy)											
No evidence reported											
Ovarian hyperstimulation syndrome (OHSS)											
Support with hCG vs. placebo support											

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
1 (van der Linden et al., 2011)	Cochrane review of 1 RCT	Very serious [b, c]	-	None	None	No	30/193 (16%) women	8/194 (4%) women	OR 3.6 (1.9 to 7.1)	93 more per 1000 (from 32 more to 192 more)	Low
Congenital abnormalities											
No evidence reported											
Patient satisfaction											
No evidence reported											
Health related quality of life											
No evidence reported											
Anxiety and/or depression											
No evidence reported											

[a] The method of randomisation was not clearly reported in one or more studies

[b] Allocation concealment was not clearly reported in one or more studies

[c] Blinding of participants and/or assessors was not clearly reported in one or more studies

[d] May include pre-term births and births from multiple pregnancies

[e] 95% confidence intervals hit or cross 0.75 and 1, and/or 1 and 1.25

[f] I^2 value is greater than 33% but less than 66%

Table I.15.32 GRADE findings for comparison of types of support

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Live full-term singleton birth											
Progesterone vs. hCG											
1 (van der Linden et al., 2011)	Cochrane review of 2 RCTs	Very serious [a, b, c]	None	Serious [d]	Serious [e]	No	4/96 (4%) women	11/107 (10%) women	OR 0.4 (0.1 to 1.2)	58 fewer per 1000 (from 87 fewer to 16 more)	Very low
Progesterone vs. oestrogen											
1 (Ata et al., 2010)	RCT	Serious [a]	-	None	Very serious [e, f]	No	11/30 (37%) women	10/30 (33%) women	RR 1.1 (0.6 to 2.2)	33 more per 1000 (from 150 fewer to 397 more)	Very low
Progesterone vs. progesterone + hCG											
1 (van der Linden et al., 2011)	Cochrane review of 1 RCT	Very serious [a, c]	-	Serious [d]	Serious [e]	No	3/70 (4%) women	5/62 (8%) women	OR 0.5 (0.1 to 2.2)	37 fewer per 1000 (from 70 fewer to 79 more)	Very low
Progesterone vs. progesterone + oestrogen											
1 (van der Linden et al., 2011)	Cochrane review of 1 RCT	Very serious [a, b, c]	-	Serious [d]	Serious [e]	No	11/50 (22%) women	10/50 (20%) women	OR 1.1 (0.4 to 2.9)	20 more per 1000 (from 103 fewer to 224 more)	Very low

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Clinical pregnancy											
Progesterone vs. hCG											
1 (van der Linden et al., 2011)	Cochrane review of 14 RCTs	Very serious [a, b, c]	None	None	Serious [e]	No	285/943 (30%) women	248/852 (29%) women	OR 1.1 (0.9 to 1.3)	12 more per 1000 (from 30 fewer to 59 more)	Very low
Progesterone vs. oestrogen											
1 (Ata et al., 2010)	RCT	Serious [a]	-	None	Very serious [e, f]	No	16/30 (53%) women	14/30 (47%) women	RR 1.1 (0.7 to 1.9)	65 more per 1000 (from 145 fewer to 420 more)	Very low
Progesterone vs. progesterone + hCG											
1 (van der Linden et al., 2011)	Cochrane review of 7 RCTs	Very serious [a, c]	None	None	Serious [e]	No	169/540 (31%) women	173/540 (32%) women	OR 1.0 (0.7 to 1.3)	9 fewer per 1000 (from 62 fewer to 50 more)	Very low
Progesterone vs. progesterone + oestrogen											
1 (van der Linden et al., 2011)	Cochrane review of 7 RCTs	Very serious [a, b, c]	Very serious [g]	None	Serious [e]	No	312/664 (47%) women	237/546 (43%) women	OR 0.8 (0.6 to 1.0)	54 fewer per 1000 (from 112 fewer to 7 more)	Very low

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Adverse pregnancy outcome											
Progesterone vs hCG (miscarriage)											
1 (van der Linden et al., 2011)	Cochrane review of 5 RCTs	Very serious [a, b, c]	None	None	Serious [e]	No	21/381 (6%) women	16/389 (4%) women	OR 1.3 (0.7 to 2.6)	13 more per 1000 (from 12 fewer to 59 more)	Very low
							21/134 (16%) pregnancies	16/113 (14%) pregnancies	OR 1.1 (0.6 to 2.3)	16 more per 1000 (from 57 fewer to 133 more)	
Progesterone vs oestrogen (miscarriage)											
1 (Ata et al., 2010)	RCT	Serious [a]	-	None	Very serious [e, f]	No	4/30 (13%) women	2/30 (7%) women	RR 2 (0.4 to 10.1)	67 more per 1000 (from 40 fewer to 607 more)	Very low
							4/16 (25%) pregnancies	2/14 (14%) pregnancies	RR 1.8 (0.4 to 8.2)	107 more per 1000 (from 89 fewer to 1000 more)	

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Progesterone vs. progesterone + hCG (miscarriage)											
1 (van der Linden et al., 2011)	Cochrane review of 1 RCT	Very serious [a, c]	-	None	Serious [e]	No	4/70 (6%) women	4/62 (7%) women	OR 0.9 (0.2 to 3.7)	7 fewer per 1000 (from 50 fewer to 137 more)	Very low
							4/13 (31%) pregnancies	4/13 (31%) pregnancies	OR 1 (0.2 to 5.1)	0 fewer per 1000 (from 226 fewer to 387 more)	
Progesterone vs. progesterone + oestrogen (miscarriage)											
1 (van der Linden et al., 2011)	Cochrane review of 6 RCTs	Very serious [a, b, c]	None	None	Serious [e]	No	95/649 (15%) women	58/497 (12%) women	OR 1.0 (0.7 to 1.4)	5 fewer per 1000 (from 38 fewer to 38 more)	Very low
	Cochrane review of 4 RCTs		Very serious [g]				82/267 (31%) pregnancies	43/161 (27%) pregnancies	OR 1.0 (0.6 to 1.5)	10 fewer per 1000 (from 90 fewer to 89 more)	

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Multiple pregnancies (the number of pregnancies with more than one fetus)											
Progesterone vs. hCG											
1 (van der Linden et al., 2011)	Cochrane review of 1 RCT	Very serious [a, c]	-	None	Serious [e]	No	1/70 (1%) women	3/77 (4%) women	OR 0.4 (0.1 to 2.9)	23 fewer per 1000 (from 37 fewer to 66 more)	Very low
							1/13 (8%) pregnancies	3/15 (20%) pregnancies	OR 0.4 (0.1 to 3.1)	113 fewer per 1000 (from 188 fewer to 233 more)	
Progesterone vs. progesterone + hCG											
1 (van der Linden et al., 2011)	Cochrane review of 1 RCT	Very serious [a, c]	-	None	Serious [e]	No	1/70 (1%) women	3/62 (5%) women	OR 0.3 (0.0 to 2.3)	32 fewer per 1000 (from 46 fewer to 56 more)	Very low
							1/13 (8%) women	3/13 (23%) women	OR 0.3 (0.0 to 2.6)	143 fewer per 1000 (from 219 fewer to 206 more)	
Multiple births (the number of babies born from a multiple pregnancy)											
No evidence reported											

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Ovarian hyperstimulation syndrome (OHSS)											
Progesterone vs. hCG											
1 (van der Linden et al., 2011)	Cochrane review of 5 RCTs	Very serious [a, b, c]	None	None	None	No	30/524 (6%) women	46/484 (10%) women	OR 0.6 (0.4 to 0.9)	39 fewer per 1000 (from 6 fewer to 60 fewer)	Low
Progsterone vs. progesterone + hCG											
1 (van der Linden et al., 2011)	Cochrane review of 3 RCTs	Very serious [a, c]	None	None	None	No	18/359 (5%) women	37/354 (11%) women	OR 0.5 (0.3 to 0.8)	55 fewer per 1000 (from 20 fewer to 75 fewer)	Low
Progesterone vs. progesterone + oestrogen											
1 (van der Linden et al., 2011)	Cochrane review of 1 RCT	Very serious [a]	-	None	Serious [e]	No	0/29 (0%) women	2/30 (7%) women	OR 0.1 (0.0 to 2.2)	57 fewer per 1000 (from 66 fewer to 70 more)	Very low
Congenital abnormalities											
No evidence reported											
Patient satisfaction											
No evidence reported											
Health related quality of life											
No evidence reported											

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Anxiety and/or depression											
No evidence reported											

[a] Blinding of participants and/or assessors was not clearly reported in one or more studies
[b] The method of randomisation was not clearly reported in one or more studies
[c] Allocation concealment was not clearly reported in one or more studies
[d] May include pre-term births and births from multiple pregnancies
[e] 95% confidence intervals hit or cross 0.75 and 1, and/or 1 and 1.25
[f] A power calculation was reported, but the required sample size was not met
[g] I^2 value was greater than 66%

Table I.15.33 GRADE findings for comparisons for length of luteal phase support

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Live full-term singleton birth											
Progesterone daily on day of oocyte retrieval until pregnancy confirmation with ultrasound (5 to 6 weeks) vs. progesterone daily on day of embryo transfer until pregnancy test (11 days)											
1 (Goudge et al., 2010)	RCT	Very serious [a, b]	-	Serious [c]	Serious [d]	Yes [e]	20/46 (44%) women	13/51 (26%) women	RR 1.7 (1.0 to 3.0)	181 more per 1000 (from 10 fewer to 517 more)	Very low

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Progesterone from day of embryo transfer until day of positive hCG test (2 weeks) vs. progesterone from day of embryo transfer until three weeks after positive hCG test (5 weeks)											
1 (Nyboe et al., 2002)	RCT	Serious [b]	-	Serious [c]	None	No	86/150 (57%) women	94/153 (61%) women	RR 0.9 (0.8 to 1.1)	43 fewer per 1000 (from 141 fewer to 74 more)	Low
GnRH agonist from 21st day of preceding cycle until 12th day after ET vs. GnRH agonist from 21st day of preceding cycle until trigger administration											
1 (Isikoglu et al., 2007)	RCT	Serious [a]	-	Serious [c]	Serious [d]	No	34/90 (38%) women	32/91 (35%) women	RR 1.1 (0.7 to 1.6)	25 more per 1000 (from 95 fewer to 204 more)	Very low
Clinical pregnancy											
Progesterone daily on day of oocyte retrieval until pregnancy confirmation with ultrasound (5 to 6 weeks) vs. progesterone daily on day of embryo transfer until pregnancy test (11 days)											
1 (Goudge et al., 2010)	RCT	Very serious [a, b]	-	Serious [f]	Serious [d]	Yes [e]	29/46 (63%) women	32/51 (63%) women	RR 1 (0.7 to 1.4)	0 fewer per 1000 (from 163 fewer to 226 more)	Very low
Progesterone from day of embryo transfer until day of positive hCG test (2 weeks) vs. progesterone from day of embryo transfer until three weeks after positive hCG test (5 weeks)											
1 (Nyboe et al., 2002)	RCT	Serious [b]	-	Serious [g]	None	No	133/150 (89%) women	139/153 (91%) women	RR 1.0 (0.9 to 1.1)	18 fewer per 1000 (from 91 fewer to 45 more)	Low

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Progesterone until 16 days after embryo transfer vs. progesterone until 7 weeks of gestation											
1 (Kyrou et al., 2011)	RCT	Serious [b]	-	Serious [g]	Serious [h]	No	90/100 (90%) women	83/100 (83%) women	RR 1.1 (1.0 to 1.2)	66 more per 1000 (from 25 fewer to 174 more)	Very low
Adverse pregnancy outcome											
Progesterone from day of embryo transfer until day of positive hCG test (2 weeks) vs. progesterone from day of embryo transfer until three weeks after positive hCG test (5 weeks) (miscarriage)											
1 (Nyboe et al., 2002)	RCT	Serious [b]	-	None	Serious [d]	No	22/300 (7%) women	18/306 (6%) women	RR 1.3 (0.7 to 2.3)	15 more per 1000 (from 18 fewer to 75 more)	Very low
							Not reported per clinical pregnancy				
Progesterone from day of embryo transfer until day of positive hCG test (2 weeks) vs. progesterone from day of embryo transfer until three weeks after positive hCG test (5 weeks) (ectopic pregnancy)											
1 (Nyboe et al., 2002)	RCT	Serious [b]	-	None	Serious [d]	No	0/150 (0%) women	2/153 (1%) women	RR 0.2 (0.0 to 4.2)	10 fewer per 1000 (from 13 fewer to 42 more)	Very low
							Not reported per clinical pregnancy				

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Progesterone until 16 days after embryo transfer vs. progesterone until 7 weeks of gestation (abortion)											
1 (Kyrou et al., 2011)	RCT	Serious [b]	NA	None	Very serious [d, h]	No	17/100 (17%) women	22/100 (22%) women	RR 0.8 (0.4 to 1.4)	51 fewer per 1000 (from 123 fewer to 81 more)	Very low
							17/90 (19%) pregnancies	22/83 (27%) pregnancies	RR 0.7 (0.4 to 1.3)	77 fewer per 1000 (from 156 fewer to 66 more)	
Progesterone until 16 days after embryo transfer vs. progesterone until 7 weeks of gestation (ectopic)											
1 (Kyrou et al., 2011)	RCT	Serious [b]	-	None	Very serious [d, h]	No	1/100 (1%) women	4/100 (4%) women	RR 0.3 (0.0 to 2.2)	30 fewer per 1000 (from 39 fewer to 48 more)	Very low
							1/90 (1%) pregnancies	4/83 (5%) pregnancies	RR 0.2 (0.0 to 2.0)	37 fewer per 1000 (from 47 fewer to 49 more)	

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Multiple pregnancies (the number of pregnancies with more than one fetus)											
Progesterone daily on day of oocyte retrieval until pregnancy confirmation with ultrasound (5 to 6 weeks) vs. progesterone daily on day of embryo transfer until pregnancy test (11 days)											
1 (Goudge et al., 2010)	RCT	Very serious [a, b]	-	None	Serious [d]	Yes [e, i]	4/46 (9%) women	12/51 (24%) women	RR 0.4 (0.1 to 1.1)	148 fewer per 1000 (from 205 fewer to 16 more)	Very low
							4/29 (14%) pregnancies	12/39 (31%) pregnancies	RR 0.5 (0.2 to 1.3)	169 fewer per 1000 (from 258 fewer to 77 more)	
Progesterone from day of embryo transfer until day of positive hCG test (2 weeks) vs. progesterone from day of embryo transfer until three weeks after positive hCG test (5 weeks)											
1 (Nyboe et al., 2002)	RCT	Serious [b]	-	Serious [j]	Serious [d]	Yes [k]	37/150 (25%) women	39/153 (26%) women	RR 1.0 (0.7 to 1.4)	8 fewer per 1000 (from 87 fewer to 110 more)	Very low
							37/133 (28%) pregnancies	39/139 (28%) pregnancies	RR 1.0 (0.7 to 1.5)	3 fewer per 1000 (from 90 fewer to 126 more)	

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Progesterone until 16 days after embryo transfer vs. progesterone until 7 weeks of gestation											
1 (Kyrou et al., 2011)	RCT	Serious [b]	-	None	Very serious [d, h]	No	9/100 (9%) women	7/100 (7%) women	RR 1.3 (0.5 to 3.3)	20 more per 1000 (from 35 fewer to 162 more)	Very low
							9/90 (10%) pregnancies	7/83 (8%) pregnancies	RR 1.2 (0.5 to 3.0)	16 more per 1000 (from 46 fewer to 172 more)	
Multiple births (the number of babies born from a multiple pregnancy)											
Progesterone daily on day of oocyte retrieval until pregnancy confirmation with ultrasound (5 to 6 weeks) vs. progesterone daily on day of embryo transfer until pregnancy test (11 days)											
1 (Goudge et al., 2010)	RCT	Very serious [a, b]	-	None	None	Yes [e, i]	8/28 (29%) babies	24/37 (65%) babies	RR 0.4 (0.2 to 0.8)	363 fewer per 1000 (from 110 fewer to 499 fewer)	Very low
Progesterone from day of embryo transfer until day of positive hCG test (2 weeks) vs. progesterone from day of embryo transfer until three weeks after positive hCG test (5 weeks)											
1 (Nyboe et al., 2002)	RCT	Serious [b]	-	None	Serious [d]	Yes [l]	64/150 (43%) babies	64/158 (41%) babies	RR 1.1 (0.8 to 1.4)	20 more per 1000 (from 77 fewer to 150 more)	Low
Ovarian hyperstimulation syndrome (OHSS)											
No evidence reported											

Quality assessment							Summary of findings				
							No. of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Congenital abnormalities											
No evidence reported											
Patient satisfaction											
No evidence reported											
Health related quality of life											
No evidence reported											
Anxiety and/or depression											
No evidence reported											

[a] Power calculation was not reported

[b] Blinding was not reported

[c] May include pre-term births and/or births from multiple pregnancies

[d] 95% confidence intervals hit or cross 0.75 and 1, and/or 1 and 1.25

[e] Women in the 11 day group continued progesterone treatment if progesterone levels were less than 15ng/ML

[f] Clinical pregnancy was not defined

[g] Defined as 'ongoing pregnancy at 7 weeks'

[h] The study was not adequately powered

[i] All of the multiple pregnancies and multiple births were twins

[j] Defined as 'ongoing multiple pregnancy'

[k] These were all twin pregnancies apart from one triplet pregnancy in the three week progesterone group

[l] All of the babies born from multiple pregnancies were twins. It is not clear what happened to the triplet pregnancy

Table I.19.2 GRADE findings for cryopreservation of embryos, oocytes and ovarian tissue: clinical outcomes

Quality assessment							Summary of findings				
							No. of samples		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Vitrification	Slow-freezing	Relative (95% CI)	Absolute (95% CI)	
Live full-term singleton births											
Oocytes											
No evidence reported											
Embryos											
1 (Wilding et al., 2010)	RCT	None	-	Serious [a]	Serious [b]	None	19/147 (13%)	17/141 (12%)	OR 1.1 (0.5 to 2.2)	8 more per 1000 (from 52 fewer to 110 more)	Moderate
Ovarian tissue											
No evidence reported											
Clinical pregnancy											
Oocytes											
1 (Smith et al., 2010)	RCT	None	-	None	None	None	18/48 (38%)	4/30 (13%)	OR 3.9 (1.2 to 13.0)	242 more per 1000 (from 19 more to 533 more)	High
Embryos											
1 (Wilding et al., 2010)	RCT	None	-	None	Serious [b]	None	21/147 (14%)	19/141 (14%)	OR 1.1 (0.6 to 2.1)	8 more per 1000 (from 56 fewer to 111 more)	Moderate
Ovarian tissue											
No evidence reported											

Quality assessment							Summary of findings				
							No. of samples		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Vitrification	Slow-freezing	Relative (95% CI)	Absolute (95% CI)	
Adverse pregnancy outcomes											
Oocytes											
No evidence reported											
Embryos											
No evidence reported											
Ovarian tissue											
No evidence reported											
Multiple pregnancies (the number of pregnancies with more than one fetus)											
Oocytes											
No evidence reported											
Embryos											
No evidence reported											
Ovarian tissue											
No evidence reported											
Multiple births (the number of babies born from a multiple pregnancy)											
Oocytes											
No evidence reported											
Embryos											
No evidence reported											

Quality assessment							Summary of findings				
							No. of samples		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Vitrification	Slow-freezing	Relative (95% CI)	Absolute (95% CI)	
Ovarian tissue											
No evidence reported											
Ovarian hyperstimulation syndrome (OHSS)											
Oocytes											
No evidence reported											
Embryos											
No evidence reported											
Ovarian tissue											
No evidence reported											
Fetal abnormalities											
Oocytes											
No evidence reported											
Embryos											
No evidence reported											
Ovarian tissue											
No evidence reported											
Patient satisfaction											
Oocytes											
No evidence reported											

Quality assessment							Summary of findings				
							No. of samples		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Vitrification	Slow-freezing	Relative (95% CI)	Absolute (95% CI)	
Embryos											
No evidence reported											
Ovarian tissue											
No evidence reported											
Health related quality of life											
Oocytes											
No evidence reported											
Embryos											
No evidence reported											
Ovarian tissue											
No evidence reported											
Anxiety and/or depression											
Oocytes											
No evidence reported											
Embryos											
No evidence reported											
Ovarian tissue											
No evidence reported											

[a] It is not clear whether this also includes pre-term births and/or births from multiple pregnancies

[b] 95% Confidence interval hits or crosses 0.75 and 1, and/or 1 and 1.25

Table I.19.3 GRADE findings for cryopreservation of embryos, oocytes and ovarian tissue: procedural outcomes

Quality assessment							Summary of findings				
							No. of samples		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	vitrification	Slow-freezing	Relative (95% CI)	Absolute (95% CI)	
Post-thaw survival [c]											
Oocytes											
2 (Cao et al., 2009; Fasano et al., 2010)	RCTs	None	Serious[a]	None	None	None	376/423 (89%)	150/230 (65%)	OR 3.9 (2.6 to 5.9)	228 more per 1000 (from 179 more to 265 more)	Moderate
Embryos											
4 (Balaban et al., 2008; Huang et al., 2005; Kim et al., 2000; Zheng et al., 2005)	RCTs	None	Serious[a]	None	None	None	441/505 (87%)	829/1147 (72%)	OR 1.9 (1.4 to 2.6)	109 more per 1000 (from 60 more to 148 more)	Moderate
Ovarian tissue											
No evidence reported											
Number with abnormal Morphology[d]											
Oocyte											
No evidence reported											

Quality assessment							Summary of findings				
							No. of samples		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	vitrification	Slow-freezing	Relative (95% CI)	Absolute (95% CI)	
Embryos											
2 (Balaban et al., 2008; Zheng et al., 2005)	RCTs	None	Serious[a]	None	None	None	59/271 (22%)	135/259 (52%)	OR 0.3 (0.2 to 0.4)	301 fewer per 1000 (from 229 fewer to 357 fewer)	Moderate
Ovarian tissue											
2 (Isachenko et al., 2009; Li et al., 2007)	RCTs	None	None	None	Serious[b]	None	25/126 (20%)	34/140 (24%)	OR 0.8 (0.4 to 1.4)	43 fewer per 1000 (from 122 fewer to 67 more)	Moderate

[a] Heterogeneity was high (I^2 > 33%)

[b] 95% Confidence interval hits or crosses 0.75 and 1.0, and/or 1.0 and 1.25

[c] 'Post thaw survival' was defined differently between studies: Balaban - >50% of the blastomeres were intact or at least 3 viable cells and at least blatomere dividing by 18hrs post thaw culture; Zheng – 2hrs incubation, embryos assessed for integrity and number of surviving blastomeres. Those with half or more were classified as survived; Cao - microscopic evaluation 2 to 3 hours after culture based on the morphology of the oocyte membrane intergrity; Fasano - absence of overt cell degeneration, elongated shape, thick or distorted zona, expended perivitelline space and dark pronounced cytoplasm; Huang - 16 to 24 hrs culture then presented an ICM, trophoectoderm and a re-expanding blastocoels cavity; Kim – main article in Korean.

[d] 'abnormal morphology' was defined differently between studies: Balaban - 100% intact blastomere; Zheng – intact embryos; Li – Eosinophilia of the ooplasm, contraction and clumping of the chromatin material, and wrinkling of the nuclear membrane of the oocyte signs of atresia; Isachenko – grading of morphology of follicles grade 3 = partly or fully disrupted granulose or cytoplasm and picnotic nucleua classified as abnormal.

