

Fertility: assessment and treatment for people with fertility problems

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

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Evidence Tables

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Study type codes

CA	Case series
CCS	Case-control study
CH	Cohort study
CHR	Chart review
CR	Case report, case review
CS	Cross-sectional study
DBC	Double-blind crossover trial
DBRCT	Double blind randomised controlled trial
DBRP	Double blind randomised placebo controlled trial
DE	Descriptive
MA	Meta-analysis
NCC	Nested case-control
OB	Observational study
QA	Questionnaire
QR	Quasi-randomised study
QS	Questionnaire survey
RCR	Retrospective chart review
RCT	Randomised controlled trial
RRR	Retrospective record review
RV	Review
SR	Systematic review
SV