Table I.20.1 GRADE findings for long-term safety of ovulation induction and ovarian stimulation agents in women

Quality assessment							Summary of findings				
							No. of people		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Breast cancer											
Proportion of cases and rate ratios – GnRH (treated vs. control)											
1 (Jensen et al., 2007)	Case control study	None	-	-	Serious[a]	Yes[b]	18/98	313/1,128	1.3 (0.8 to 2.2)	-	Very low
Number of cases and rate ratios – Clomifene (treated vs. general population)											
1 (Brinton et al., 2004)	Retrospective Cohort Study	Serious[c]	-	-	Serious[a]	Yes[d]	80	-	1.0 (0.7 to 1.3)	-	Very low
Number of cases and relative risk – Clomifene (treated vs. control)											
1 (Gauthier et al 2004)	Prospective cohort study	Serious[e]	-	-	None	Yes[f]	66	2,388	1.0 (0.8 to 1.2)	-	Very low
Proportion of cases and rate ratios - Clomifene (treated vs. Control)											
1 (Jensen et al., 2007)	Case control study	None	-	-	Serious[a]	Yes[b]	102/405	229/82	1.1 (0.9 to 1.4)	-	Very low
Hazard ratio - Clomifene (treated vs. General population)											
1 (Calderon-Margalit et al., 2009)	Retrospective Cohort Study	Serious[c]	-	-	Serious[a]	Yes[g]	Not reported	Not reported	1.3 (0.8 to 2.0)	-	Very low
Risk ratios - Clomifene											
1 (Zreik et al., 2010)	Meta-analysis	Very serious[h]	None	-	None	No	Not reported	Not reported	1.1 (1.0 to 1.2)	-	Very low

Quality assessment							Summary of findings				
							No. of people		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Number of cases and rate ratios - Clomifene + Gonadotrophin (treated vs. general population)											
1 (Brinton et al., 2004)	Retrospective Cohort Study	Serious[c]	-	-	serious[a]	Yes[d]	28	-	1.2 (0.8 to 1.7)	-	Very low
Risk ratio - Clomifene + hMG											
4 (Zreik et al., 2010)	Meta-analysis	Very Serious[h]	None	-	None	No	Not reported	Not reported	1.2 (1.0 to 1.5)	-	Very low
Number of cases and rate ratios - Gonadotrophins (treated vs. general population)											
1 (Brinton et al., 2004)	Retrospective Cohort Study	Serious[c]	-	-	Serious[a]	Yes[d]	3	-	0.6 (0.2 to 1.8)	-	Very low
Number of cases and relative risk - Gonadotrophins (treated vs. Control)											
1 (Gauthier et al., 2004)	Prospective cohort study	Serious[e]	-	-	Serious[a]	Yes[f]	23	2,388	1.0 (0.7 to 1.5)	-	Very low
Proportion of cases and rate ratios - Gonadotrophins (treated vs. control)											
1 (Jensen et al., 2007)	Case control study	None	-	-	Serious[a]	Yes[b]	36/165	295/1,061	1.2 (0.8 to 1.8)	-	Very low
Number of cases and relative risk - hCG (treated vs. Control)											
1 (Gauthier et al 2004)	Prospective cohort study	Serious[e]	-	-	Serious[a]	Yes[f]	56	2,388	1.0 (0.7 to 1.3)	-	Very low
Proportion of cases and rate ratio - hCG (treated vs. control)											
1 (Jensen et al., 2007)	Case control study	None	-	-	Serious[a]	Yes[b]	94/395	237/831	0.9 (0.7 to 1.2)	-	Very low

Quality assessment							Summary of findings				
							No. of people		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Cases vs. control – HCG											
1 (Salhab et al., 2005)	Systematic Review	None	-	-	Serious[a]	Yes[i]	45/744	65/744	0.8 (0.5 to 1.2)	-	Very low
Proportion of cases and rate ratio – Progesterone (treated vs. control)											
1 (Jensen et al., 2007)	Case control study	None	-	-	Serious[a]	Yes[b]	8/13	323/1,213	3.4 (1.6 to 7.1)	-	Very low
Risk ratio - Other specific drugs (hCG, hMG, hMG +GnRH, GnRH, Gonadotrophins)											
11 (Zreik et al., 2010)	Meta-analysis	Very serious[h]	None	-	None	No	Not reported	Not reported	1.0 (0.9 to 1.1)	-	Very low
Uterine Cancer											
Proportion of cases and rate ratio – GnRH (treated vs. control)											
1 (Jensen et al., 2009)	Case control study	None	-	-	Serious[a]	Yes[j]	7/110	76/1,133	1.1 (0.5 to 2.5)	-	Very low
Number of cases and risk ratios – Clomifene (treated vs. control)											
1 (Althuis et al., 2005)	RCS	Serious[c]	-	-	Serious[a]	No	19	20	1.8 (0.9 to 3.4)	-	Very low
Proportion of cases and rate ratio – Clomifene (treated vs. control)											
1 (Jensen et al., 2009)	Case control study	None	-	-	Serious[a]	Yes[j]	29/417	54/826	1.4 (0.8 to 2.2)	-	Very low
Hazard ratio – Clomifene (treated vs. General population)											
1 (Calderon-Margalit et al., 2009)	Retropsective Cohort Study	Serious[c]	-	-	Serious[a]	Yes[g]	Not reported	Not reported	4.6 (1.6 to 13.3)	-	Very low

Quality assessment							Summary of findings				
							No. of people		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Proportion of cases and rate ratio – Gonadotrophin (treated vs. control)											
1 (Jensen et al., 2009)	Case control study	None	-	-	Serious[a]	Yes[j]	17/184	66/1,059	2.2 (1.1 to 4.5)	-	Very low
Proportion of cases and rate ratio – hCG (treated vs. control)											
1 (Jensen et al., 2009)	Case control study	None	-	-	Serious[a]	Yes[j]	31/413	52/830	1.4 (0.8 to 2.2)	-	Very low
Cervical cancer											
Number of cases and risk ratios - Clomifene (treated vs. control)											
1 (Althuis et al., 2005)	Retropsective Cohort Study	Serious[c]	-	-	Serious[a]	No	7	7	1.6 (0.5 to 4.7)	-	Very low
Number of cases and risk ratios – Gonadotrophins											
1 (Althuis et al., 2005)	Retropsective Cohort Study	Serious[c]	-	-	Serious[a]	No	2	12	1.4 (0.3 to 6.4)	-	Very low
Melanoma											
Proportion of cases and rate ratio - GnRH (treated vs. control)											
1 (Hannibal et al., 2008)	Case control study	None	-	-	Serious[a]	Yes[k]	14/98	98/1,128	1.6 (0.8 to 3.1)	-	Very low
Number of cases and risk ratios – Clomifene (treated vs. control)											
1 (Althuis et al., 2005)	Retropsective Cohort Study	Serious[c]	-	-	Serious[a]	No	21	21	1.7 (0.9 to 3.1)	-	Very low

Quality assessment							Summary of findings				
							No. of people		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Proportion of cases and rate ratio – Clomifene (treated vs. control)											
1 (Hannibal et al., 2008)	Case control study	None	-	-	Serious[a]	Yes[k]	42/406	70/820	1.1 (0.7 to 1.7)	-	Very low
Hazard ratio – Clomifene (treated vs. General population)											
1 (Calderon-Margalit et al., 2009)	Retropsective Cohort Study	Serious[c]	-	-	Serious[a]	Yes[g]	Not reported	Not reported	2.6 (1.1 to 6.0)	-	Very low
Number of cases and risk ratios – Gonadotrophins (treated vs. control)											
1 (Althuis et al., 2005)	Retropsective Cohort Study	Serious[c]	-	-	Serious[g]	No	4	38	0.9 (0.3 to 2.6)	-	Very low
Proportion of cases and rate ratio - Gonadotrophins (treated vs. control)											
1 (Hannibal et al., 2008)	Case control study	None	-	-	Serious[a]	Yes[k]	25/165	87/1061	1.7 (0.9 to 2.9)	-	Very low
Proportion of cases and rate ratio – hCG (treated vs. control)											
1 (Hannibal et al., 2008)	Case control study	None	-	-	Serious[a]	Yes[k]	40/396	72/830	1.1 (0.7 to 1.7)	-	Very low
Non-Hodgkin's lymphoma											
Hazard ratio – Clomifene (treated vs. General population)											
1 (Calderon-Margalit et al., 2009)	Retropsective Cohort Study	serious[c]	-	-	Serious[a]	Yes[g]	Not reported	Not reported	2.5 (0.7 to 8.1)	-	Very low

Quality assessment							Summary of findings				
							No. of people		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Thyroid											
Proportion of cases and risk ratios – GnRH (treated vs. control)											
1 (Hannibal et al., 2008)	Case control study	None	-	-	Serious[a]	Yes[l]	4/98	25/1,213	1.8 (0.5 to 7.0)	-	Very low
Number of cases and risk ratios - Clomifene											
1 (Althuis et al., 2005)	Retropsective Cohort Study	Serious[c]	-	-	Serious[g]	No	8	10	1.4 (0.5 to 3.7)	-	Very low
Proportion of cases and rate ratio – Clomifene											
1 (Hannibal et al., 2008)	Case control study	None	-	-	Serious[a]	Yes[l]	16/406	13/820	2.3 (1.1 to 4.8)	-	Very low
Number of cases and risk ratios – Gonadotrophins											
1 (Althuis et al., 2005)	Retropsective Cohort Study	Serious[c]	-	-	Serious[g]	No	2	16	1.1 (0.2 to 4.9)	-	Very low
Proportion of cases and rate ratio – Gonadotrophins											
1 (Hannibal et al., 2008)	Case control study	None	-	-	Serious[a]	Yes[l]	6/165	23/1,061	1.4 (0.5 to 3.8)	-	Very low
Proportion of cases and rate ratio – hCG											
1 (Hannibal et al., 2008)	Case control study	None	-	-	Serious[a]	Yes[l]	13/396	16/830	1.7 (0.8 to 3.5)	-	Very low
Proportion of cases and rate ratio – Progesterone											
1 (Hannibal et al., 2008)	Case control study	None	-	-	Serious[a]	Yes[l]	2/13	27/1,213	10.14 (1.9 to 53.3)	-	Very low

Quality assessment							Summary of findings				
							No. of people		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Colon											
Number of cases and risk ratios - Clomifene (treated vs. control)											
1 (Althuis et al., 2005)	Retropsective Cohort Study	Serious[c]	-	-	Serious[g]	No	8	20	0.8 (0.4 to 1.9)	-	Very low
Number of cases and risk ratios – Gonadotrophins											
1 (Althuis et al., 2005)	Retropsective Cohort Study	Serious[c]	-	-	Serious[g]	No	0	28	Not calculable	-	Very low
Ovarian cancer											
Proportion of cases and rate ratio - GnRH (treated vs. control)											
1 (Jensen et al., 2009)	Case control study	None	-	-	Serious[a]	Yes[j]	15/110	141/1,133	0.8 (0.4 to 1.5)	-	Very low
Number of cases and rate ratios – Clomifene (treated vs. population)											
1 (Brinton et al., 2004)	Retropsective Cohort Study	serious[c]	-	-	serious[a]	No	11	-	0.8 (0.4 to 1.6)	-	Very low
Proportion of cases and rate ratio – Clomifene (treated vs. control)											
1 (Jensen et al., 2009)	Case control study	None	-	-	Serious[a]	Yes[j]	58/417	98/824	1.1 (0.8 to 1.6)	-	Very low
Odds ratio – Clomifene											
1 (Klip et al., 2000)	Review	Serious[m]	-	-	Serious[a]	No	Not reported	Not reported	0.9 (0.3 to 2.3)	-	Very low
1 (Klip et al., 2000)	Review	Serious[m]	-	-	Serious[a]	No	Not reported	Not repoted	0.7 (0.2 to 2.0)	-	Very low

Quality assessment							Summary of findings				
							No. of people		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Invasive ovarian cancer – Clomifene											
1 (Sanner et al., 2009)		None	-	-	Serious[a]	Yes[n]	Not reported	Not reported	1.5 (0.3 to 7.4)	-	Very low
Number of cases and rate ratios - Clomifene + Gonadotrophins (treated vs. population)											
1 (Brinton et al., 2004)	Retropsective Cohort Study	serious[c]	-	-	serious[a]	None	4	-	1.0 (0.3 to 2.8)	-	Very low
Invasive ovarian cancer											
Rate ratio - Clomifene + Gonadotrophins (treated vs. General population)											
1 (Sanner et al., 2009)		None	-	-	Serious[a]	Yes[n]	Not reported	Not reported	0.7 (0.1 to 6.0)	-	Very low
Number of cases and rate ratio – Gonadotrophins (treated vs. General population)											
1 (Brinton et al., 2004)	Retropsective Cohort Study	serious[c]	-	-	serious[a]	No	1	-	1.2 (0.1 to 8.2)	-	Very low
Proportion of cases and rate ratio – Gonadotrophins (treated vs. control)											
1 (Jensen et al., 2009)	Case control study	None	-	-	Serious[a]	Yes[j]	26/184	130/1,057	0.8 (0.5 to 1.4)	-	Very low
Invasive ovarian cancer											
Rate ratio - Gonadotrophins (treated vs. General population)											
1 (Sanner et al., 2009)		None	-	-	Serious[a]	Yes[n]	Not reported	Not reported	5.2 (1.7 to 16.2)	-	Very low
Proportion of cases and rate ratio – hCG (treated vs. control)											
1 (Jensen et al., 2009)	Case control study	None	-	-	Serious[a]	Yes[j]	49/413	107/828	0.9 (0.6 to 1.3)	-	Very low

Quality assessment							Summary of findings				
							No. of people		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Odds ratio – hMG											
1 (Klip et al., 2000)	Review	Serious[m]	-	-	Serious[a]	No	Not reported	Not reported	3.2 (0.9 to 11.8)	-	Very low
Odds ratio - Clomifene/hMG											
1 (Klip et al., 2000)	Review	Serious[m]	-	-	Serious[a]	No	Not reported	Not reported	1.4 (0.7 to 3.1)	-	Very low
Odds ratio - Clomifene/hCG											
1 (Klip et al., 2000)	Review	Serious[m]	-	-	Serious[a]	No	Not reported	Not reported	1.2 (0.3 to 4.0)	-	Very low
hMG/hCG											
1 (Klip et al., 2000)	Review	Serious[m]	-	-	Serious[a]	No	Not reported	Not reported	0.8 (0.2 to 3.7)	-	Very low
Ovarian tumour											
Relative risk – Clomifene (treated vs. control)											
1 (Rossing et al.,1994)	Case control study	None	-	-	Serious[a]	Yes[o]	Not reported	Not reported	2.3 (0.5 to 11.4)	-	Very low
Borderline ovarian tumour											
Rate ratio - Clomifene (treated vs. General population)											
1 (Sanner et al., 2009)		None	-	-	Serious[a]	Yes[n]	Not reported	Not reported	3.1 (0.7 to 13.7)	-	Very low
Odds ratio – Clomifene											
1 (Klip et al., 2000)	Review	Serious[m]	-	-	Serious[a]	None	Not reported	Not reported	1.3 (0.3 to 6.9)	-	Very low

Quality assessment							Summary of findings				
							No. of people		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Borderline ovarian tumour											
Rate ratio - Clomifene + Gonadotrophins (treated vs. General population)											
1 (Sanner et al., 2009)		None	-	-	Serious[a]	Yes[n]	Not reported	Not reported	2.7 (0.6 to 12.7)	-	Very low
Rate ratio – Gonadotrophins (treated vs. General population)											
1 (Sanner et al., 2009)		None	-	-	Serious[a]	Yese[n]	Not reported	Not reported	1.1 (0.1 to 10.2)	-	Very low
Odds ratio – hMG											
1 (Klip et al., 2000)	Review	Serious[m]	-	-	Serious[a]	No	Not reported	Not reported	9.4 (1.7 to 52.1)	-	Very low
Odds ratio - CC/hMG											
1 (Klip et al., 2000)	Review	Serious[m]	-	-	Serious[a]	No	Not reported	Not reported	3.1 (1.0 to 9.7)	-	Very low
Relative risk - hCG (treated vs. control)											
1 (Rossing et al.,1994)	Case control study	None	-	-	Serious[a]	Yes[o]	Not reported	Not reported	1.0 (0.2 to 4.3)	-	Very low

[a]. Wide confidence interval.

[b]. Results were adjusted for childbirth and number of additional births (Jensen et al., 2007)

[c.] Retrospective study design

[d]. Results were adjusted for calendar year and age at follow-up, study site and mother or sister with breast cancer (Brinton et al., 2004)

[e]. Loss to follow-up (Gauthier et al., 2004).

[f.]Results were adjusted for educational level, active smoking, BMI, family history of breast cancer in first-degree relatives, personal history of benign breast disease, age at menarche, menopausal status, composite variable for parity and age at first full-term pregnancy. (Gauthier et al., 2004).

[g]. Results were adjusted for age, socioeconomic status, country of birth, BMI and family size (Calderon-Margalit et al., 2009).

[h]. The inability of the studies to adjust for the essential factors in the aetiology of breast cancer. The nature of some of the included studies with the inherent weaknesses in their design (Zreik et al, 2010).
[i]. It is unclear whether the results were adjusted for confounding factors.
[j]. Results were stratified according to calendar year and age at start of follow-up, adjusted for parity and number of additional births (Jensen et al., 2009).
[k]. Results were stratified for age at cohort entry and calendar year of cohort entry, adjusted for parity status (Hannibal et al., 2008).
[l]. Results were stratified for age at cohort entry and calendar year of cohort entry, adjusted for age at first live birth (Hannibal et al., 2008).
[m]. No detailed description of the individual studies (Klip et al., 2000).
[n]. Results were adjusted for age and indication (Sanner et al., 2009).
[o]. Results were adjusted for age, year of and gravidity at enrolment (Rossing et al.,1994).

Table I.20.2 GRADE findings for long-term safety of ovulation induction and ovarian stimulation agents in children

Quality assessment							**Summary of findings**				
							No. of people		**Effect**		**Quality**
No. of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Intervention**	**Comparator**	**Relative (95% CI)**	**Absolute (95% CI)**	
Malformation											
Proportion of cases – Clomifene vs. letrozole vs. natural conception											
1 (Forman et al., 2007)	Retropsective Cohort Study	Serious[a]	-	-	-	-	7/271 (2.6%)	0/94 (0%)	3/112 (3.2%)	-	Very low
Major malformation (VSD, oesophageal atresia, cleft palate, trisomy 18, down's syndrome, potters syndrome)											
Proportion of cases - Clomifene											
1 (Tulandi et al., 2006)	Retropsective Cohort Study	Very serious[b]	-	-	-	No	10/293 (3.4%)	-	Not reported	-	Very low
Letrozole											
1 (Tulandi et al., 2006)	Retropsective Cohort Study	Very serious[b]	-	-	-	No	1/252 (0.4%)	-	Not reported	-	Very low
Clomifene + FSH											
1 (Tulandi et al., 2006)	Retropsective Cohort Study	Very serious[b]	-	-	-	No	2/104 (2%)	-	Not reported	-	Very low

Quality assessment							Summary of findings				
							No. of people		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Clomifene + FSH + Progesterone											
1 (Tulandi et al., 2006)	Retropsective Cohort Study	Very serious[b]	-	-	-	No	0/104 (0%)	-	Not reported	-	Very low
Letrozole											
1 (Tulandi et al., 2006)	Retropsective Cohort Study	Very serious[b]	-	-	-	No	2/262 (0.8%)	-	Not reported	-	Very low
Letrozole + Progesterone											
1 (Tulandi et al., 2006)	Retropsective Cohort Study	Very serious[b]	-	-	-	No	1/262 (0.4%)	-	Not reported	-	Very low
Letrozole + Metformin											
1 (Tulandi et al., 2006)	Retropsective Cohort Study	Very serious[b]	-	-	-	No	2/262 (0.8%)	-	Not reported	-	Very low
Minor malformations (Preauricular skin tag, congenital ptosis, plagiocephaly, dydrocele, hypospadia, polydactyly, syndactyly, umblilical and inguinal hernias)											
Proportion of cases – Clomifene											
1 (Tulandi et al., 2006)	Retropsective Cohort Study	Very seriousb	-	-	-	No	6/293 (2.0%)	-	Not reported	-	Very low
Letrozole											
1 (Tulandi et al., 2006)	Retropsective Cohort Study	Very serious[b]	-	-	-	No	4/252 (1.6%)	-	Not reported	-	Very low
Clomifene + FSH											
1 (Tulandi et al., 2006)	Retropsective Cohort Study	Very serious[b]	-	-	-	No	0/104 (0%)	-	Not reported	-	Very low

Quality assessment							Summary of findings				
							No. of people		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Clomifene + FSH + Progesterone											
1 (Tulandi et al., 2006)	Retropsective Cohort Study	Very serious[b]	-	-	-	No	1/104 (1.0%)	-	Not reported	-	Very low
Letrozole											
1 (Tulandi et al., 2006)	Retropsective Cohort Study	Very serious[b]	-	-	-	No	2/262 (0.8%)	-	Not reported	-	Very low
Letrozole + Progesterone											
1 (Tulandi et al., 2006)	Retropsective Cohort Study	Very serious[b]	-	-	-	No	1/262 (0.4%)	-	Not reported	-	Very low
Letrozole + Metformin											
1 (Tulandi et al., 2006)	Retropsective Cohort Study	Very serious[b]	-	-	-	No	0/262 (0%)	-	Not reported	-	Very low
Autism spectrum disorder											
Hazard rate ratio – Down regulation (study group vs. general population)											
1 (Hovidtjorn et al., 2011)	Retropsective Cohort Study	Serious[a]	-	-	Serious[c]	No	Not reported	Not reported	1.1 (0.5 to 2.5)	-	Very low
FSH											
1 (Hovidtjorn et al., 2011)	Retropsective Cohort Study	Serious[a]	-	-	Serious[c]	No	Not reported	Not reported	1.3 (0.9 to 1.9)	-	Very low

Quality assessment							Summary of findings				
							No. of people		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
hCG											
1 (Hovidtjorn et al., 2011)	Retropsective Cohort Study	Serious[a]	-	-	Serious[c]	No	Not reported	Not reported	1.2 (0.8 to 1.7)	-	Very low
Clomifene											
1 (Hovidtjorn et al., 2011)	Retropsective Cohort Study	Serious[a]	-	-	Serious[c]	No	Not reported	Not reported	0.8 (0.5 to 1.3)	-	Very low
Childhood tumours											
Proportion and rate ratio – Clomifene (study group vs. control)											
1 (Brinton et al., 2004)	Case control study	None	-	-	Serious[c]	No	11/265	34/594	0.8 (0.4 to 1.6)	-	Very low
hCG											
1 (Brinton et al., 2004)	Case control study	None	-	-	Serious[c]	No	10/260	35/600	0.7 (0.3 to 1.5)	-	Very low
hMG											
1 (Brinton et al., 2004)	Case control study	None	-	-	Serious[c]	No	2/83	44/779	0.6 (0.1 to 3.1)	-	Very low

[a]. Retrospective study design.

[b]. Incomplete follow-up. The fact that infertile women are more likely to adopt healthy lifestyles might have attenuated the risks of some congenital abnormalities (Tulandi et al., 2006).

[c]. Wide confidence interval

Table I.20.3 GRADE findings for **l**ong-term safety of IVF in women

Quality assessment							Summary of findings				
							Number of patients/women		Effect		Quality
No. of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Intervention**	**Comparator**	**Relative (95% CI)**	**Absolute (95% CI)**	
Breast cancer/tumour											
Number of cases and standardized incidence ratios (IVF vs general population)											
1 (Pappo et al., 2008)	Retropsective Cohort Study	Very serious[a]	-	-	Serious[b]	No	35/24.8	-	1.4 (1.0 to 2.0)	-	Very low
Proportions and adjusted rate ratios (IVF/non-IVF)											
1 (Kristiansson et al., 2006)	Prospective Cohort Study	Serious[c]	-	-	Serious[b]	Yes[d]	13/617	-	0.7 (0.4 to 1.3)	-	Very low
Proportions and standardized incidence ratios in IVF women											
1 (Lerna-Geva et al., 2003)	Case control study	None	-	-	Serious[b]	No	4/4.9	-	0.8 (0.2 to 2.1)	-	Very low
Cervix											
Proportions and adjusted rate ratios (IVF/ non-IVF)											
1 (Kristiansson et al., 2006)	Prospective Cohort Study	Serious[c]	-	-	Serious[b]	Yes[d]	35/2,328	-	0.9 (0.6 to 1.2)	-	Very low
Proportions and standardized incidence ratios in IVF women											
1 (Lerna-Geva et al., 2003)	Case control study	None	-	-	Serious[b]	No	3/0.7	-	4.6 (0.9 to 13.5)	-	Very low

Quality assessment							Summary of findings				
							Number of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Non-invasive tumour											
Proportions and adjusted rate ratios (IVF/non-IVF)											
1 (Kristiansson et al., 2006)	Prospective Cohort Study	Serious[c]	-	-	Serious[b]	Yes[d]	48/2,890	-	0.9 (0.6 to 1.2)	-	Very low
Invasive tumour											
Proportions and adjusted rate ratios (IVF/non-IVF)											
1 (Kristiansson et al., 2006)	Prospective Cohort Study	Serious[c]	-	-	Serious[b]	Yes[d]	41/1,565	-	1.0 (0.7 to 1.4)	-	Very low
All malignancies IVF group											
IVF vs. General population – standardised incidence ratios											
1 (Van Leeuwen et al., 2011)	Retropsective Cohort Study	Very serious[e]	-	-	Serious[b]	No	61/19146	-	1.6 (1.2 to 2.0)	-	Very low
Non IVF vs. General population – standardised incidence ratios											
1 (Van Leeuwen et al., 2011)	Retropsective Cohort Study	Very serious[e]	-	-	Serious[b]	No	16/6006	-	1.0 (0.6 to 1.7)	-	Very low
IVF vs. Non IVF subfertility group – hazard ratios											
1 (Van Leeuwen et al., 2011)	Retropsective Cohort Study	Very serious[e]	-	-	Serious[b]	Yes[f]	-	-	2.1 (1.1 to 3.8)	-	Very low

Quality assessment							Summary of findings				
							Number of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Invasive ovarian cancer											
IVF vs. General population – standardised incidence ratios											
1 (Van Leeuwen et al., 2011)	Retropsective Cohort Study	Very serious[e]	-	-	Serious[b]	No	30/19146	-	1.4 (0.9 to 1.9)	-	Very low
Non IVF vs. General population – standardised incidence ratios											
1 (Van Leeuwen et al., 2011)	Retropsective Cohort Study	Very serious[e]	-	-	Serious[b]	No	12/6006	-	1.2 (0.6 to 2.2)	-	Very low
IVF vs. Non IVF subfertility group – hazard ratios											
1 (Van Leeuwen et al., 2011)	Retropsective Cohort Study	Very serious[e]	-	-	Serious[b]	Yes[f]	-	-	1.1 (0.5 to 2.4)	-	Very low
Borderline ovarian tumours											
IVF vs. General population – standardised incidence ratios											
1 (Van Leeuwen et al., 2011)	Retropsective Cohort Study	Very serious[e]	-	-	Serious[b]	No	31/19146	-	1.9 (1.3 to 2.7)	-	Very low
Non IVF vs. General population – standardised incidence ratios											
1 (Van Leeuwen et al., 2011)	Retropsective Cohort Study	Very serious[e]	-	-	Serious[b]	No	4/6006	-	0.7 (0.2 to 1.7)	-	Very low

Quality assessment							Summary of findings				
							Number of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
IVF vs. Non IVF subfertility group – hazard ratios											
1 (Van Leeuwen et al., 2011)	Retropsective Cohort Study	Very serious[e]	-	-	Serious[b]	Yes[f]	-	-	6.4 (2.1 to 19.8)	-	Very low
Ovary											
Proportions and standardized incidence ratios in IVF women											
1 (Lerna-Geva et al., 2003)	Case control study	None	-	-	Serious[b]	No	1/0.6	-	1.7 (0 to 9.3)	-	Very low
Other cancers – melanoma, hodgkin's lymphoma, multiple myeloma, angiosarcoma, brain and sarcoma											
Proportions and standardized incidence ratios IVF women											
1 Lerna-Geva et al., 2003)	Case control study	None	-	-	Serious[b]	No	8/4.9	-	1.6 (0.7 to 3.2)	-	Very low
All cancers											
Proportions and standardized incidence ratios IVF women											
1 Lerna-Geva et al., 2003)	Case control study	None	-	-	Serious[b]	No	16/11	-	1.5 (0.8 to 2.4)	-	Very low
Deaths by cause and IVF treatment status – standardized mortality ratios											
All causes of death											
IVF-treated women											
1 (Venn et al., 2001)	Prospective Cohort Study	None	-	-	None	No	72/124.9	-	0.6 (0.5 to 0.7)	-	Low

Quality assessment							Summary of findings				
							Number of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Non-IVF women											
1 (Venn et al., 2001)	Prospective Cohort Study	None	-	-	Serious[b]	No	51/82.4	-	0.6 (0.5 to 0.8)	-	Very low
Diseases of the circulatory system											
IVF-treated women											
1 (Venn et al., 2001)	Prospective Cohort Study	None	-	-	Serious[b]	No	7/16	-	0.4 (0.3 to 0.7)	-	Very low
Non-IVF women											
1 (Venn et al., 2001)	Prospective Cohort Study	None	-	-	Serious[b]	No	7/10.5	-	0.7 (0.4 to 1.2)	-	Very low
Injury and poisoning											
IVF treated women											
1 (Venn et al., 2001)	Prospective Cohort Study	None	-	-	Serious[b]	No	14/27.1	-	0.5 (0.4 to 0.8)	-	Very low
Non-IVF women											
1 (Venn et al., 2001)	Prospective Cohort Study	None	-	-	Serious[b]	No	9/19.3	-	0.5 (0.3 to 0.7)	-	Very low
Suicide											
IVF treated women											
1 (Venn et al., 2001)	Prospective Cohort Study	None	-	-	Serious[b]	No	3/10.2	-	0.3 (0.2 to 0.6)	-	Very low

Quality assessment							Summary of findings				
							Number of patients/women		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Non-IVF women											
1 (Venn et al., 2001)	Prospective Cohort Study	None	-	-	Serious[b]	No	4/6.9	-	0.6 (0.3 to 1.2)	-	Very low
Death by all neoplasms											
IVF treated women											
1 (Venn et al., 2001)	Prospective Cohort Study	None	-	-	Serious[b]	No	51/68.6	-	0.7 (0.6 to 0.9)	-	Very low
Non-IVF women											
1 (Venn et al., 2001)	Prospective Cohort Study	None	-	-	Serious[b]	No	29/39.2	-	0.7 (0.5 to 1.0)	-	Very low
Death by breast cancer											
IVF treated women											
1 (Venn et al., 2001)	Prospective Cohort Study	None	-	-	Serious[b]	No	26/23.1	-	1.1 (0.8 to 1.7)	-	Very low
Non-IVF women											
1 (Venn et al., 2001)	Prospective Cohort Study	None	-	-	Serious[b]	No	9/12.9	-	0.7 (0.4 to 1.2)	-	Very low

a. Retrospective study design. Over 40% of the women in the cohort received more than one treatment protocol and individual analysis per protocol was not performed.
b. Wide confidence interval.
c. Average follow-up of 7 years may be too short to reveal any carcinogenic effects of IVF.
d. Rate ratios were standardized by age at follow-up, number of parities and multiple births.
e. Analysis was based on protocols between 1983 and 1995. Protocols have changed substantially since this period so generalisability of this finding is limited. Severity of subfertility could differ between groups. Poor response to patient questionnaires. Low absolute event rates means that small changes can have significant effect on relative rates
f. Cox hazard ratios based on total life years covered in cohort. This data was not presented.

Table I.20.4 GRADE findings for long-term safety of IVF in children

Quality assessment							Summary of findings				
							No. of people		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Cerebral palsy											
Proportions and adjusted ORs (children in IVF vs. control group)											
1 (Klemetti et al., 2006)	Retropsective Cohort Study	Serious[a]	-	-	Serious[b]	Yes[c]	3.8	1.4	2.9 (1.6 to 5.3)	-	Very low
Singletons											
1 (Klemetti et al., 2006)	Retropsective Cohort Study	Serious[a]	-	-	Serious[b]	Yes[c]	1.4	1.3	1.2 (0.4 to 3.3)	-	Very low
Proportions and adjusted ORs (all children in IVF vs control group)											
1 (Stromberg et al., 2002)	Retropsective Cohort Study	Serious[a]	-	-	Serious[b]	Yes[d]	31/5,680 (0.5%)	17/11,360 (0.1%)	3.7 (2.0 to 6.6)	-	Very low
Singletons											
1 (Stromberg et al., 2002)	Retropsective Cohort Study	Serious[a]	-	-	Serious[b]	Yes[d]	12/3,228 (0.37%)	15/11,070 (0.14%)	2.8 (1.3 to 5.8)	-	Very low
Number of cases and adjusted ORs (children in IVF vs. control group)											
1 (Kallen et al., 2005)	Retropsective Cohort Study	Serious[a]	-	-	Serious[b]	Yes[e]	37	2,754	1.1 (0.7 to 1.8)	-	Very low
Proportions and adjusted ORs (IVF-ICSI twins vs. control twins)											
1 (Pinborg et al., 2004)	Case control study	Serious[a]	-	Serious[f]	Serious[b]	No	11/3,393 (0.3%)	41/10,239 (0.4%)	1.2 (0.6 to 2.3)	-	Very low
IVF-ICSI twins vs. IVF-ICSI singletons											
1 (Pinborg et al., 2004)	Case control study	Serious[a]	-	Serious[f]	Serious[b]	No	11/3,393 (0.3%)	13/5130 (0.3%)	0.8 (0.4 to 1.8)	-	Very low

Quality assessment							Summary of findings				
							No. of people		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Behavioural disorders											
Number of cases and adjusted ORs (children in IVF vs. control group)											
1 (Kallen et al., 2005)	Retropsective Cohort Study	Serious[a]	-	-	Serious[b]	Yes[e]	37	3,657	1.6 (1.1 to 2.2)	-	Very low
Proportions and adjusted ORs (children in IVF vs. control group)											
1 (Klemetti et al., 2006)	Retropsective Cohort Study	Serious[a]	-	-	Serious[b]	Yes[c]	6.6	4.1	1.7 (1.1 to 2.5)	-	Very low
Singletons											
1 (Klemetti et al., 2006)	Retropsective Cohort Study	Serious[a]	-	-	Serious[b]	Yes[c]	4.1	4.1	1.1 (0.6 to 1.9)	-	Very low
Proportion of children in IVF vs control											
1 (Stromberg et al., 2002)	Retropsective Cohort Study	Serious[a]	-	-	Serious[b]	Yes[d]	3/5,680 (0.05%)	10/11,360 (0.08%)	0.6 (0.2 to 2.2)	-	Very low
Singletons											
1 (Stromberg et al., 2002)	Retropsective Cohort Study	Serious[a]	-	-	Serious[b]	Yes[d]	1/3,228	10/11,070	0.4 (0.1 to 3.0)	-	Very low
Mental retardation											
Number of cases and adjusted ORs (children in IVF vs. control group)											
1 (Kallen et al., 2005)	Retropsective Cohort Study	Serious[a]	-	-	Serious[b]	Yes[e]	17	2,023	1.0 (0.5 to 2.0)	-	Very low
Proportions and adjusted ORs (all children in IVF vs. control)											
1 (Stromberg et al., 2002)	Retropsective Cohort Study	Serious[a]	-	-	Serious[b]	Yes[d]	7/5,680 (0.1%)	18/11,360 (0.2%)	0.8 (0.3 to 1.9)	-	Very low

Quality assessment							Summary of findings				
							No. of people		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Singletons											
1 (Stromberg et al., 2002)	Retropsective Cohort Study	Serious[a]	-	-	Serious[b]	Yes[d]	3/3228 (0.09)	17/11,070 (0.15%)	0.8 (0.2 to 2.6)	-	Very low
Proportions and adjusted ORs (IVF-ICSI twins vs. control twins)											
1 (Pinborg et al., 2004)	Case control study	Serious[a]	-	Serious[f]	Serious[b]	No	19/3,393 (0.6%)	57/10,239 (0.6%)	1.0 (0.6 to 1.7)	-	Very low
IVF-ICSI twins vs. IVF-ICSI singletons											
1 (Pinborg et al., 2004)	Case control study	Serious[a]	-	Serious[f]	Serious[b]	No	19/3,393 (0.6%)	29/5,130 (0.6%)	1.1 (0.6 to 1.9)	-	Very low
Pneumonia											
Number of cases and adjusted ORs (children in IVF vs. control group)											
1 (Kallen et al., 2005)	Retropsective Cohort Study	Serious[a]	-	-	Serious[b]	Yes[e]	449	42,293	1.1 (0.9 to 1.3)	-	Very low
Proportions and adjusted ORs (children in IVF vs. control group)											
1 (Klemetti et al., 2006)	Retropsective Cohort Study	Serious[a]	-	-	Serious[b]	Yes[c]	9.9	11.4	0.9 (0.6 to 1.2)	-	Very low
Singletons											
1 (Klemetti et al., 2006)	Retropsective Cohort Study	Serious[a]	-	-	Serious[b]	Yes[c]	9.6	11.4	0.8 (0.5 to 1.2)	-	Very low
Rate of hospitalisation											
Number of cases and adjusted ORs (children in IVF vs. control group)											
1 (Kallen et al., 2005)	Retropsective Cohort Study	Serious[a]	-	-	None	Yes[e]	Not reported	Not reported	2.1 (2.0 to 2.2)	-	Very low

Quality assessment							Summary of findings				
							No. of people		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Proportions and adjusted ORs (children in IVF vs. control group)											
1 (Klemetti et al., 2006)	Retropsective Cohort Study	Serious[a]	-	-	None	Yes[c]	40/4,397 (0.91%)	33/136,782 (0.02%)	1.4 (1.3 to 1.5)	-	Very low
Singletons											
1 (Klemetti et al., 2006)	Retropsective Cohort Study	Serious[a]	-	-	None	Yes[c]	34/2911 (1.17%)	32/131,459 (0.02%)	1.1 (1.0 to 1.2)	-	Very low
Any accident											
Number of cases and adjusted OR (children in IVF vs. control group)											
1 (Kallen et al., 2005)	Retropsective Cohort Study	Serious[a]	-	-	None	Yes[e]	2,234	220,166	1.6 (1.5 to 1.7)	-	Very low
Proportions and p-values (children in IVF vs sterility vs. control group)											
							IVF	Sterility	Control		
1 (Raoul-Duval et al., 1994)	Prospective Cohort Study	Very serious[g]	-	-	-	Yes[h]	5/25 (20%)	1/11 (9%)	4/13 (31%)	NS	-	Very low
Asthma											
Number of cases and adjusted ORs (children in IVF vs. control group)											
1 (Kallen et al., 2005)	Retropsective Cohort Study	Serious[a]	-	-	Serious[b]	Yes[e]	816	61,572	1.4 (1.3 to 1.6)	-	Very low
Proportions and adjusted ORs (children in IVF vs. control group)											
1 (Klemetti et al., 2006)	Retropsective Cohort Study	Serious[a]	-	-	Serious[b]	Yes[c]	30.3	38.1	1.1 (0.9 to 1.3)	-	Very low

Quality assessment							Summary of findings				
							No. of people		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Singletons											
1 (Klemetti et al., 2006)	Retropsective Cohort Study	Serious[a]	-	-	Serious[b]	Yes[c]	26.5	27.8	1.0 (0.7 to 1.2)	-	Very low
Epilepsy											
Number of cases and adjusted ORs (children in IVF vs. control group)											
1 (Kallen et al., 2005)	Retropsective Cohort Study	Serious[a]	-	-	Serious[b]	Yes[e]	70	5,767	1.5 (1.3 to 1.9)	-	Very low
Proportions and adjusted ORs (children in IVF vs. control group)											
1 (Klemetti et al., 2006)	Retropsective Cohort Study	Serious[a]	-	-	Serious[b]	Yes[c]	3.3	2.5	1.3 (0.8 to 2.3)	-	Very low
Singletons											
1 (Klemetti et al., 2006)	Retropsective Cohort Study	Serious[a]	-	-	Serious[b]	Yes[c]	3.4	2.5	1.4 (0.7 to 2.7)	-	Very low
Psychomotor development Index											
Mean±SD and p-value (ICSI vs. IVF vs. control)											
							ICSI	IVF	Control		
1 (Bowen et al., 1998)	Prospective Cohort Study	Very serious[i]	-	-	-	Yes[j]	95.9±10.7	101.8±8.5	102.5±7.6	0.86	-	Very low
Mean±SD and p-value (IVF vs. control)											
1 (Morin et al., 1989)	Case control study	Serious[k]	-	-	-	Yes[l]	114±14	108±15		0.04	-	Very low

Quality assessment							Summary of findings					
							No. of people			Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator		Relative (95% CI)	Absolute (95% CI)	
Mental development index												
Mean±SD and p-value (ICSI vs. IVF vs. control)												
							ICSI	IVF	Control			
1 (Bowen et al., 1998)	Prospective Cohort Study	Very serious[i]	-	-	-	Yes[j]	89.8±16.6	89.2±15.1	88.3±15.7	P-value <0.001	-	Very low
Mean±SD and p-value (IVF vs. control)												
1 (Morin et al., 1989)	Case control study	Serious[k]	-	-	-	Yes[l]	115±13	111±13		0.12	-	Very low
Mean±SD and p-value (all children in IVF vs. Control group)												
1 (Brandes et al., 1992)	Retropsective Cohort Study	Serious[a]	-	-	-	Yes[m]	106±19.3	110.6±19.3		NS	-	Very low
Performance skills/IQ												
Mean±SD and p-values (ICSI vs. IVF vs. control)												
							ICSI	IVF	Control			
1 (Leslie et al., 2003)	Case control study	None	-	-	-	No	112±16	112±13	114±13	0.66	-	Very low
1 (Place and Englert, 2003)	Prospective Cohort Study	Very serious[n]	-	-	Serious[b]	Yes[o]	92.4±12.6	90.5±14.7	100.6±12.2	0.2 (91.7 to 97.9)	-	Very low

Quality assessment							Summary of findings					
							No. of people			Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator		Relative (95% CI)	Absolute (95% CI)	
Verbal skills/IQ												
Mean±SD and p-values (ICSI vs. IVF vs. control)												
							ICSI	IVF	Control			
1 (Leslie et al., 2003)	Case control study	None	-	-	-	No	107±15	107±12	111±14	0.10	-	Very low
1 (Place and Englert, 2003)	Prospective Cohort Study	Very serious[n]	-	-	Serious[b]	Yes[o]	97.2±13.1	94.1±14.7	106.3±14.7	0.1 (96.2 to 103)	-	Very low
IQ/ Full scale IQ												
Mean±SD and p-values (ICSI vs. IVF vs. control)												
							ICSI	IVF	Control			
1 (Leslie et al., 2003)	Case control study	None	-	-	-	No	110±18	111±13	114±13	0.20	-	Very low
1 (Place and Englert, 2003)	Prospective Cohort Study	Very serious[n]	-	-	Serious[b]	Yes[o]	94.1±12.7	91.7±15.4	103.9±14.1	0.1 (93.7 to 100.3)	-	Very low
Retinoblastoma												
Number of cases in IVF vs. general population												
1 (Marees et al., 2009)	Retropsective Cohort Study	Very serious[p]	-	-	Serious[b]	Yes[q]	7/2.57	-		2.5 (1.0 to 5.2)	-	Very low
Number of cases and risk ratio in IVF vs. general population												
1 (Moll et al., 2003)	Retropsective Cohort Study	None	-	-	Serious[b]	Yes[q]	5/0.69	-		7.2 (2.4 to 17.0)	-	Very low

Quality assessment							Summary of findings				
							No. of people		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Allergy											
Proportions and adjusted ORs (children in IVF vs. control group)											
1 (Klemetti et al., 2006)	Retropsective Cohort Study	Serious[a]	-	-	Serious[b]	Yes[c]	59.9	53.8	1.1 (0.9 to 1.2)	-	Very low
Singletons											
1 (Klemetti et al., 2006)	Retropsective Cohort Study	Serious[a]	-	-	Serious[b]	Yes[c]	61.8	54.0	1.1 (0.9 to 1.3)	-	Very low
Appendicitis											
Number of cases and adjusted OR (children in IVF vs. control group)											
1 (Kallen et al., 2005)	Retropsective Cohort Study	Serious[a]	-	-	Serious[b]	Yes[e]	64	12,458	1.3 (0.9 to 1.9)	-	Very low
Attention problems											
Proportion with normal scores (<85th percentile) and p-value (IVF males vs. controls)											
1 (Montgomery et al., 1999)	Case control study	Very serious[r]	-	-	-	Yes[s]	94	85	0.99	-	Very low
Proportion with normal scores (>95th percentile) and p-value (IVF males vs. control group)											
1 (Montgomery et al., 1999)	Case control study	Very serious[r]	-	-	-	Yes[s]	1.1	5	0.99	-	Very low

Quality assessment							Summary of findings				
							No. of people		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Body length											
Percentile and p-value (all children in IVF vs. Control group)											
1 (Brandes et al., 1992)	Retropsective Cohort Study	Serious[a]	-	-	-	Yes[m]	39.3±29.0	40.9±28.3	NS	-	Very low
Child disability allowance											
Proportions and adjusted ORs (all children in IVF vs. control group)											
1 (Klemetti et al., 2006)	Retropsective Cohort Study	Serious[a]	-	-	None	Yes[c]	10.6	9.5	1.1 (1.0 to 1.2)	-	Very low
Singletons											
1 (Klemetti et al., 2006)	Retropsective Cohort Study	Serious[a]	-	-	None	Yes[c]	10.5	9.5	1.1 (1.0 to 1.3)	-	Very low
Childhood cancer											
Number of cases and adjusted RR (IVF vs. control group)											
1 (Klip et al., 2001)	Case control study	Serious[t]	-	-	Serious[b]	Yes[u]	5	9	0.8 (0.2 to 2.4)	-	Very low
Chromosomal aberration											
Proportions and adjusted ORs (IVF vs. control group)											
1 (Stromberg et al., 2002)	Retropsective Cohort Study	Serious[a]	-	-	Serious[b]	Yes[d]	9/5,680 (0.16%)	15/11,360 (0.13%)	1.2 (0.5 to 2.7)	-	Very low
Singletons											
1 (Stromberg et al., 2002)	Retropsective Cohort Study	Serious[a]	-	-	Serious[b]	Yes[d]	5/3,228 (0.15%)	15/11,070 (0.14%)	1.1 (0.4 to 3.0)	-	Very low

Quality assessment							Summary of findings				
							No. of people		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Composite index											
Mean±SD and p-values (all children in IVF vs. Control group)											
1 (Brandes et al., 1992)	Retropsective Cohort Study	Serious[a]	-	-	-	Yes[m]	106.2±8.0	104.4±10.2	NS	-	Very low
Convulsion											
Number of cases and adjusted OR (children in IVF vs. control group)											
1 (Kallen et al., 2005)	Retropsective Cohort Study	Serious[a]	-	-	Serious[b]	Yes[e]	272	12,459	1.5 (1.2 to 1.8)	-	Very low
Diabetes mellitus											
Proportions and adjusted ORs (all children in IVF vs. control group)											
1 (Klemetti et al., 2006)	Retropsective Cohort Study	Serious[a]	-	-	Serious[b]	Yes[c]	0.9	0.5	1.6 (0.5 to 4.8)	-	Very low
Singletons											
1 (Klemetti et al., 2006)	Retropsective Cohort Study	Serious[a]	-	-	Serious[b]	Yes[c]	1.0	0.5	2.0 (0.6 to 7.1)	-	Very low
Diarrhoea											
Proportions and adjusted ORs (all children in IVF vs. control group)											
1 (Klemetti et al., 2006)	Retropsective Cohort Study	Serious[a]	-	-	Serious[b]	Yes[c]	44.2	38.6	1.2 (1.0 to 1.4)	-	Very low
Singletons											
1 (Klemetti et al., 2006)	Retropsective Cohort Study	Serious[a]	-	-	Serious[b]	Yes[c]	35.4	38.1	0.9 (0.8 to 1.2)	-	Very low

Quality assessment							Summary of findings				
							No. of people		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Externalising problems											
Proportion with normal scores (<85th percentile) and p-value (IVF males vs. controls)											
1 (Montgomery et al., 1999)	Case control study	Very serious[r]	-	-	-	Yes[s]	94.3	85	0.99	-	Very low
Proportion with normal scores (>95th percentile) and p-value (IVF males vs. control group)											
1 (Montgomery et al., 1999)	Case control study	Very serious[r]	-	-	-	Yes[s]	1.7	5	0.98	-	Very low
Feeding difficulties											
Proportions and p-value (children in IVF vs. Sterility vs. Control group)											
							IVF	Sterility	Control		
1 (Raoul-Duval et al., 1994)	Prospective Cohort Study	Very serious[g]	-	-	-	Yes[h]	6/25 (0.2%)	3/11 (0.3%)	2/13 (0.2%)	NS	-	Very low
Fracture											
Number of cases and adjusted OR (children in IVF vs. control group)											
1 (Kallen et al., 2005)	Retropsective Cohort Study	Serious[a]	-	-	Serious[b]	Yes[e]	228	32,969	1.1 (0.9 to 1.4)	-	Very low
Head circumference											
Percentile and p-value (all children in IVF vs. Control group)											
1 (Brandes et al., 1992)	Retropsective Cohort Study	Serious[a]	-	-	-	Yes[m]	45.5±22.5	45.9±23.1	NS	-	Very low

Quality assessment							Summary of findings				
							No. of people		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Hypospadias											
Proportions and p-value (IVF vs. control group)											
1 (Silver et al., 1999)	Retropsective Cohort Study	Serious[a]	-	-	-	Yes[u]	7/481 (1.5%)	461/173,055 (0.3%)	p-value <0.001	-	Very low
Infant illnesses											
Proportions and p-value (children in IVF vs. Sterility vs. Control group)											
							IVF	Sterility	Control		
1 (Raoul-Duval et al., 1994)	Prospective Cohort Study	Very serious[g]	-	-	-	Yes[h]	23/25 (90%)	10/11 (91%)	13/13 (100%)	NS	-	Very low
Infant insomnia											
Proportions and p-values (children in IVF vs. sterility vs. Control group)											
							IVF	Sterility	Control		
1 (Raoul-Duval et al., 1994)	Prospective Cohort Study	Very serious[g]	-	-	-	Yes[h]	4/25 (16%)	0/11 (0%)	3/13 (23%)	NS	-	Very low
Internalising problems											
Proportion with normal scores (<85th percentile) and p-value (IVF males vs. controls)											
1 (Montgomery et al., 1999)	Case control study	Very serious[r]	-	-	-	Yes[s]	87.3	85	0.8	-	Very low

Quality assessment							Summary of findings				
							No. of people		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Proportion with normal scores (>95th percentile) and p-value (IVF males vs. control group)											
1 (Montgomery et al., 1999)	Case control study	Very serious[r]	-	-	-	Yes[s]	2.1	5	0.98	-	Very low
Long-term medication use											
Proportions and adjusted ORs (all children in IVF vs. control group)											
1 (Klemetti et al., 2006)	Retropsective Cohort Study	Serious[a]	-	-	Serious[b]	Yes[c]	3.3	2.8	1.2 (1.0 to 1.4)	-	Very low
Singletons											
1 (Klemetti et al., 2006)	Retropsective Cohort Study	Serious[a]	-	-	Serious[b]	Yes[c]	2.9	2.8	1.0 (0.8 to 1.3)	-	Very low
Major birth defects											
Proportion and adjusted OR (all children in IVF vs. control group)											
1 (Hansen et al., 2002)	Retropsective Cohort Study	Serious[a]	-	-	Serious[b]	Yes[v]	75/837 (9%)	168/4,000 (4.2%)	2.0 (1.3 to 3.2)	-	Very low
Mother-child relationship problems											
Proportion and p-values (children in IVF vs. sterility vs. control group)											
							IVF	Sterility	Control		
1 (Raoul-Duval et al., 1994)	Prospective Cohort Study	Very serious[g]	-	-	-	Yes[h]	2/25 (8%)	0/11 (0%)	1/13 (8%)	NS	-	Very low

Quality assessment							Summary of findings				
							No. of people		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Neurological sequelae											
Proportions and adjusted ORs (IVF-ICSI twins vs. control twins)											
1 (Pinborg et al., 2004)	Case control study	Serious[a]	-	Serious[f]	Serious[b]	No	30/3,393 (0.9%)	98/10,239 (1.0%)	1.1 (0.7 to 1.6)	-	Very low
IVF-ICSI twins vs. IVF-ICSI singletons											
1 (Pinborg et al., 2004)	Case control study	Serious[a]	-	Serious[f]	Serious[b]	No	30/3,393 (0.9%)	42/5130 (0.8%)	1.0 (0.6 to 1.5)	-	Very low
Sepsis											
Number of cases and adjusted OR (children in IVF vs. control group)											
1 (Kallen et al., 2005)	Retropsective Cohort Study	Serious[a]	-	-	Serious[b]	Yes[e]	43	3,388	1.1 (0.7 to 1.8)	-	Very low
Social problems											
Proportion with normal scores (<85th percentile) and p-value (IVF males vs. controls)											
1 (Montgomery et al., 1999)	Case control study	Very serious[r]	-	-	-	Yes[s]	93.8	85	0.99	-	Very low
Proportion with normal scores (>95th percentile) and p-value (IVF males vs. control group)											
1 (Montgomery et al., 1999)	Case control study	Very seriousr	-	-	-	Yes[s]	2.8	5	0.09	-	Very low

Quality assessment							Summary of findings				
							No. of people		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Suspected developmental delay											
Proportions and adjusted ORs (all children in IVF vs. control group)											
1 (Stromberg et al., 2002)	Retropsective Cohort Study	Serious[a]	-	-	Serious[b]	Yes[d]	22/5,680 (0.4%)	11/11,360 (0.1%)	4.0 (1.9 to 8.3)	-	Very low
Singletons											
1 (Stromberg et al., 2002)	Retropsective Cohort Study	Serious[a]	-	-	Serious[b]	Yes[d]	6/3228 (0.19%)	10 (.09%)	2.0 (0.7 to 5.4)	-	Very low
Thought problems											
Proportion with normal scores (<85th percentile) and p-value (IVF males vs. controls)											
1 (Montgomery et al., 1999)	Case control study	Very serious[r]	-	-	-	Yes[s]	94.7	85	0.99	-	Very low
Proportion with normal scores (>95th percentile) and p-value (IVF males vs. control group)											
1 (Montgomery et al., 1999)	Case control study	Very serious[r]	-	-	-	Yes[s]	1.1	5	0.99	-	Very low
URTI											
Number of cases and adjusted OR (children in IVF vs. control group)											
1 (Kallen et al., 2005)	Retropsective Cohort Study	Serious[a]	-	-	None	Yes[e]	891	95,112	1.2 (1.1 to 1.3)	-	Very low

Quality assessment							Summary of findings				
							No. of people		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Weight											
Percentiles and p-values (all children in IVF vs. Control group)											
1 (Brandes et al., 1992)	Retropsective Cohort Study	Serious[a]	-	-	-	Yes[m]	32.6±28.7	36.1±38.5	NS	-	Very low

a. Retrospective study design.
b. Wide confidence interval.
c. Results were adjusted for mother's socioeconomic position. When outcomes were analysed for multiples, there was no difference in any of the outcomes between IVF and Non-IVF children.
d. Results were adjusted for sex, year of birth and birth hospital. When the results were analysed for multiples, there was no difference in any of the outcomes between IVF and non-IVF children.
e. Results were adjusted for year of birth, maternal age, parity and smoking.
f. Indirectness of comparator: The non-IVF group potentially includes women that may have received some form of ovarian stimulation or IUI.
g. Risk of attrition bias: no comparison was made between patients that were lost and those that continued. Small sample size.
h. The results remained non-significant when children were examined at 9 months, 18 months and 36 months.
i. Likelihood of investigator bias. Confidence interval not reported
j. ICSI children differed from IVF children in being more likely to have fathers with unskilled occupation; adjusting the results for this factor still made no difference.
k. Confidence interval not reported.
l. There were no differences between the two groups in matching factors.
m. The outcomes were compared in IVF singletons and non-IVF singletons and the results were not significant. The same results were obtained when multiples were compared.
n. At 3 years, there was at least 50% loss to follow-up from each group. It is not clear whether the study was adequately powered to detect any differences between the groups at 3 years.
o. Intellectual assessment at 3 years was adjusted for levels of education of the parents.
p. Poor quality of data.
q. Results were calculated based on assumptions; therefore, they may be overestimated or underestimated.
r. When females were compared with the control group, the results were the same as the result of the comparison between males and controls.
s. Selection and/or reporting bias since the results were collected retrospectively. IVF significantly younger than children in the control group.
t. Results were adjusted for gender.
u. There was a significant difference in fetal exposure to exogenous maternal progestin in the IVF group
v. Poor quality of data.

Appendix J Key priorities for research

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

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

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

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

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

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

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

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

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

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

Appendix K Deleted material from 2004 version

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.[1,2] However, the presence of disorders in both the man and the woman has been reported to occur in about 39% of cases.[3] 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.[4] Those procedures which involve the handling of embryos or donated gametes (indicated by * above) are regulated by the Human Fertilisation and Embryology Authority (HFEA). 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.

Areas outside the remit of this 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.

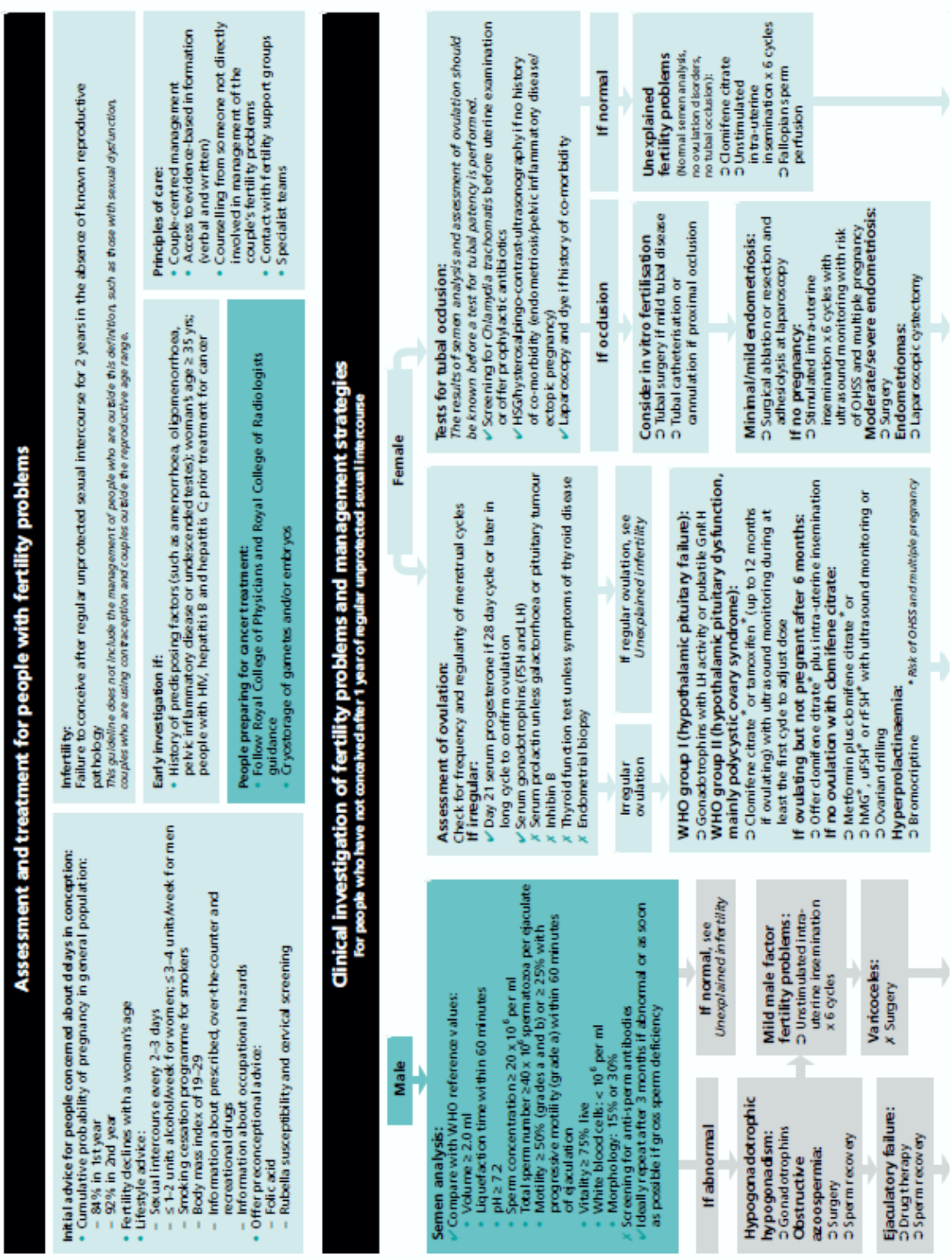
The guideline does not address laboratory standards or service configuration that may impact on the quality of care. It also does not include assessment of social criteria that might be relevant to access for fertility services funded by the NHS for example whether there are any existing children in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

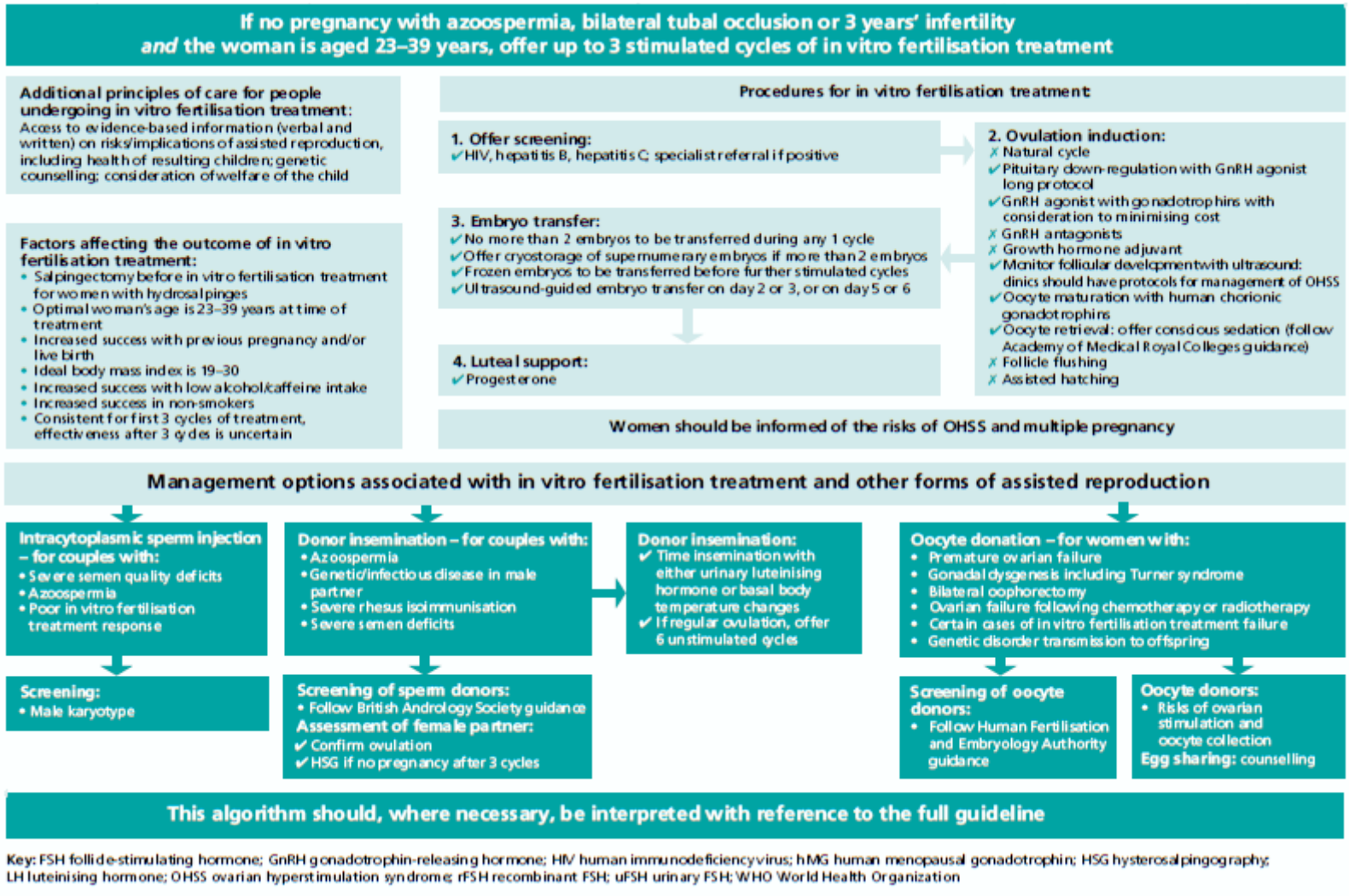
For whom is this guideline intended

This guidance is of relevance to those who work in or use the National Health Service (NHS) in England and Wales, in particular:

- 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.

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 1st year
– 92% in 2nd year
• Fertility declines with a woman's age
• Lifestyle advice:
– Sexual intercourse every 2–3 days
– ≤ 1–2 units alcohol/week for women; ≤ 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 ≥ 35 yrs; 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
Female
Semen analysis:
✓ Compare with WHO reference values:
• Volume ≥ 2.0 ml
• Liquefaction time within 60 minutes
• pH ≥ 7.2
• Sperm concentration ≥ 20 x 10⁶ per ml
• Total sperm number ≥ 40 x 10⁶ spermatozoa per ejaculate
• Motility ≥ 50% (grades a and b) or ≥ 25% with progressive motility (grade a) within 60 minutes of ejaculation
• Vitality ≥ 75% live
• White blood cells: < 10⁶ per ml
• Morphology: 15% or 30%
✗ Screening for anti-sperm antibodies
✓ Ideally repeat after 3 months if abnormal or as soon as possible if gross sperm deficiency
If normal, see Unexplained infertility
If abnormal
Hypogonadotrophic hypogonadism:
Ↄ Gonadotrophins
Obstructive azoospermia:
Ↄ Surgery
Ↄ Sperm recovery
Mild male factor fertility problems:
Ↄ Unstimulated intra-uterine insemination x 6 cycles
Varicoceles:
✗ Surgery
Ejaculatory failure:
Ↄ Drug therapy
Ↄ Sperm recovery
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):
Ↄ Gonadotrophins with LH activity or pulsatile GnRH
WHO group II (hypothalamic pituitary dysfunction, mainly polycystic ovary syndrome):
Ↄ 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:
Ↄ Offer clomifene citrate* plus intra-uterine insemination
If no ovulation with clomifene citrate:
Ↄ Metformin plus clomifene citrate* or
Ↄ hMG*, uFSH* or rFSH* with ultrasound monitoring or
Ↄ Ovarian drilling
Hyperprolactinaemia:
Ↄ 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
✓ HSGhysterosalpingo-contrast-ultrasonography if no history of co-morbidity (endometriosis/pelvic inflammatory disease/ectopic pregnancy)
✓ Laparoscopy and dye if history of co-morbidity
If occlusion
If normal
Consider in vitro fertilisation
Ↄ Tubal surgery if mild tubal disease
Ↄ Tubal catheterisation or cannulation if proximal occlusion
Minimal/mild endometriosis:
Ↄ Surgical ablation or resection and adhesiolysis at laparoscopy
If no pregnancy:
Ↄ Stimulated intra-uterine insemination x 6 cycles with ultrasound monitoring with risk of OHSS and multiple pregnancy
Moderate/severe endometriosis:
Ↄ Surgery
Endometriomas:
Ↄ Laparoscopic cystectomy
Unexplained fertility problems
(Normal semen analysis, no ovulation disorders, no tubal occlusion):
Ↄ Clomifene citrate
Ↄ Unstimulated intra-uterine insemination x 6 cycles
Ↄ Fallopian sperm perfusion



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

Natural conception

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.[21,23] The effect of age on male fertility is less clear.[24] [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 XX) With regular intercourse, 94% and 77% of fertile women aged 35 years and 38 years conceive after three years of trying.22,25 [Evidence level 3]

Frequency and timing of sexual intercourse or artificial insemination

Six cohort studies that evaluated the use of basal body temperature or urinary luteinising hormone (LH) kits as indicators of ovulation to time intercourse did not report improvement in the chance of natural conception.[34–39] [Evidence level 2b] Timed intercourse has been suggested to be an emotionally stressful intervention in the initial evaluation of infertility.[40] [Evidence level 3] However, for the minority of couples who find it difficult to have frequent sexual intercourse every two to three days the prediction of ovulation using LH kits can be useful. In people who are trying to conceive using some form of artificial insemination, that insemination should be timed to coincide with ovulation.

Folic acid supplementation

A systematic review[119] of four RCTs (n = 6425 women) showed that periconceptional folate supplementation reduced the incidence of neural rube defects (anencephaly and spina bifida) in children (RR 0.28, 95% CI 0.13 to 0.58). 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.[179] [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.[180] 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 teratogenecity.[181] 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.[182,183]

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.[207,218] [Evidence level 4] Two surveys have reported that women were more satisfied when seen with their partners at their infertility consultation.[219,220] [Evidence level 3] A further survey reported that couples were seen together in only 35% of clinics.[221] However, there was strong agreement among GPs that couples should be seen together as part of infertility management.[222] [Evidence level 3]

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

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 XX).[285,287] [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%.[286] [Evidence level 2b] Definitions relating to semen quality are given in Table XX.

Assessing ovulation

Female fecundability is related to the total number of primordial follicles remaining within the ovaries (referred to as ovarian reserve), which declines with age.[323] 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.[324,325] [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,[326,327] women undergoing complex ovulation induction and women participating in assisted reproductive technology cycles.[328–331]

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.[332] [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%)[328] 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.[333] [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.[334] 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.[335] [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.[336] [Evidence level 2b]

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

One study reported that none of these markers accurately reflected ovarian reserve.[341] 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.[341] [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.[329] [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.[342] [Evidence level 4]

Tests of ovarian reserve do not currently have the necessary sensitivity or specificity for general application.[325]

Number	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]

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 X and X, respectively.

Strategies for management of fertility problems

Male factor fertility problems

Assisted reproduction methods are indicated by the quantity and quality of spermatozoa that can be isolated by semen preparation techniques. While IUI (see Chapter XX) or IVF (see Chapter XX) are feasible in mild–moderate oligozoospermia, ICSI (see Chapter XX) 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.

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 XX). 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 XX). Alternatively, women can be treated with gonadotrophins (see Section XX).

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 XX.

World Health Organization Group III ovulation disorders

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

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[418] and 8–28% of infertility in couples.[1,3] In couples with unexplained infertility, the chance of spontaneous conception will relate to the duration of infertility (see Section XX). The spontaneous cumulative pregnancy rate has been estimated to lie between 33% and 60% at three years[419,420] and 36% at seven years, although this will be influenced by other known prognostic factors such as the age of the woman.[421–425] [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.[422]

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.[426]. Antioestrogens (usually clomifene citrate; see Section XX) and IUI (see Chapter XX) are usually used as intermediate options, with the final stage of management being IVF treatment (see Chapter XX). There is no

evidence to suggest that ICSI improves pregnancy rates above those achieved with IVF in unexplained fertility problems (see Section XX).

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

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 procude more follicles. The evidence relating to anti-oestrogens predominantly involves clomifene citrate. The adverse effects of antioestrogens such as clomifene citrate include hot flushes, ovarian hyperstimulation, abdominal discomfort and multiple pregnancy.[181]

Anti-oestrogens in women with ovulatory disorders

A systematic review of four crossover RCTs that compared clomiphene 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).[485] [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.[486] [Evidence level 1b] Similar results were found in three other studies, including a quasi-randomised study.[487–489] [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).[490] [Evidence level 1b]

About 70% of anovulatory women ovulate in response to clomifene citrate treatment,[491,492] and they do so at a dose of 50–100 mg,[493] 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.[494] In anovulatory women, there is a significant association between clomifene citrate treatment failure and increased BMI (BMI greater than 27.2 kg/m2 or greater than 30.6 kg/m2).[495,496] [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 XX and XX).[497,498] [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.[499] Lifestyle modification may improve insulin sensitivity and restore ovulation in women with PCOS.[500] [Evidence level 2b]

Although the British National Formulary recommends a maximum of six cycles of clomifene citrate,[181] 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.[495,501] [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).[502] [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.[503] [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).[503] 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.[504]

Number	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]

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.[505] The earlier review is of poorer quality and includes 12 RCTs and a number of observational studies.[506] 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/m2, 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.[505] [Evidence level 1a] Metformin can be used as an adjuvant to general lifestyle improvements (see Sections XX and XX).

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

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

Number	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]

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.[508] [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.[508] [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.[509] [Evidence level 1b]

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

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

Number	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]

Number	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.

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.[512] [Evidence level 2a]

For women with PCOS who do not respond to clomifene citrate, gonadotrophins have been used as ovulation induction agents.[513] 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).[513] [Evidence level 1a] No significant differences on the above outcomes were found between the use of subcutaneous pulsatile and intramuscular injection of gonadotrophins;[513] daily and alternate day administration; or step-up' and standard regimens.[513] [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).[514] [Evidence level 1a] No significant differences were shown in these outcomes between administering rFSH as a chronic low dose or conventional regimen.[514]

Number	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]

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.[515] 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.[516] [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.[517–520] [Evidence level 1a] The first systematic review (18 RCTs) included only trials comparing uFSH with rFSH.[517] [Evidence level 1a] The second systematic review (20 RCTs) included trials comparing urinary gonadotrophins (including hMG, FSH-P and FSH-HP) versus rFSH.[518] [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.[519] [Evidence level 1b–2a] The fourth systematic review (eight RCTs) included only trials comparing hMG versus rFSH.[520] [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,[522,523,1148] two studies in which a short GnRH agonist protocol was used,[524,525] one study in which a quasi-randomisation method was used,[526] one study published only as an abstract in which no data were presented,[527] and one other study published only as an abstract that we were unable to obtain a copy of.[528]

We found three RCTs[529,530,1148] 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).[529–549] 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 XX. 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]

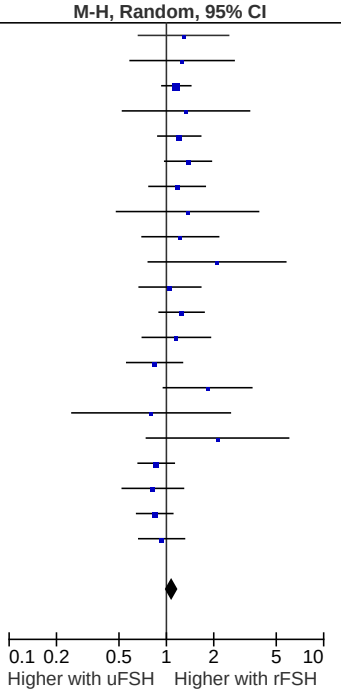
A recent RCT (n = 191) reported a significantly higher convenience score and less rFSH used with self injection by IVF patients with a pen device when compared with a conventional syringe.[550] [Evidence level 1b]

Figure XX Comparison between urinary follicule-stimulating hormone and recombinant follicule-stimulating hormone showing clinical pregnancy, ongoing pregnancy and live birth rates

01 Clinical pregnancy rates/cycle

Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year
Hedon 1995	20	57	9	33	1.9%	1.29 [0.67, 2.49]	1995
RHFSG 1995	12	60	10	63	1.4%	1.26 [0.59, 2.70]	1995
Out 1995	171	585	100	396	16.4%	1.16 [0.94, 1.43]	1995
Alvino 1995	8	30	6	30	1.0%	1.33 [0.53, 3.38]	1995
Bergh 1997	53	119	42	114	8.0%	1.21 [0.88, 1.65]	1997
Kornilov 1999	18	28	51	109	6.8%	1.37 [0.98, 1.93]	1999
Hoomans 1999	32	83	27	82	4.7%	1.17 [0.78, 1.77]	1999
Ghosh 1999	6	22	5	25	0.8%	1.36 [0.48, 3.86]	1999
Berger 1999	23	89	16	76	2.6%	1.23 [0.70, 2.15]	1999
Nardo 2000	18	75	4	35	0.8%	2.10 [0.77, 5.74]	2000
Lenton 2000	27	80	24	75	4.0%	1.05 [0.67, 1.66]	2000
Schats 2000	62	247	50	249	7.3%	1.25 [0.90, 1.74]	2000
Franco 2000	22	60	19	60	3.3%	1.16 [0.70, 1.91]	2000
Frydman 2000	32	139	38	139	4.8%	0.84 [0.56, 1.27]	2000
Germond 2000	16	35	10	40	2.0%	1.83 [0.96, 3.49]	2000
Ng 2001	4	20	5	20	0.6%	0.80 [0.25, 2.55]	2001
Gordon 2001	11	39	4	30	0.8%	2.12 [0.75, 5.99]	2001
Westergaard 2001	65	190	75	189	11.0%	0.86 [0.66, 1.12]	2001
Dickey 2002	18	58	45	119	4.0%	0.82 [0.52, 1.28]	2002
EISG 2002	76	354	95	373	10.9%	0.84 [0.65, 1.10]	2002
Kilani 2003	28	50	30	50	7.1%	0.93 [0.67, 1.30]	2003
Total (95% CI)		**2420**		**2307**	**100.0%**	**1.08 [0.98, 1.18]**	
Total events	722		665				

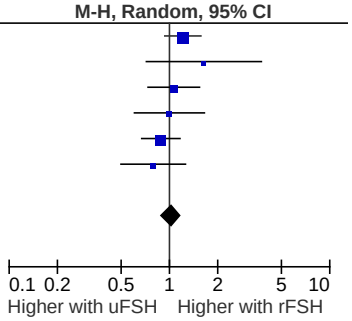
Heterogeneity: Tau² = 0.00; Chi² = 20.71, df = 20 (P = 0.41); I² = 3%
Test for overall effect: Z = 1.63 (P = 0.10)



02 Ongoing pregnancy rates/cycle

Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year
Out 1995	129	585	72	396	32.0%	1.21 [0.94, 1.57]	1995
Hedon 1995	17	57	6	33	3.4%	1.64 [0.72, 3.75]	1995
Bergh 1997	40	119	36	114	16.4%	1.06 [0.74, 1.54]	1997
Frydman 2000	25	139	25	139	9.1%	1.00 [0.61, 1.65]	2000
EISG 2002	73	354	87	373	28.6%	0.88 [0.67, 1.16]	2002
Dickey 2002	17	58	44	119	10.6%	0.79 [0.50, 1.26]	2002
Total (95% CI)		**1312**		**1174**	**100.0%**	**1.03 [0.88, 1.20]**	
Total events	301		270				

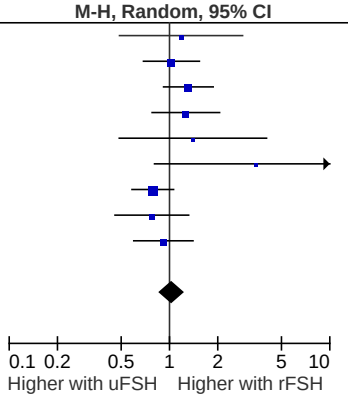
Heterogeneity: Tau² = 0.00; Chi² = 5.21, df = 5 (P = 0.39); I² = 4%
Test for overall effect: Z = 0.37 (P = 0.71)



03 Live birth rates/cycle

Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year
RHFSG 1995	9	60	8	63	4.0%	1.18 [0.49, 2.86]	1995
Frydman 2000	36	139	35	139	15.3%	1.03 [0.69, 1.54]	2000
Schats 2000	56	247	43	249	18.1%	1.31 [0.92, 1.87]	2000
Lenton 2000	27	80	20	75	11.5%	1.27 [0.78, 2.06]	2000
Nardo 2000	12	75	4	35	2.9%	1.40 [0.49, 4.03]	2000
Gordon 2001	9	39	2	30	1.6%	3.46 [0.81, 14.85]	2001
Westergaard 2001	53	190	67	189	22.7%	0.79 [0.58, 1.06]	2001
Dickey 2002	14	58	37	119	10.0%	0.78 [0.46, 1.32]	2002
Kilani 2003	22	50	24	50	14.0%	0.92 [0.60, 1.40]	2003
Total (95% CI)		**938**		**949**	**100.0%**	**1.02 [0.85, 1.23]**	
Total events	238		240				

Heterogeneity: Tau² = 0.02; Chi² = 10.07, df = 8 (P = 0.26); I² = 21%
Test for overall effect: Z = 0.26 (P = 0.79)



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.[551,552] [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).[553] [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.[518] 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.[554] 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[181] 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.

Number	Recommendation
	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]

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).[555] [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).[556] [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.[513] [Evidence level 1a]

Number	Recommendation
	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]

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.[557] [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).[557] [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.[557] [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).[558] [Evidence level 1a]

An earlier meta-analysis of 17 RCTs included quasi-randomised trials and is therefore excluded from this review.[557]

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).559 However, the use of depot GnRH agonist increased gonadotrophin requirements and duration of ovarian stimulation when compared with daily GnRH agonist.[559] [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.[560] [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.[561] [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).[561] [Evidence level 1a] Patient satisfaction was not considered in this systematic review.

A second systematic review[562] 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)[564] 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).[564] [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.[565–567] [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).[568] [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). The drug costs, which were obtained from the British National Formulary,[181] 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.

Number	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]

Number	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.

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.[609] 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).[502] [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).[502] [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.[610–614] 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.[615–620] 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.[621] [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.[622] A survey of reproductive endocrinologists reported that 83% of those surveyed said they addressed this risk when obtaining consent from patients for infertility treatment,[623] and 40% of physicians routinely discussed the topic of ovarian cancer with their patients before prescribing fertility drugs.[622] [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.[624]

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

Number	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]

Number	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.

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[684] with timed intercourse or intracervical insemination. The second review[685] 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).[685] [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.[686] 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.[687] [Evidence level 1b]

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%, $p < 0.01$).[688] [Evidence level 1b] The corresponding pregnancy rates per treatment cycle were 2%, 5%, 4% and 9% ($p< 0.01$).[688] [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).[689] [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.[684,690,691] [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.[691] [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).[691] [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).[688] [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.[688]

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.[692] [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.[686] 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).[693] [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).[694] [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.[695] [Evidence level 1a]

A further RCT (n = 91 couples,[695] 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).[696] [Evidence level 1b]

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

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).[698] [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%).[699] [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).[700] [Evidence level 1b] Multiple pregnancy rates were reported to be between 18% and 33% in these three trials.

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).[701] [Evidence level 1a]

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.[702]

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).[397] [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).[703] [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).[704] [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.[705] [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[703,705] but no complications were reported.

One of the studies described above[703] 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.

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.[706] 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[688] 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.[707] 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.

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.[708] 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.[686] 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.[710] 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.

Number	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]

Number	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.

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.[218]

Introduction

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.[711] 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.[711]

Immediate versus delayed in vitro fertilisation

A recent multicentred RCT (n = 139 couples) reported significantly higher live birth rates per IVF/ICI cycle when compared with no treatment for three months in women with fallopian tube patency (29% with IVF/ICSI versus 4% with no treatment).[712] [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.[713] [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).[714] [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.[715] 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.[716] [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.[714] [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.[714] [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).[717] [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.[718–721] [Evidence level 3]

Duration of infertility has been shown to be an important factor in determining the chance of pregnancy, with or without treatment.[722] 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 XX). [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.[723] 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.[724] [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.[725,726] [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 X). 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.[727] 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.[707] 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.[728] 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.[729] 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.

Number	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.

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.[723] [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 XX, XX, XX, XX and XX 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 XX 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 XX 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 XX 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

Age (years)	Treatment cycles (n)	Live births (n)	Live birth rate per treatment cycle (%)
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.[735] Freezing poor quality embryos will lead to poor cryosurvival and low implantation rates.[736] As with fresh embryos, pregnancy rates are affected by factors such as patient age.[736–739] A beneficial outcome is also more likely if a pregnancy resulted from the original stimulation cycle from which the frozen embryos were derived.[738–740] The number of oocytes retrieved in the initial stimulation cycle and the number of embryos available for cryopreservation also affects outcome.[741] [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.[742] The corresponding figure for 1999–2000 was 13.8% of 5131 treatment cycles.[743] [Evidence level 3]

The most recent data on live birth rates with frozen IVF cycles obtained from the HFEA are shown in Table XX. This analysis was based on 22,546 IVF treatment cycles that were registered between January 1995 and March 1999 and involved use of the woman's own eggs and frozen embryo transfer. The overall live birth rate per treatment cycle was 11.5%. Between the ages of 23 years and 38 years the live birth rate per treatment cycle varied between 10% and 16%. The live birth rates for women aged 18 years to 22 years are shown in Table XX, 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]

Table XX 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 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	2020	257	12.7
35	1909	209	10.9
36	1746	195	11.2
37	1486	177	11.9
38	1246	128	10.3
39	985	88	8.9
40	770	58	7.5
41	467	31	6.6
42	354	25	7.1
43	223	6	2.7
44	150	3	2.0
45	92	1	1.1

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

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%.741 [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.[748] 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.[749] [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.[750] A retrospective study compared babies (n = 283) from births from cryopreserved embryos with babies (n = 961) after conventional IVF. There was no differernce 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%).[751] 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.[752] [Evidence level 3]

Pregnancy rates

Table XX relates to clinical pregnancy rates from IVF cycles. This analysis was based on 110,538 IVF treatment cycles that were registered by the HFEA between January 1995 and March 1999 and involved use of the woman's own eggs and fresh embryo transfer. The overall pregnancy rate per treatment cycle was 21.0%. Between the ages of 22 years and 36 years the pregnancy rate per treatment cycle exceeded 20%. The pregnancy rates for women aged 18 years to 22 years are shown in Table XX, 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]

Table XX 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

Age (years)	Treatment cycles (n)	Clinical pregnancies (n)	Clinical pregnancy rate per treatment cycle (%)
28	4342	1100	25.3
29	5656	1413	25.0
30	6991	1769	25.3
31	8266	2016	24.4
32	9061	2201	24.3
33	9435	2257	23.9
34	9850	2307	23.4
35	9301	2053	22.1
36	8337	1709	20.5
37	7623	1403	18.4
38	6597	1114	16.9
39	5602	805	14.4
40	4021	520	12.9
41	2780	272	9.8
42	1818	126	6.9
43	1238	81	6.5
44	730	29	4.0
45	390	7	1.8

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

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

The decline in pregnancy rates with age may be related to declining embryo quality.[746] Embryo quality is difficult to assess. For apparently equal embryo quality, maternal age does not significantly reduce pregnancy rates.[764] 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.[588] [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.[765–767] [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%).[768] [Evidence level 3]

Ectopic pregnancy rates

Table XX 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.[755] [Evidence level 3]

Table XX 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

Miscarriage rates

Table XX 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 XX 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,[726] 35 years[755,757,769] and 40 years.[758,759,762,770] [Evidence level 3]

Table XX 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

Fertilisation rates

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

Implantation rates

Two studies have reported decreased implantation rates following IVF in women aged more than 35 years[755] and 37 years.[774] However, a third study showed no significant difference in implantation rates between women aged over 35 years and younger women.[775] 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.[775] [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.[776] 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.[756] [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.[777] [Evidence level 3]

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.[778,779] [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.[780] [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).[745] [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.

Number	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. 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]

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,[592] as well as significant financial[593,594] and psychological[595] consequences for the parents. Surveys have suggested that the prospect of multiple pregnancies may not be viewed as an adverse outcome by prospective patients.[598–602] [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.[596,597] [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.[781] [Evidence level 2b]

The increase in triplet deliveries following assisted reproduction has been linked to the increased sale and use of ovulation induction agents.[782] [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.[783] [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.[784] The HFEA 6th Code of Practice, 2004, [218] 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.[785] [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.[688] [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.[786] [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.[787] [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.[743] [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.[743] [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.[788–790] [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.[789,790] [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.[790] 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.[789]

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[791] 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.[792] 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.[786] [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.[786] [Evidence level 3]

Economic consequences

An American study based on a single retrospective cohort study in one IVF centre followed [413] treatment cycles.[793] 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).[794] 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.[795] 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.

Number	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]

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

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).[723] [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 XX). The data show that the live birth rate per treatment cycle is largely unchanged over the first four attempts, but the sample sizes for the fifth, sixth and seventh attempts are too small to make valid conclusions. [Evidence level 3]

Table XX 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 (n)	Treatment cycles (n)	Live births (n)	Live birth rate per cycles (%)
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

Previous treatment (n)	Treatment cycles (n)	Live births (n)	Live birth rate per cycles (%)
6	2	0	0.0
7	1	0	0.0

Table XX Women aged less than 39 years: 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)

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

Table XX Women aged 39 years and over: 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)

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[a]

a 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.

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 XX). 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.[778] 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.[779] 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.[779] [Evidence level 3]

Another study reported data from 4225 women (8207 IVF cycles) who underwent IVF treatment in Australia between 1993 and 1997.796 [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.[796] [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.[797] [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.[726] [Evidence level 3] Another small study found that implantation rate was significantly associated with rank of attempt.[774] [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).[758] [Evidence level 3]

Number	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]

Pregnancy history

Number	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]

Alcohol, smoking and caffeine consumption

Number	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]

Body weight

Number	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]

Number	Research Recommendations
	Further randomised controlled trials are needed to evaluate the effectiveness of assisted reproduction procedures in relation to female body mass index.

Clinical effectiveness and referral for in vitro fertilisation treatment

The cost-effectiveness models for IVF treatment are described in detail in Appendix XX. 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 XX. 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 XX.

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 XX. 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 XX) 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 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.[811] The data reported in Table XX are for the year 1994.

Table 12.8 Cost of in vitro fertilisation per delivery (1994)[811]

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

Number	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]

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 seropostive for the hepatitis B virus and 0.54% were seropositive for the hepatitis C virus.[819] 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.[820] 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.[821] [Evidence level 3]

Screening for C. trachomatis infection before uterine instrumentation is discussed in Chapter X, Section XX.

Number	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]

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.[822–824] 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.[825] [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.[826,827]

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[828,829] has been used as a risk-reduction option in which infected sperm are washed to reduce the titre of virus[830,831] 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.[828,832,833] [Evidence level 3] However, the risk of transmission still exists, as shown by the persistence of virus in washed sperm.[834,835]

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.[830] [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.

Number	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]

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 X, 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.[836] [Evidence level 2b–3] Natural cycle IVF was associated with no risk of OHSS or multiple pregnancy rate when a single embryo was transferred.[836] [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).[837] [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).[838] [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.[839]

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.[840,841]

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.[840] [Evidence level 2a]

In replacing frozen-thawed embryos, pregnancy rates were reported to be similar between natural cycle and programmed cycles;[737] 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),[842] between natural cycles and cycles controlled with exogenous oestradiol and progesterone administration,[843] between natural cycle and GnRHa administration followed by oestradiol valerate supplementation,[844] between spontaneous cycles, artificial preparation and ovarian stimulation cycles[845] and between spontaneous cycles, an ovarian stimulation and oestrogen/progesterone replacement therapy.[846] [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).[847] [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 (cetrorelix and ganirelix). Since many aspects of

gonadotrophin and GnRHa use overlap with their uses in ovulation induction for ovulatory disorders, the evidence relating to these agents in IVF treatment is discussed in Chapter X.

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.[848,849] [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.[849] 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.849 [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, 9%% CI 0.64 to 10.12).[850] [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%).[851] [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.[852] [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.[853] [Evidence level 2a]

Number	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]

Number	Recommendations
	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]

Number	Recommendations
	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]

Day two to three versus day five to six transfers

This has been the subject of a systematic review.[953] 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.[954–957] 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.

Number	Recommendations
	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]

Number	Recommendations
	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 chrionic gonadotrophin or progesterone for luteal phase support is not recommended because of the increased likelihood of ovarian hyperstimulation

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[1104] has recommended procedures to be followed before commencing chemotherapy or radiotherapy likely to affect fertility and the management of posttreatment infertility. A strategy for developing policy and practice in fertility preservation for survivors of cancer has recently been proposed by the British Fertility Society.[1105] [Evidence level 4]

Ovarian hyperstimulation syndrome

A number of other methods of preventing OHSS have been advocated. These include the use of recombinant LH[872] and GnRH antagonists such as ganirelix or cetrorelix.[873,874] A meta-analysis of five RCTs[561] 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]

Screening of sperm donors

The British Andrology Society has published consensus guidelines on the selection and screening of semen donors specifically for the protection of the offspring of donor insemination treatment from heritable genetic disorders and of the recipient women from infection. The British Andrology Society guidelines suggest an upper age limit of 40 years for sperm donors.[1028] [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.[1028] [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.

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.[1053–1056] 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[1057] 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[1056] found a significant reduction in number of patient visits per insemination cycle. [Evidence level 1a] Another study[1054] 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%).[1038] [Evidence level 3]

Number	Recommendation
	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. **[2004]**

Screening of oocyte donors

Given the high prevalence of cystic fibrosis, which is the most common autosomal recessive disorder in northern Europeans, the HFEA[218] 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 XX). 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.[1082] [Evidence level 4]

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%).[1150] [Evidence level 3]

Another possible treatment, available after anticancer treatment has been concluded, is IVF using donated oocytes (see Section XX).

Anticancer treatment can cause ovarian failure; however, cryopreservation of oocytes has had very limited success.[1105,1121,1151] [Evidence level 3–4] Live births following ICSI for fertilisation of in vitro cryopreserved oocytes has been reported in women with[1121] and without cancer.[1122,1123] [Evidence level 3]

Cryopreservation of ovarian cortex before cancer treatment may be a valuable fertility conservation option[1124] but its clinical practicality followed by ovarian transplantation needs further development and evaluation, as there has been no pregnancy in humans with this technique.[1105,1121,1125] [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.[218]

Number	Recommendations
	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 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]

Genetic risks and congenital malformations

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).[1129] [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[1130,1131] and Angelman syndrome,[1132] in children born after assisted reproduction. The reports on Beckwith–Wiedermann syndrome suggest a six-fold increase in risk against a background prevalence of around 1.3 per

100,000 newborn infants.[1130,1131] [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.[1133] [Evidence level 2b–3] There is a need for further research on the clinical outcomes of ICSI IVF pregnancies.

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.[1134] [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.[1135] [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.[1136] [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.[1137] [Evidence level 2b]

A report on childhood cancer from the Netherlands suggested an increased risk of childhood retinoblastoma.[1138] [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.

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.[1139] [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.[1140] [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.[1141] [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.[1142] [Evidence level 3]

Number	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. [C]

Number	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.

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 XX).

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 XX Suggested audit criteria

Criterion	Exception	Definition of terms
Percentage of women with documented offer of screening for *Chlamydia trachomatis* before undergoing uterine instrumentation	Women currently being treated for *C. trachomatis*	Screening for *C. trachomatis* using an appropriately sensitive technique
Percentage of women with pelvic inflammatory disease, previous ectopic disease, 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

Criterion	Exception	Definition of terms
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	

Glossary

Assisted reproduction	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.
Bias	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.
Blinding or masking	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
Case–control study	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.
Case report (or case study)	Detailed report on one patient (or case), usually covering the course of that person's disease and their response to treatment.
Case series	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.
Clinical trial	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.
Cohort	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.
Cohort study	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.)
Cryopreservation	The freezing and storage of eggs, sperm and/or embryos that may be thawed for use in future in vitro fertilisation treatment cycles.
Donor insemination	The placement of donor sperm into the vagina, cervix or womb.
Double blind study	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.
Evidence based	The process of systematically finding, appraising, and using research findings as the basis for clinical decisions.
Evidence-based clinical practice	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.
Evidence table	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.
Exclusion criteria	see Selection criteria.
Experimental study	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.
Gamete intrafallopian transfer	A procedure in which eggs are retieved 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.
Gold standard	A method, procedure or measurement that is widely accepted as being the best available.
Gonadotrophins	Hormones that stimulate the ovaries.
Health economics	A field of conventional economics that examines the benefits of healthcare interventions (e.g. medicines) compared with their financial costs.
Heterogeneity	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.
Homogeneity	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.
Inclusion criteria	see Selection criteria.
Intervention	Healthcare action intended to benefit the patient, e.g. drug treatment, surgical procedure, psychological therapy.

Intracytoplasmic sperm injection	A variation of in vitro fertilisation in which a single sperm is injected into the inner cellular structure of an egg.
Intrauterine insemination	Placement of sperm into the uterus of a woman.
In vitro fertilisation	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.
Longitudinal study	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.)
Masking	see Blinding.
Meta-analysis	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 Systematic review and Heterogeneity.
Non-experimental study	A study based on subjects selected on the basis of their availability, with no attempt having been made to avoid problems of bias.
Nulliparous	Having never given birth to a viable infant
Number needed to treat (NNT)	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.
Observational study	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.
Odds ratio	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 Relative risk, Risk ratio.
Ooctye donation	The process by which a fertile woman donates her eggs to be used in the treatment of others or for research.
Ovarian hyperstimulation syndrome	A serious complication following stimulation of the ovaries with gonadotrophin drugs.
Parous	Having borne at least one viable offspring.
Peer review	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.

Pilot study	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.
Placebo	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.
	A beneficial (or adverse) effect produced by a placebo and not due to any property of the placebo itself.
	see Statistical power.
	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.
	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.
	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.
	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.
	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.
	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.)
Relative risk	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.
Reliability	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.
Retrospective study	A retrospective study deals with the present and past and does not involve studying future events. This contrasts with studies that are prospective.
Risk ratio	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.
Sample	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.
Screening	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.
Selection criteria	Explicit standards used by guideline development groups to decide which studies should be included and excluded from consideration as potential sources of evidence.
Sensitivity	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.
Specificity	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.
Statistical power	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.

Appendix B Economic models

Aim of the economic models

The purpose of the economic modelling was to synthesise the estimates of the costs and clinical effectiveness of assisted reproduction for couples seeking treatment for fertility problems after initial investigation. The assisted reproduction techniques for which sufficient data were available to construct models were IVF alone and IVF with ICSI. The economic analysis focused on the effect of age on the cost-effectiveness of IVF and ICSI, and the cost-effectiveness of these treatments according to the number of previous unsuccessful cycles. Different scenarios were explored using sensitivity analysis since a published evidence reported a range of estimates for several important parameters.

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 on age was structured so that couples were offered up to six fresh cycles of IVF treatment. This model was based on age-specific success rates obtained from the HFEA (see Tables XX to XX). The lowest age used in the economic mode was 24 years because below this age there were fewer than 100 treatment cycles (see Table XX). 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 potential outcomes of each (fresh or frozen) IVF cycle are: a live birth (in which case treatment ceases); an ectopic pregnancy; a miscarriage; or no pregnancy. The options for couples without a live birth are: to discontinue treatment; to attempt a frozen embryo transfer; or to proceed straight to the next fresh

cycle of IVF treatment if there are no embryos suitable for frozen embryo transfer. The model assumed that no couples would choose to discontinue treatment until they has used up all embryos suitable for frozen embryo transfer.

The model also allowed for the possibility of OHSS, but it was assumed that having OHSS would not affect the outcome of IVF treatment. A detailed description of the clinical effectiveness data used in this model is presented in Table XX. The discontinuation rates used in the model were estimated in studies based on experience in the independent sector, which may be higher than those that would occur if couples were not paying for treatment themselves.

There is very little robust clinical evidence to determine whether any long-term adverse outcomes are associated with IVF treatment, and so long-term consequences of treatment were not included in our models. Such consequences would include the potential costs to people with fertility problems in terms of psychological ill-health relating to waiting for treatment and the stress associated with assisted reproduction, irrespective of the outcome of treatment.

Figure XX Structure of the in vitro fertilisation treatment model for deriving age-specific cost per live birth

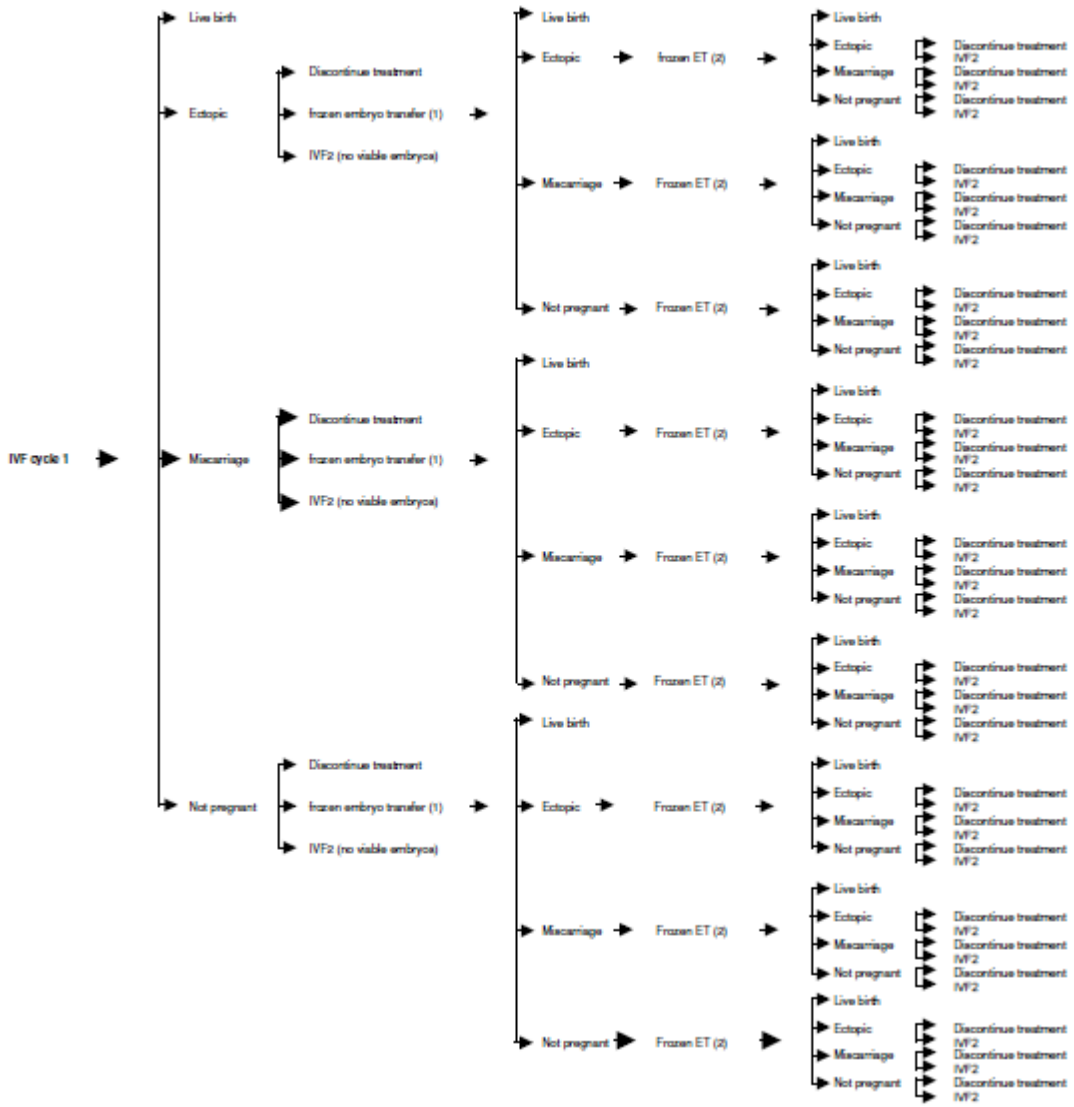


Table XX Clinical effectiveness data used in the in vitro fertilisation treatment model for deriving age-specific cost per live birth

Outcome	Cycle	Rate (%)	Source
Live birth	All fresh cycles	Age-specific rates used	HFEA data 1995–99 (see Table xx)
	All frozen cycles	Age-specific rates used	HFEA data 1995–99 (see Table xx)
Ectopic pregnancy	All cycles	Age-specific rates used	HFEA data 1995–99 (see Table xx)
Miscarriage	All cycles	Age-specific rates used	HFEA data 1995–99 (see Table xx)
Discontinuation	All fresh cycles	40–50% including pregnancy 20% without pregnancy	FIVNAT 1998[619]
	All fresh cycles, under 30 years All fresh cycles, 38–40 years	17.7% 50.0%	Mardesic et al. 1984[620]
Ovarian hyperstimulation syndrome	All cycles	0.2–1.0%	Various[435-437]

Cycle-specific models

The models based on the number of cycles were structured so that couples were offered up to four fresh cycles of IVF treatment and no frozen embryo transfers. Two models were used because two data sets with different structures were available.

The first cycle-specific model was based on live birth rates by number of previous unsuccessful cycles obtained from the HFEA (see Table XX) This dataset included estimates for up to four fresh (not frozen) cycles of treatment (see Section XX). 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 XX and XX respectively). The structure of the model is presented in Figure XX, which shows all four potential fresh cycles of IVF treatment. The potential outcomes of each IVF cycle are: a live birth (in which case treatment ceases); an ectopic pregnancy; a miscarriage; or no pregnancy. The options for couples without a live birth are: to discontinue treatment; or to proceed straight to the next fresh cycle of IVF treatment. A detailed description of the clinical effectiveness data used in this model is presented in Table XX.

Figure XX Structure of the in vitro fertilisation treatment model for deriving cycle-specific cost per live birth [included as a separate file

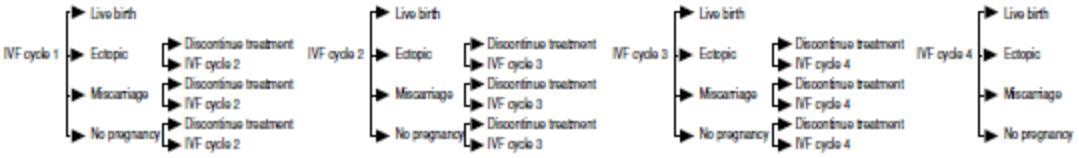


Table XX Clinical effectiveness data used in the first in vitro fertilisation treatment model for deriving cycle-specific cost per live birth

Outcome	Cycle	Rate (%)	Source
Live birth	Cycle 1 Cycle 2 Cycle 3 Cycle 4	18.2 17.2 18.8 19.4	HFEA data 1995–99 (see Table xx)
Ectopic pregnancy	All cycles	Overall rate (0.5%) used	HFEA data 1995–99 (see Table xx)
Miscarriage	All cycles	Overall rate (2.7%) used	HFEA data 1995–99 (see Table xx)
Discontinuation	All fresh cycles	40–50% including pregnancy 20% without pregnancy	FIVNAT 1998[619]
	All fresh cycles, under 30 years All fresh cycles, 38–40 years	17.7% 50.0%	Mardesic et al. 1984[620]

The second cycle-specific model was based on live birth rates by number of previous unsuccessful cycles obtained from the Oxford Fertility Unit (see Table XX) This dataset included estimates for up to three fresh (not frozen) cycles of treatment for two different age group (under 39 years vs 39 years and over; see Section XX). 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 XX, 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 XX.

Table XX Clinical effectiveness data used in the second in vitro fertilisation treatment model for deriving cycle-specific cost per live birth

Outcome	Cycle	Rate (%)	Source
Live birth	Cycle 1 - under 39 years	24.0	Oxford Fertility Unit, 1995–2001 (see Table xx)
	- 39 years and over	10.2	
	Cycle 2 - under 39 years	24.2	
	- 39 years and over	9.7	
	Cycle 3 - under 39 years	21.9	
	- 39 years and over	16.4*	
Miscarriage	Cycle 1 - under 39 years	10.2	Oxford Fertility Unit, 1995–2001
	- 39 years and over	19.4	
	Cycle 2 - under 39 years	9.9	
	- 39 years and over	35.3	
	Cycle 3 - under 39 years	9.8	
	- 39 years and over	16.1	

Outcome	Cycle	Rate (%)	Source
Discontinuation	All fresh cycles	40–50% including pregnancy 20% without pregnancy	FIVNAT 1998[619]
	All fresh cycles, under 30 years All fresh cycles, 38–40 years	17.7% 50.0%	Mardesic et al. 1984[620]

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

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 XX). 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 XX to XX). A detailed description of the clinical effectiveness data used in this model is presented in Table XX.

Table XX Clinical effectiveness data used in the intracytoplasmic sperm injection model for deriving overall cost per live birth

Outcome	Cycle	Rate (%)	Source
Live birth	All fresh cycles	Overall rate (17.6%) used	HFEA data 1995–99 (see Table xx)
	All frozen cycles	Overall rate (11.5%) used	HFEA data 1995–99 (see Table xx)
Ectopic pregnancy	All cycles	Overall rate (0.5%) used	HFEA data 1995–99 (see Table xx)
Miscarriage	All cycles	Overall rate (2.7%) used	HFEA data 1995–99 (see Table xx)
Discontinuation	All fresh cycles	40–50% including pregnancy 20% without pregnancy	FIVNAT 1998[619]
	All fresh cycles, under 30 years All fresh cycles, 38–40 years	17.7% 50.0%	Mardesic et al. 1984[620]
Ovarian hyperstimulation syndrome	All cycles	0.2–1.0%	Various[435-437]

Costs used in the economic models

Treatment costs were estimated using a variety of published and unpublished sources of data. Table A.5 summarises the cost data used in the model. NHS reference costs were used where no published research papers reporting specific costs could be identified. NHS reference costs are second best cost estimates since they show wide variation and are not derived from detailed bottom-up calculation of the true inputs into a service. The best cost data are derived from United Kingdom based economic evaluation studies that report resource use and unit costs as well as a cumulative mean cost estimates. Such data were not available for many of the estimates used in the model.

A range of estimates for the cost of an IVF cycle was obtained from different sources. A web-published review by the voluntary organisation, Fertility Confidential, reported in 2002 that the average charge for IVF treatment in the UK at the 71 fee-paying clinics was £1,737 per treatment cycle, with the lowest reported charge around £1000 and the highest around £2500. The HFEA reported on its website that the cost of an IVF cycle is around £1771 excluding drug costs. The HFEA also reported on its website that the cost of an ICSI cycle is £1936 (without drugs).

A United Kingdom study[959] reported the cost of a stimulated cycle of IVF to be around £4250 and a natural cycle to be around £898. An earlier study reported the cost per couple of IVF to range from £1786 to £5749, and a single cycle to cost £1100.[6] Another United Kingdom study undertaken earlier in the 1990s reported a cost of IVF to be £1005 for stimulated IVF.[572]

In our models we have explored the cost per live birth of IVF at the lower and higher ranges of cost estimates. We have also estimated the cost per live birth with and without the costs of IVF drugs since gonadotrophins can increase the cost per cycle by around £500-1000, depending on the drugs used. We used three costs in our models. The baseline cost was £2771 (£1771, which includes the costs associated with health services use and counselling, plus £1000 for drugs); a lower value of £1771 (the cost without drugs); and a higher value of £3500 (£2500, which was the highest value reported in the Fertility Confidential survey, plus £1000 for drugs). The cost for an ICSI cycle in our model was £2936 (£1936, plus £1000 for drugs).

The costs of miscarriage and ectopic pregnancy after IVF treatment could not be estimated from the published literature, and so we used NHS reference costs relating to miscarriage and upper genital tract (intermediate procedures) for ectopic pregnancy.

A detailed description of the cost data used in this model is presented in Table XX5.

Table B.5 Cost data used in the in vitro fertilisation treatment models

Procedure/event	Baseline estimate	Source of data	Range of estimates found in published studies/other sources	Source of data
IVF without drugs per fresh cycle	£1771	HFEA Internet Site 2002	£1500-2500 £1786 (stimulated IVF) £1786-5749	Upper and lower limits of private clinic costs reported by Fertility Confidential Nargund et al, 2001[959] (UK) Phillips et al, 2000[6] (UK)
IVF per frozen cycle	£666	HFEA Internet Site 2002	£300-760	Private clinic costs published on the Internet 2003
IVF drugs per attempt: Urinary FSH HMG	 Range £320-£490		 Menogon £10.64 per 75 units 30 doses £319 35 doses £372 Menopur £14.75 per 75	 BNF March, 2003[236]

Procedure/event	Baseline estimate	Source of data	Range of estimates found in published studies/other sources	Source of data
Recombinant FSH	Range £790-£1100		units 30 doses £420 35 doses £490 Merional £13.95 per 75 units 30 doses £419 35 doses £488 Gonal –F £26.25 30 doses £788 35 doses £919 Puregon £20.00 30 doses £900 35 doses £1050	
Ovarian hyperstimulation syndrome	£800	Daya et al, 2001{?} (Canada)		
Frozen embryo transfer	£666	HFEA Internet Site 2002		
Cost of ICSI	£1936	HFEA Internet Site 2002	££2664-5278 £3121	Phillips et al 2000 (UK)[6] Granberg 1996[960] (Sweden)
Ectopic pregnancy	£769	NHS reference cost 2001		NHS reference cost for upper genital tract (intermediate procedures; nearest relevant cost)
Miscarriage	£233.64	NHS reference cost 2001		

Sensitivity analysis

Sensitivity analyses were undertaken to explore the effects on the total cost and cost per live birth of changing the following parameters in the models:

- the cost (without drugs) per cycle of IVF/ICSI;
- the number of couples who would choose to discontinue treatment rather than starting a new fresh cycle;
- the rate of OHSS per fresh cycle of IVF/ICSI; and
- the source of clinical effectiveness data (HFEA or Oxford Fertility Unit).

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 XX. The figure shows that the costs per live birth are very similar for ages 24 years to 33 years, after which they rise steeply with increasing age. Detailed tables of costs for three specific ages (24 years, 35 years and 39 years) using the baseline cost of IVF treatment (£2771) are presented in Tables XX, XX and XX, respectively. The tables show that the costs per live birth were £11,917 at 24 years, £12,931 at 35 years, and £20,056 at 39 years. The total costs after three cycles of treatment based on 1000 couples at the start of treatment and using the baseline cost of IVF treatment and a discontinuation rate of 17.7% were £6.2 million in women aged 24 years, £6.3 million in women aged 35 years, and £6.8 million in women aged 39 years. The percentage of couples who achieved a live birth after three cycles of treatment were 52% at 24 years, 49% at 35 years, and 34% at 39 years.

The sensitivity analyses using lower and higher costs for IVF treatment (£1771 and £3500, respectively) resulted in costs per live birth of £8,103 and £14,697 at 24 years, £8,800 and £15,943 at 35 years, and £13,723 and £24,673 at 39 years. The sensitivity analyses using the baseline cost of IVF treatment and the higher discontinuation rate (50%) resulted in total costs after three cycles of IVF treatment based on 1000 couples at the start of treatment of £4.9 million for women aged 24 years, £5.0 million for women aged 35 years, and £5.3 million for women aged 39 years.

Cycle-specific models

Cycle-specific costs per live birth using the baseline cost estimate for IVF treatment and HFEA clinical effectiveness data are shown in Table XX. The cost per live birth in the first cycle of IVF treatment was £15,281. The corresponding costs for the second, third and fourth cycles of IVF treatment were £16,169, £14,793, and £14,336. These costs reflect the varying live birth rates by number of previous unsuccessful IVF cycles (see Table XX). The total cost at the end of three cycles based on 1000 couples at the start of treatment was £5.9 million, with 38% of couples achieving a live birth.

The sensitivity analyses using the lower costs for IVF treatment (£1,771) resulted in costs per live birth of £9,787 for the first cycle, £10,356 for the second cycle, £9,474 for the third cycle, and £9,181 for the fourth cycle. The corresponding costs per live birth using the higher cost for IVF treatment (£3,500) were £19,287, £20,408, £18, 671 and £18,094. The sensitivity analyses using the baseline cost of IVF treatment and the higher discontinuation rate (50%) resulted in a total cost after three cycles of IVF treatment based on 1000 couples at the start of treatment of £4.4 million, with 28% of couples achieving a live birth.

Cycle-specific costs per live birth using the baseline cost estimate for IVF treatment and Oxford Fertility Unit clinical effectiveness data are shown in Tables XX (women aged less than 39 years) and XX (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 XX), and the cost per live birth for the third cycle of treatment is not very reliable because of the small number of cycles on which the live birth rate was based. For women aged less than 39 years, the total cost at the end of three cycles based on 1000 couples at the start of treatment was £5.6 million, with 48% of couples achieving a live birth. For women aged 39 years and over, the total cost at the end of three cycles based on 1000 couples at the start of treatment was £6.4 million, with 29% of couples achieving a live birth. These costs are consistent with those obtained using the HFEA clinical effectiveness data, reflecting the differences in live birth rates according to the woman's age, rather than variations in live birth rates between clinics.

International comparison

The cost-effectiveness ratios (cost per live birth) presented here can be compared with cost-effectiveness ratios reported for other countries using RCT clinical effectiveness evidence. A recent review of this evidence shows far higher cost-effectiveness ratios (cost of IVF per delivery) in the

United States (as might be expected), but similar results in Scandinavian countries.{Granberg et al. 1998} The data reported below are for the year 1994.

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

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 XX. The table show that the cost per live birth was £14,029. The total cost after three cycles of ICSI treatment was £6.5 million, with 48% of couples achieving a live birth. At a lower cost per ICSI treatment (£1936, which excludes drugs) the cost per live birth was £9,056. The sensitivity analysis for exploring the effect of a higher OHSS incidence rate (1.0%) resulted in a cost per live birth of £14,029, which is almost the same as the cost per live birth at the lower rate.

Figure XX Age-specific cost per live birth using three cost estimates for a cycle of in vitro fertilisation treatment

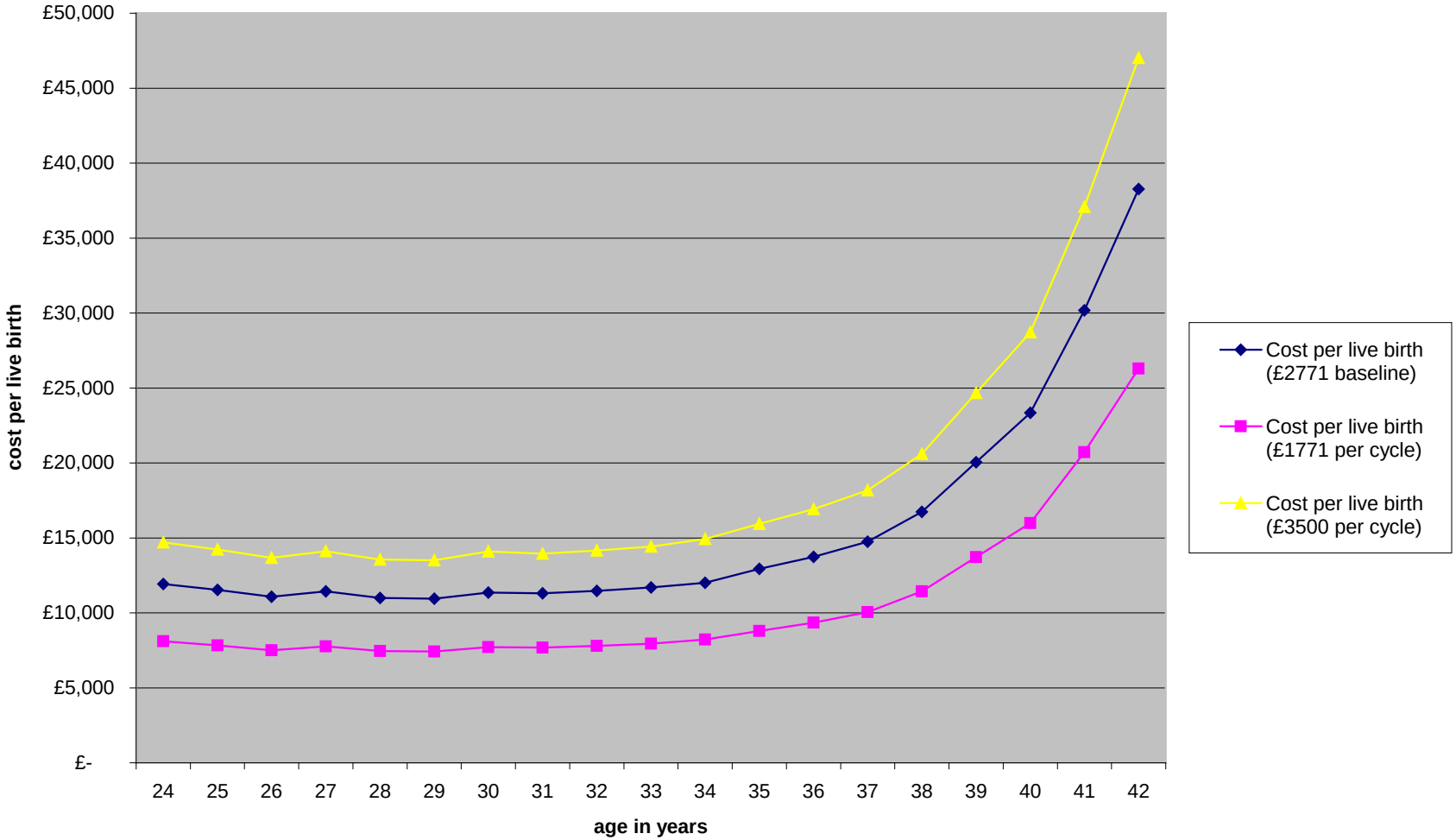


Table XX Cost per live birth for women aged 24 years using baseline cost for a cycle of in vitro fertilisation treatment

Age	**24 years**		**Live birth rate (fresh)**	**20.68%**		
Cost	**£2,771**		**Ectopic preg. rate**	**1.09%**		
Discontinuation Rate	**17.7%**		**Miscarriage rate**	**1.93%**		
OHSS rate	**0.2%**		**Live birth rate (frozen)**	**11.1%**		
	cycle 1	cycle 2	cycle 3	cycle 4	cycle 5	cycle 6
Cumulative No. Fresh Cycles	1000	1607	1976	2200	2336	2414
Cum. frozen ET	499	803	987	1099	1167	1208
Cum. Couples with baby	262	421	518	577	612	634
Difference	262	159	97	59	35	22
Cum. Ectopic	11	21	27	30	33	34
Cum. Miscarriage	29	47	57	64	68	70
Cum. OHSS	2.00	3.21	3.95	4.40	4.67	4.84
Discontinuation	131	79	48	29	18	61
Cum. Discontinuation	138	210	258	287	305	366
Total cost per cycle for 1000 couples	£ 3,108,098	£ 1,897,323	£ 1,152,053	£ 699,525	£ 424,937	£ 258,534
Cum. cost per cycle for 1000 couples	£ 3,108,098	£ 5,005,420	£ 6,157,473	£ 6,856,998	£ 7,281,935	£ 7,540,469
Cost per live birth	£ 11,917					
(all cycles)						

Table XX Cost per live birth for women aged 35 years using baseline cost for a cycle of in vitro fertilisation treatment

Age	**35 years**		**Live birth rate (fresh)**	**18.61%**		
Cost	**£2,771**		**Ectopic preg. rate**	**0.44%**		
Discontinuation Rate	**17.7%**		**Miscarriage rate**	**2.89%**		
OHSS rate	**0.2%**		**Live birth rate (frozen)**	**10.9%**		
	cycle 1	cycle 2	cycle 3	cycle 4	cycle 5	cycle 6
Cumulative No. Fresh Cycles	1000	1624	2013	2256	2407	2502
Cum. frozen ET	513	833	1033	1157	1236	1284
Cum. Couples with baby	242	393	487	546	582	605
Difference	242	151	94	59	36	23
Cum. Ectopic	4	9	11	13	14	14
Cum. Miscarriage	44	71	88	99	105	110
Cum. OHSS	2.00	3.25	4.03	4.51	4.81	5.0
Discontinuation	134	84	52	33	20	72
Cum. Discontinuation	138	218	270	303	323	395
Total cost per cycle for 1000 couples	£ 3,108,713	£ 1,952,383	£ 1,217,917	£ 759,750	£ 474,383	£ 297,152
Cum. Cost per cycle for 1000 couples	£ 3,108,713	£ 5,061,096	£ 6,279,013	£ 7,038,763	£ 7,513,146	£ 7,810,298
Cost per live birth	£ 12,931					
(all cycles)						
			Live birth	17.60%		

Table XX Cost per live birth for women aged 39 years using baseline cost for a cycle of in vitro fertilisation treatment

Age	**39 years**		**Live birth rate (fresh)**	**10.73%**		
Cost	**£2,771**		**Ectopic preg. rate**	**0.34%**		
Discontinuation Rate	**17.7%**		**Miscarriage rate**	**3.03%**		
OHSS rate	**0.2%**		**Live birth rate (frozen)**	**8.9%**		
	cycle 1	cycle 2	cycle 3	cycle 4	cycle 5	cycle 6
Cumulative No. Fresh Cycles	1000	1693	2173	2506	2737	2899
Cum. frozen ET	569	963	1236	1425	1559	1651
Cum. Couples with baby	158	267	343	396	430	455
Difference	158	109	76	53	34	26
Cum. Ectopic	3	7	10	11	13	14
Cum. Miscarriage	48	81	103	119	130	138
Cum. OHSS	2.00	3.39	4.35	5.01	5.47	5.80
Discontinuation	149	103	72	50	35	136
Cum. Discontinuation	138	252	324	374	408	545
Total cost per cycle for 1000 couples	£ 3,126,080	£ 2,194,692	£ 1,521,039	£ 1,054,161	£ 732,231	£ 512,101
Cum. cost per cycle for 1000 couples	£ 3,126,080	£ 5,320,772	£ 6,841,811	£ 7,895,972	£ 8,628,202	£ 9,140,303
Cost per live birth	£ 20,056					
(all cycles)						

Table XX Cost per live birth by cycle of in vitro fertilisation treatment using baseline cost estimate and Human Fertilisation and Embryology Authority clinical effectiveness rates

Human Fertilisation and Embryology Authority		**cycle 1**	**cycle 2**	**cycle 3**	**cycle 4**
No. cycles starting with 1000 couples		1000	673	459	307
No. births		182	116	86	59
No. ectopic pregnancies (0.5%)		5	3	2	2
No. miscarriages (2.7%)		27	18	12	8
No. couples discontinuing treatment		145	99	66	0
Discontinuation rate	17.7%				
Cumulative births		182	298	384	444
Cum. miscarriages		27	45	58	66
Cum. no. discontinuing		145	243	309	309
Cum. no. cycles		1000	1673	2132	2439
Cost per cycle	£ 2,771				
Cost of ectopic pregnancies	£ 769				
Cost of miscarriages	£ 234				
Total cost per cycle for 1000 couples		£ 2,781,153	£ 1,872,311	£ 1,275,875	£ 852,637
Mean cost per live brith		£ 15,281	£ 16,169	£ 14,793	£ 14,336
Cum. cost per cycle for 1000 couples		£ 2,781,153	£ 4,653,465	£ 5,929,340	£ 6,781,977
Cum. % couples with a baby		18%	30%	38%	44%

Table XX Cost per live birth by cycle of in vitro fertilisation treatment for women aged less than 39 years using baseline cost estimate and Oxford Fertility Unit clinical effectiveness rates

Oxford Fertility Unit				
Less than 39 years		**cycle 1**	**cycle 2**	**cycle 3**
No. cycles starting with 1000 couples		1000	626	391
No. births		239	152	86
No. miscarriages		102	62	38
No. of couples discontinuing treatment		135	84	n/a
Discontinuation rate	17.7%			
Cumulative births		239	391	476
Cum. miscarriages		102	164	202
Cum. no. discontinuing		135	219	n/a
Cum. no. cycles		1000	1626	2017
Cost per cycle	£ 2,771			
Cost of miscarriages	£ 234			
Total cost per cycle for 1000 couples		£ 2,794,831	£ 1,750,305	£ 1,091,601
Mean cost per live birth		£ 11,694	£ 11,548	£ 12,758
Cum. cost per cycle for 1000 couples		£ 2,794,831	£ 4,545,136	£ 5,636,737
Cum. % couples with a baby		23.9%	39.1%	47.6%

Table XX Cost per live birth by cycle of in vitro fertilisation treatment for women aged 39 years and over using baseline cost estimate and Oxford Fertility Unit clinical effectiveness rates

Oxford Fertility Unit				
39 years and over		**cycle 1**	**cycle 2**	**cycle 3**
No. cycles starting with 1000 couples		1000	739	549
No. births		102	72	120
No. miscarriages		194	261	88
No. of couples discontinuing treatment		159	0	n/a
Discontinuation rate	18%			
Cumulative births		102	174	294
Cum. miscarriages		194	455	543
Cum. no. discontinuing		159	159	n/a
Cum. no. cycles		1000	1739	2288
Cost per cycle	£ 2,771			
Cost of miscarriages	£ 234			
Total cost per cycle for 1000 couples		£ 2,816,326	£ 2,074,529	£ 1,542,610
Mean cost per llive birth		£ 27,611	£ 28,938	£ 12,825
Cum. cost per cycle for 1000 couples		£ 2,816,326	£ 4,890,855	£ 6,433,465
Cum. % couples with a baby		10.2%	17.4%	29.4%

Table XX Cost per live birth using baseline cost for intracytoplasmic sperm injection

All ages			**Live birth (fresh)**	**17.60%**		
Cost	**£ 2,936**		**Ectopic preg. rate**	**0.50%**		
Discontinuation Rate	**17.7%**		**Miscarriage rate**	**2.70%**		
OHSS rate	**0.2%**		**Live birth rate (frozen)**	**11.5%**		
	cycle 1	cycle 2	cycle 3	cycle 4	cycle 5	cycle 6
Cumulative No. Fresh Cycles	1000	1629	2025	2274	2431	2530
Cum frozen ET	518	843	1048	1177	1260	1311
Cum. Couples with baby	236	384	477	536	572	595
Difference	236	148	93	59	36	23
Cum. Ectopic	5	10	13	15	16	17
Cum. Miscarriage	41	67	83	93	100	104
Cum. OHSS	2.00	3.26	4.05	4.55	4.86	5.06
Discontinuation	135	85	54	34	21	76
Cum. Discontinuation rate	138	220	274	308	329	405
Total cost per cycle for 1000 couples	£ 3,136,015	£ 2,074,920	£ 1,305,436	£ 821,315	£ 517,516	£ 327,892
Cum. cost per cycle for 1000 couples	£ 3,136,015	£ 5,210,935	£ 6,516,371	£ 7,337,686	£ 7,855,202	£ 8,183,093
Cost per live birth	**£ 14,002**					
(all cycles)						

Understanding NICE guidance – information for people with fertility problems, their partners and the public

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.

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**). 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.

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 in 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. Tel: 0845 46 47 if you are in England or Wales. Website: 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**). This version and the NICE guideline are also available from the NHS Response Line – phone 0870 1555 455.

About fertility problems

Fertility problems affect one in seven couples in the UK. Most couples 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 84 out of every 100). 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**.

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 or nurse 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 your 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 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 are a woman who smokes your doctor or nurse should offer you help to stop if you wish. The NHS Pregnancy Smoking Helpline can also provide advice and support – the phone number is 0800 169 9 169.

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 (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 (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 (with 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 or nurse 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 or nurse 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 is not enough research available about 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 or nurse 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 or nurse should recommend that you take a larger dose of 5 mg a day.

German measles (rubella)

Your doctor or nurse should offer you a test to find out whether you 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 will be advised to avoid pregnancy for one month following your rubella vaccination.

Cervical smear tests

Your doctor or nurse 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 GP 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 GP 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. 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 maybe 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 straight away for specialist treatment.

If you have 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 GP or nurse 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. 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 be reach the egg and **fertilise** it. About one in ten 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 can be repeated within 2 to 4 weeks. Only 2 men out of 100 will have a second abnormal test. If you have two abnormal tests you should be offered further appropriate 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 GP or nurse 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) is not reliable and 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 ovary 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. However 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** (producing breast milk) 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 2 years 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. Your 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.

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 outpatient clinics, 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 laparoscope (a very small telescopic instrument). Dye is injected through the neck of the womb. 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 miscroscope (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.

Routine tests on your cervical mucus after sexual intercourse (known as a post-coital test) do not help to predict your chances of getting pregnant, so they are not necessary.

You should not be offered a biopsy (a procedure to take a small sample of tissue) on 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, 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 XX) or in vitro fertilisation (IVF; see page xx).

You should not be offered the following treatments because are not known to improve fertility.

- surgery for varicose veins in the scrotum (known as a varicocele)
- 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 ejaculate and improve your fertility. Alternatively you may be offered **surgical sperm recovery** (see page xx) or **assisted reproduction procedures** (see page xx).

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 XX for more information.
- moderately abnormal – you may be offered IVF. See page XX 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 XX 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 intrauterine insemination (IUI, see page XX).

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 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. However you need to be aware that metformin can have side effects (such as nausea and vomiting).

Alternatively, if you have not ovulated on clomifene citrate or tamoxifen 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 (see page XX**)**. 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)). 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 therapy 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 (FSH and LH), 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, **galactorrhoea** and fertility problems) you may be offered treatment with drugs such as bromocriptine. Your doctors should take into account considerations about the safety of bromocriptine (and similar drugs known as dopamine agonists) for women who are intending to get pregnant, when prescribing them.

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 intra-uterine insemination (IUI, see page xx).
- 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 (hystercoscope) 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:
- intra-uterine insemination using **fallopian sperm perfusion** (IUI-FSP) – see page XX.
- in vitro fertilisation (IVF) - see page XX**.**

Other methods of assisted reproduction called g**amete 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 Reproduction 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 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 both instances the women should not be offered drugs for ovulation induction. 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 cases.

If you have unexplained fertility problems, you should be offered IUI with fallopian sperm perfusion. Fallopian sperm perfusion is 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, it is has been proved that using drugs for ovulation induction with IUI will increase your chances of getting pregnant. It is not clear how effective IUI is without ovulation induction.

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.

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:

- 'switching off' the woman's natural cycle of egg production in the ovaries (**downregulation**)
- stimulating the ovaries to produce more than one egg (**ovulation induction**)
- collecting the mature eggs from a woman's ovaries
- mixing them with a man's sperm in the laboratory
- incubating the fertilised eggs for a few days (fertilised eggs that have started to develop are called **embryos**)
- 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 ever 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 about 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 (BMI between 19 and 30).

If you drink more than one unit of alcohol a day (see page X) 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. It 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 (a 'keyhole' operation done with a very small telescopic instrument) 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 and includes collecting eggs and sperm, and the transfer of one or two resulting embryos back into the womb. A 'stimulated' cycle is one that uses an embryo produced from an egg collected in the same cycle. It does not include embryos that have previously been frozen (see page XX) for more information on freezing embryos). If you have two or more frozen embryo's 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 **downregulation**) 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

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.

Another type of drug for downregulation, 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 downregulation with gonadotrophin-releasing hormone agonists for IVF, you should also be offered either progesterone or human chorionic gonadotrophin (HCG, see page xx) to help any resulting embryo attach to the womb. This will improve your chances of a pregnancy.

Ovulation induction

Using fertility drugs to stimulate your ovaries helps to produce more than one egg at a time. You should be offered IVF with ovarian 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 xx). 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 downregulation 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 on 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 or 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 (see page xx). HCG increases the risk of developing OHSS, and so it should 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

Your eggs should be collected through a needle, guided through your vagina by ultrasound. 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

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. 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 XX).

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 XX) and donor insemination (see page XX).

Fertilisation of the eggs

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 XX and XX).

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

With IVF, the risk of getting pregnant with more than one baby increases with the number 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 chances pregnancy.

If you have taken gonadotrophins for downregulation, 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 through if the lining 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 back 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. In this 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, it makes no difference to the chances of a successful pregnancy once this has happened.

You should be offered ICSI if:

- you have few sperm in your semen or your sperm are of poor quality, or
- you have no sperm in your semen (this is 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 and so were unsuccessful.

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. 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.

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, you do not need routine 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 have azoospermia that 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 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 (known as azoospermia), or
- he has a genetic or infectious disease which could be passed on to any children, or
- his blood group is not compatible with the woman's.

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 potential 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) 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 other forms of treatment.

Egg donation

Some women cannot produce eggs, usually because their ovaries are not functioning or have been removed. Some women have a genetic disorder that they could pass on to a child.

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, if 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 genetic 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.

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 women 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 cycle of IVF involving downregulation, ovulation induction and egg recovery. 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. If you ovulate regularly your chances of a successful birth are the same whether your cycle is natural or artificially controlled.

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 health care 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. 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)
- 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 4647; website www.nhsdirect.nhs.uk).

Glossary

Assisted hatching A technique used in **IVF** 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 back into the womb.

Assisted reproduction The name for treatments enable people to conceive by means other than sexual intercourse. Assisted reproduction techniques include **intra-uterine insemination**, **in vitro fertilisation**, **intracytoplasmic sperm injection** and **donor insemination**.

Azoospermia When a man has no sperm in his semen.

Biopsy A procedure to take a small sample of tissue.

Chlamydia trachomatis A sexually transmitted infection which can damage a man 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.

Clomifene citrate A fertility drug which stimulates a woman's ovaries to produce one or more **follicles**.

Cryopreservation The freezing and storage of **eggs**, **sperm** and/or **embryos** that may be thawed for use in future **in vitro fertilisation** treatment cycles.

Donor insemination The placing of donor **sperm** into a woman's vagina.

Downregulation Drug treatment used as part of **ovulation induction** to prevent the **ovaries** producing **eggs**.

Egg collection A procedure by which a woman's **eggs** are collected from her **ovaries**, usually using a needle guided by **ultrasound**. Also known as egg retrieval.

Egg (or oocyte) donation The process by which a fertile woman donates her **eggs** for use in the treatment of other women or for use in research.

Egg sharing When a woman having IVF donates half of her **eggs** for use by another women or a number of women.

Embryo A fertilised **egg**.

Embryo transfer Transfer of one or two **embryos** into the womb as part of **IVF**.

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 Technique where the sperm is mixed with a larger volume of fluid than standard IUI.

Fallopian tube(s) The pair of tubes leading from a woman's **ovaries** to the womb. Each month the ovary releases an egg into the fallopian tube, and the **egg** travels through the tube to the womb. The fallopian tube is where the egg is **fertilised** by a **sperm** in the natural conception process.

Fertilisation When a **sperm** penetrates an **egg** and forms an embryo. Natural fertilisation takes place in a woman's fallopian tubes, but fertilisation can also be done in the laboratory for **IVF**.

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 **egg** develops

Follicle stimulating hormone (FSH) A hormone produced by the pituitary gland which stimulated the **ovary** to produce **follicles**. It can be used as part of **ovulation induction** therapy.

Galactorrhoea production of breast milk

Gamete A male **sperm** or female **egg**.

Gamete intrafallopian transfer (GIFT) A technique by which a woman's **eggs** are collected, mixed with **sperm** and immediately replaced in one or other of her **fallopian tubes**, so that they can fertilise there.

Gonadotrophin releasing hormone A hormone which stimulates the pituitary gland to produce **gonadotrophins**.

Gonadotrophin releasing hormone agonist A drug that temporarily switches off the release of **gonadotrophins** thus preventing ovulation.

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: **Follicle stimulating hormone** (FSH) and **luteinising hormone** (LH) are two kinds of gonadotrophin hormones made by the pituitary gland. In women they stimulate the **ovaries** to produce eggs. They can be given during **ovulation induction**. Their side effects are hot flushes, multiple pregnancy and OHSS. 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. Used to mature eggs in IVF downregulated cycles.

Human menopausal gonadotrophin (HMG) One type of treatment produced from the urine of menopausal women (who have high levels of FSH and LH gonadotrophinhormones).

Hyperprolactinaemia A disorder of the pituitary gland which can cause irregular periods, galactorrhea and fertility problems.

Hysteroscopy A procedure to examine the womb with a small microscope called a hysteroscope.

Hysterosalpingogram (HSG) An x-ray of the **fallopian tubes**, using fluid injected through the neck of the womb, to check for any obstructions.

Intracytoplasmic sperm injection (ICSI) A variation of **IVF** in which a single **sperm** is injected into an **egg**.

Implantation The process by which an **embryo** attaches to the lining of the womb.

Insemination A technique to place **sperm** into a woman's vagina or womb

Intra-uterine insemination (IUI) A technique to place **sperm** into a woman's womb through the cervix.

In vitro fertilisation (IVF) A technique by which **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. If one of them attaches successfully it results in a pregnancy.

Laparoscopy A surgical procedure 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.

Laparoscopic ovarian drilling Uses a laparoscope to operate on a woman's ovaries, and apply heat (a process known as diathermy) to destroy extra follicles in the ovaries.

Luteinising hormone One of the **gonadotrophin** hormones made by the pituitary gland. It can be used as part of **ovulation induction** therapy.

Motile sperm **Sperm** that are capable of moving.

Multiple pregnancy When a woman is pregnant with more than one baby at a time

Non-motile sperm **Sperm** that do not move.

Oestrogen A female sex hormone produced by developing eggs in the **ovaries**.

Ovarian hyperstimulation syndrome (OHSS) A complication following stimulation of the **ovaries** with **gonadotrophin** drugs.

Ovarian reserve How many eggs a woman has left. Predicts how close a woman is to the menopause.

Oligozoospermia Low **sperm** count.

Oocyte The **egg** a woman produces as part of a normal monthly cycle.

Oocyte (or egg) donation The process by which a fertile woman donates her **eggs** for use in the treatment of other women or for research.

Ovaries A pair of organs in women which produce **follicles** and **eggs** (**oocytes**).

Ovulation The process by which the **ovaries** produce **eggs**. 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 **ovulation**.

Ovum Another word for the **egg** produced by a woman's **ovaries**.

Pituitary gland A gland in the brain which produces hormones.

Polycystic ovary syndrome (PCOS) A condition where the **ovaries** often produce more small **follicles** than normal but the woman does not ovulate.

Progesterone A hormone produced by the ovary after the egg is released. Used in IVF to help embryos attach to the womb.

Pulsatile gonadotrophin-releasing hormone A drug given to a woman through a pump every 90 minutes to mimic the natural delivery of **gonadotrophins**.

Sperm The **gamete** produced by men, usually through ejaculation, which fertilises a woman's **eggs**. Men usually have millions of sperm in their **semen**.

Sperm recovery Surgical procedure to obtain sperm 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 **ovaries** produce more **eggs** than usual in a monthly cycle.

Stimulation Drug treatment used as part of **ovulation induction** for **IVF** and given to stimulate a woman's **ovaries** to produce **eggs**.

Ultrasound High frequency sound waves used to provide images of the body, tissues and internal organs.

Ultrasound-guided aspiration A procedure to collect **eggs** 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 **egg** production.

Uterus The womb

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

Appendix L Proposed changes to original recommendations

Recommendation	Replaced with	Reason for change/deletion
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 over 80% of couples in the general population will conceive within 1 year if: • the woman is aged under 40 years **and** • they do not use contraception and have regular sexual intercourse. Of those who do not conceive in the first year, about half will do so in the second year (cumulative pregnancy rate over 90%). **[2004, amended 2013]**	Statement updated to reflect current conception rates. Minor wording changes to simplify statement.
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]	Inform people who are concerned about their fertility that female fertility and (to a lesser extent) male fertility decline with age. **[new 2013]**	Newer data available showing that male fertility also declines with age. Statement simplified as it repeated information given in other recommendations.
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] [2004]	People who are concerned about their fertility should be informed that vaginal sexual intercourse every 2 to 3 days optimises the chance of pregnancy. **[2004, amended 2013]**	Sentence on timing of intercourse was removed as GDG and one stakeholder stated it was factually wrong.
Men should be informed that alcohol consumption within the Department of Health's recommendations of three to four	Men should be informed that alcohol consumption within the Department of Health's recommendations of 3 to 4 units	Amended inaccuracy in interpretation of evidence.

Recommendation	Replaced with	Reason for change/deletion
units per day for men is unlikely to affect their fertility.	per day for men is unlikely to affect their semen quality. **[2004, amended 2013]**	
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]	Women intending to become pregnant should be informed that dietary supplementation with folic acid before conception and up to 12 weeks' gestation reduces the risk of having a baby with neural tube defects. The recommended dose is 0.4 mg per day. For women who have previously had an infant with a neural tube defect or who are receiving anti-epileptic medication or who have diabetes (see Diabetes in pregnancy, NICE clinical guideline 63), a higher dose of 5 mg per day is recommended. **[2004, amended 2013]**	List of conditions where higher dose of folic acid is recommended has been updated to include diabetes.
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.	Women who are concerned about their fertility should be offered testing for their rubella status so that those who are susceptible to rubella can be offered vaccination. Women who are susceptible to rubella should be offered vaccination and advised not to become pregnant for at least 1 month following vaccination. **[2004, amended 2013]**	Amended for terminology.
Infertility should be defined as failure to conceive after regular unprotected sexual intercourse for 2 years in the absence of known reproductive pathology. [D]	Healthcare professionals should define infertility in practice as the period of time people have been trying to conceive without success after which formal investigation is justified and possible treatment implemented. **[new 2013]**	The GDG stated infertility was relative. People who do not conceive after a given period of time still have a chance of conceiving with continued attempts (they are not 'infertile' but 'subfertile'. Thus, the more practical approach is to define when people should be referred for assessment, investigation and possible treatment.
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]	A woman of reproductive age who has not conceived after 1 year of unprotected vaginal sexual intercourse, in the absence of any known cause of infertility, should be offered further clinical assessment and	Amended for clarity and accuracy

Recommendation	Replaced with	Reason for change/deletion
	investigation along with her partner. **[new 2013]**.	
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]	Offer an earlier referral for specialist consultation to discuss the options for attempting conception, further assessment and appropriate treatment where: • the woman is aged 36 years or over • there is a known clinical cause of infertility or a history of predisposing factors for infertility. **[new 2013]**	Amended for clarity and to cover all groups who may need to access fertility services.
Counselling should be provided by someone who is not directly involved in the management of the couple's fertility problems. [GPP]	Counselling should be provided by someone who is not directly involved in the management of the individual's and/or couple's fertility problems. **[2004, amended 2013]**	Minor wording changes for stylistic reasons.
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]	People who experience fertility problems should be treated by a specialist team because this is likely to improve the effectiveness and efficiency of treatment and is known to improve people's satisfaction with treatment. **[2004, amended 2013]**	Minor wording changes to make statement more accurate.
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	The results of semen analysis conducted as part of an initial assessment should be compared with the following World Health Organization reference values[1]: • semen volume: 1.5 ml or more • pH: 7.2 or more • sperm concentration: 15 million spermatozoa per ml or more • total sperm number: 39 million spermatozoa per ejaculate or more • total motility (percentage of progressive motility and non-progressive motility): 40% or more motile or 32% or more	Amended to reflect current international standards

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

Recommendation	Replaced with	Reason for change/deletion
• 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]	with progressive motility • vitality: 58% or more live spermatozoa • sperm morphology (percentage of normal forms): 4% or more. **[2004, amended 2013]**	
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. [B]	Women who are undergoing investigations for infertility should be offered a blood test to measure serum progesterone in the mid-luteal phase of their cycle (day 21 of a 28-day cycle) to confirm ovulation even if they have regular menstrual cycles. **[2004, amended 2013]**	Amended for clarity
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]	Use one of the following measures to predict the likely ovarian response to gonadotrophin stimulation in IVF: • total antral follicle count of less than or equal to 4 for a low response[2] and greater than 16 for a high response[3] • anti-Müllerian hormone of less than or equal to 5.4 pmol/l for a low response[4] and greater than or equal to 25.0 pmol/l for a high response[5] • follicle-stimulating hormone greater than 8.9 IU/l for a low	New evidence on ovarian reserve testing was reviewed and the recommendation has been updated accordingly.

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

Recommendation	Replaced with	Reason for change/deletion
	response and less than 4 IU/l for a high response[6]. **[new 2013]**	
Women should be informed that the value of assessing ovarian reserve using inhibin B is uncertain and is therefore not recommended. [C]	Do not use any of the following tests individually to predict any outcome of fertility treatment: • ovarian volume • ovarian blood flow • inhibin B • oestradiol (E2). **[new 2013]**	New evidence on ovarian reserve was reviewed and and the recommendation has been updated accordingly.
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]	For women who are taking clomifene citrate, offer ultrasound monitoring during at least the first cycle of treatment to ensure that they are taking a dose that minimises the risk of multiple pregnancy. **[2013]**	Amended for terminology
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]	Offer women with WHO Group II anovulatory infertility one of the following treatments, taking into account potential adverse effects, ease and mode of use, the woman's BMI, and monitoring needed: • clomifene citrate **or** • metformin[7] **or** • a combination of the above. **[new 2013]**	New evidence reviewed on WHO group II and recommendation updated accordingly.
Women should be informed of the risk of multiple pregnancies associated with both clomifene citrate and tamoxifen. [B]	No recommendation	No recommendation applicable
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]	Inform women with unexplained infertility that clomifene citrate as a stand-alone treatment does not increase the chances of a pregnancy or a live birth. **[new 2013]**	New evidence shows that this treatment is no more effective than no treatment for women diagnosed with unexplained infertility. Therefore, the recommendation has been amended.
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	Offer women with WHO Group II anovulatory infertility one of the following treatments, taking into account potential adverse effects, ease and mode of use, the woman's BMI, and	New evidence shows that this treatment is no more effective than no treatment for women diagnosed with unexplained infertility. Therefore, the

[6] Long protocol of down-regulation: low response defined as <4 oocytes or cancellation; high response defined as >20 oocytes.
[7] At the time of publication (February 2013), metformin did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. The patient should provide informed consent, which should be documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

Recommendation	Replaced with	Reason for change/deletion
clomifene citrate because this increases ovulation and pregnancy rates. [A]	monitoring needed: • clomifene citrate **or** • metformin[8] **or** • a combination of the above. **[new 2013]**	recommendation has been amended.
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]	Offer women with WHO Group II anovulatory infertility one of the following treatments, taking into account potential adverse effects, ease and mode of use, the woman's BMI, and monitoring needed: • clomifene citrate **or** • metformin[9] **or** • a combination of the above. **[new 2013]**	New evidence showed that a range of treatments were effective in this group and the recommendation was changed accordingly.
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]	For women with WHO Group II ovulation disorders who are known to be resistant to clomifene citrate, consider one of the following second-line treatments, depending on clinical circumstances and the woman's preference: • laparoscopic ovarian drilling **or** • combined treatment with clomifene citrate and metformin[10] if not already offered as first-line treatment **or** • gonadotrophins. **[new 2013]**	New evidence showed that a range of treatments were effective in this group and the recommendation was changed accordingly..
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]	For women who are taking clomifene citrate, do not continue treatment for longer than 6 months. **[2013]**	Statement simplified for clarity.
Human menopausal	Use either urinary or	Statement shortened for

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

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

Recommendation	Replaced with	Reason for change/deletion
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]	recombinant gonadotrophins for ovarian stimulation as part of IVF treatment. **[new 2013]**	style and clarity.
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.	No recommendation	No recommendation applicable
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]	No recommendation	No recommendation new evidence reviewed on down-regulation within IVF.
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]	No new recommendation.	No longer relevant to the chapter.
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	Offer women with WHO Group I ovulation disorders pulsatile administration of gonadotrophin-releasing hormone or gonadotrophins with luteinising hormone activity to induce ovulation. **[2013]**	Amended for terminology

Recommendation	Replaced with	Reason for change/deletion
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]	For women with WHO Group II ovulation disorders who are known to be resistant to clomifene citrate, consider one of the following second-line treatments, depending on clinical circumstances and the woman's preference: • laparoscopic ovarian drilling **or** • combined treatment with clomifene citrate and metformin[11] if not already offered as first-line treatment **or** • gonadotrophins. **[new 2013]**	Updated in new review.
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]	Limit the use of ovulation induction or ovarian stimulation agents to the lowest effective dose and duration of use. **[new 2012]**	Statement revised for style and clarity.
Medical treatment of minimal and mild endometriosis does not enhance fertility in subfertile women and should not be offered. [A]	Medical treatment of minimal and mild endometriosis diagnosed as the cause of infertility in women does not enhance fertility and should not be offered. **[2004, amended 2013]**	Amended for terminology
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]	For people with unexplained infertility, mild endometriosis or 'mild male factor infertility', who are having regular unprotected sexual intercourse: • do not routinely offer intrauterine insemination, either with or without ovarian stimulation (exceptional circumstances include, for example, when people have social,	New evidence has shown that IUI with or without stimulation is no more effective than no treatment, therefore it is no longer recommended.

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

Recommendation	Replaced with	Reason for change/deletion
	cultural or religious objections to IVF) • advise them to try to conceive for a total of 2 years (this can include up to 1 year before their fertility investigations) before IVF will be considered. **[new 2013]**	
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]	For people with unexplained infertility, mild endometriosis or 'mild male factor infertility', who are having regular unprotected sexual intercourse: • do not routinely offer intrauterine insemination, either with or without ovarian stimulation (exceptional circumstances include, for example, when people have social, cultural or religious objections to IVF) • advise them to try to conceive for a total of 2 years (this can include up to 1 year before their fertility investigations) before IVF will be considered. **[new 2013]**	New evidence has shown that IUI with or without stimulation is no more effective than no treatment, therefore it is no longer recommended.
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]	For people with unexplained infertility, mild endometriosis or 'mild male factor infertility', who are having regular unprotected sexual intercourse: • do not routinely offer intrauterine insemination, either with or without ovarian stimulation (exceptional circumstances include, for example, when people have social, cultural or religious objections to IVF) • advise them to try to conceive for a total of 2 years (this can include up to 1 year before their fertility investigations) before IVF will be considered. **[new 2013]**	New evidence has shown that IUI with or without stimulation is no more effective than no treatment, therefore it is no longer recommended, and related recommendations have also been removed.

Recommendation	Replaced with	Reason for change/deletion
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]	For people with unexplained infertility, mild endometriosis or 'mild male factor infertility', who are having regular unprotected sexual intercourse: • do not routinely offer intrauterine insemination, either with or without ovarian stimulation (exceptional circumstances include, for example, when people have social, cultural or religious objections to IVF) • advise them to try to conceive for a total of 2 years (this can include up to 1 year before their fertility investigations) before IVF will be considered. **[new 2013]**	New evidence has shown that IUI with or without stimulation is no more effective than no treatment, therefore it is no longer recommended, and related recommendations have also been removed.
Where intrauterine insemination is undertaken, single rather than double insemination should be offered. [A]	For people with unexplained infertility, mild endometriosis or 'mild male factor infertility', who are having regular unprotected sexual intercourse: • do not routinely offer intrauterine insemination, either with or without ovarian stimulation (exceptional circumstances include, for example, when people have social, cultural or religious objections to IVF) • advise them to try to conceive for a total of 2 years (this can include up to 1 year before their fertility investigations) before IVF will be considered. **[new 2013]**	New evidence has shown that IUI with or without stimulation is no more effective than no treatment, therefore it is no longer recommended, and related recommendations have also been removed.
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]	For people with unexplained infertility, mild endometriosis or 'mild male factor infertility', who are having regular unprotected sexual intercourse: • do not routinely offer intrauterine insemination, either with or without ovarian stimulation (exceptional	New evidence has shown that IUI with or without stimulation is no more effective than no treatment, therefore it is no longer recommended, and related recommendations have also been removed.

Recommendation	Replaced with	Reason for change/deletion
	circumstances include, for example, when people have social, cultural or religious objections to IVF) • advise them to try to conceive for a total of 2 years (this can include up to 1 year before their fertility investigations) before IVF will be considered. **[new 2013]**	
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.	Inform women that the chance of a live birth following IVF treatment falls with rising female age (see figure 6.1). **[2013]**	Statement simplified for clarity.
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]	No more than 2 embryos should be transferred during any one cycle of IVF treatment. **[2013]**	Statement updated for clarity.
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]	Inform people that the overall chance of a live birth following IVF treatment falls as the number of unsuccessful cycles increases. **[new 2013]**	Amended for terminology.

Recommendation	Replaced with	Reason for change/deletion
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]	People should be informed that IVF treatment is more effective in women who have previously been pregnant and/or had a live birth. **[2004, amended 2013]**	Amended for terminology.
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]	People should be informed that the consumption of more than 1 unit of alcohol per day reduces the effectiveness of assisted reproduction procedures, including IVF. **[2004, amended 2013]**	Amended for terminology.
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]	People should be informed that maternal and paternal smoking can adversely affect the success rates of assisted reproduction procedures, including IVF treatment. **[2004, amended 2013]**	Amended for terminology.
Couples should be informed that caffeine consumption has adverse effects on the success rates of assisted reproduction procedures, including in vitro fertilisation treatment. [C]	People should be informed that maternal caffeine consumption has adverse effects on the success rates of assisted reproduction procedures, including IVF treatment. **[2004, amended 2013]**	Amended for terminology.
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 offeredup to three stimulated cycles of in vitro fertilisation treatment. [GPP]	In women aged under 40 years who have not conceived after 2 years of regular unprotected intercourse or 12 cycles of artificial insemination (where 6 or more are by intrauterine insemination), offer 3 full cycles of IVF, with or without ICSI. If the woman reaches the age of 40 during treatment, complete the current full cycle but do not offer further full cycles. **[new 2013]**	Updated to reflect new evidence.
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]	Inform people that normally a full cycle of IVF treatment, with or without intracytoplasmic sperm injection (ICSI), should comprise 1 episode of ovarian stimulation and the transfer of any resultant fresh and frozen embryo(s). **[new 2013]**	Updated to reflect new evidence.

Recommendation	Replaced with	Reason for change/deletion
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]	People undergoing IVF treatment should be offered testing for HIV, hepatitis B and hepatitis C. **[2004, amended 2013]**	Amended for terminology.
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]	No relevant recommendation	No recommendation applicable
The use of gonadotrophin-releasing hormone antagonists is associated with reduced pregnancy rates and is therefore not recommended outside a research context. [A]	Use either gonadotrophin-releasing hormone agonist down-regulation or gonadotrophin-releasing hormone antagonists as part of gonadotrophin-stimulated IVF treatment cycles. **[new 2013]**	New evidence shows antagonists are as effective. Therefore, this recommendation has been reversed and combined with agonist statement.
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]	Do not offer women 'natural cycle' IVF treatment. **[2013]**	Statement revised for style and clarity.
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]	Advise women who have regular ovulatory cycles that the likelihood of a live birth after replacement of frozen–thawed embryos is similar for embryos replaced during natural cycles and hormone-supplemented cycles. **[2013]**	New recommendation for ovarian stimulation in IVF replaces previous recommendation
The use of adjuvant growth hormone with gonadotrophins during in vitro fertilisation cycles does not improve pregnancy rates and is therefore not recommended. [A]	Do not use growth hormone or dehydroepiandrosterone (DHEA) as adjuvant treatment in IVF protocols. **[new 2013]**	Wording changes to make it into an active statement.
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]	Where a top-quality blastocyst is available, use single embryo transfer. **[new 2013]**	New recommendation for embryo transfer in IVF replaces previous recommendation. Timing of transfer only relevant for single embryo transfer in update.

Recommendation	Replaced with	Reason for change/deletion
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]	Offer ultrasound monitoring of ovarian response as an integral part of the IVF treatment cycle. **[2013]**	Wording changed and shortened for style.
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]	No relevant recommendation	No recommendation applicable
Women who are undergoing in vitro fertilisation treatment using gonadotrophin-releasing hormone agonists for pituitary down regulation should be informed that luteal support using human chorionic gonadotrophin or progesterone improves pregnancy rates.[A]	Offer women progesterone for luteal phase support after IVF treatment. **[new 2013]**	New evidence shows that only progesterone is useful as a luteal phase support, so the recommendation has been changed.
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]	Use either gonadotrophin-releasing hormone agonist down-regulation or gonadotrophin-releasing hormone antagonists as part of gonadotrophin-stimulated IVF treatment cycles. **[new 2013]**	New evidence shows no difference between urinary and recombinant.
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	The use of donor insemination is considered effective in managing fertility problems associated with the following conditions: • obstructive azoospermia • non-obstructive azoospermia • severe deficits in semen quality in couples who do not wish to undergo ICSI. **[2004, amended 2013]** Donor insemination should be	Statement split and updated for clarity.

Recommendation	Replaced with	Reason for change/deletion
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]	considered in conditions such as: • where there is a high risk of transmitting a genetic disorder to the offspring • where there is a high risk of transmitting infectious disease to the offspring or woman from the man • severe rhesus isoimmunisation. **[2004, amended 2013]**	
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]	Units undertaking semen donor recruitment and the cryopreservation of donor spermatozoa for treatment purposes should follow the 'UK guidelines for the medical and laboratory screening of sperm, egg and embryo donors' (2008)[12] describing the selection and screening of donors. **[2004, amended 2013]**	The GDG highlighted that reference guideline in the original recommendaiton had been updated since 2004 guidance was issued.
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. (Recommendation 1.13.7.1 in 2004 guideline)	No recommendation	Original Recommendation conflicted with recommendations made earlier in the guideline, therefore it was removed.
Couples should be offered other treatment options after six unsuccessful cycles of donor insemination. (Recommendation 1.13.8.1 in 2004 guideline)	No recommendation	Original Recommendation conflicted with recommendations made earlier in the guideline, therefore it was removed
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	Before donation is undertaken, oocyte donors should be screened for both infectious and genetic diseases in accordance with the 'UK guidelines for the medical and laboratory screening of sperm, egg and	The GDG highlighted that reference guideline in the original recommendaiton had been updated since 2004 guidance was issued.

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

Recommendation	Replaced with	Reason for change/deletion
Authority. [D]	embryo donors' (2008)[13]. **[2004, amended 2013]**	
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]	When considering and using cryopreservation for people before starting chemotherapy or radiotherapy that is likely to affect their fertility, follow recommendations in 'The effects of cancer treatment on reproductive functions' (2007)[14]. **[2013]**	Updated working party guideline was included in recommendation
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]	Offer sperm cryopreservation to men and adolescent boys who are preparing for medical treatment for cancer that is likely to make them infertile. **[new 2013]**	Wording changed to make active statement.
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]	No recommendation	The GDG stated this was outside the scope of the guideline.
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]	When using cryopreservation to preserve fertility in people diagnosed with cancer, use sperm, embryos or oocyctes. **[new 2013]**	New evidence was reviewed which showed that the success of cryopreservation has improved and can be recommended for routine use.
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]	At diagnosis, the impact of the cancer and its treatment on future fertility should be discussed between the person diagnosed with cancer and their cancer team. **[new 2013]**	The GDG stated that in counselling was undertaken within a treatment unit and it was impractical to recommend that it was not.
Where cryostorage of gametes and/or embryos is to be	Offer oocyte or embryo cryopreservation as appropriate	Statement updated for clarity.

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

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

Recommendation	Replaced with	Reason for change/deletion
undertaken because of medical treatment that is likely to make people infertile, this should occur before such treatment begins. [GPP]	to women of reproductive age (including adolescent girls) who are preparing for medical treatment for cancer that is likely to make them infertile if: • they are well enough to undergo ovarian stimulation and egg collection **and** • this will not worsen their condition **and** • enough time is available before the start of their cancer treatment. **[new 2013]**	
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]	Give people who are considering ovulation induction or ovarian stimulation up-to-date information about the long-term health outcomes of these treatments. **[new 2013].**	Wording change to make active statement.

Appendix M Cost-effective treatment of IVF analyses

[See separate appendix document]

Appendix N Sensitivity analysis of cost-effective treatment of IVF analyses

[See separate appendix document]

Appendix O UK NEQAS embryo morphology scheme

Reproductive Science

Embryo Morphology Scheme

Cleavage stage embryo grading system

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

Blastocyst grading system

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

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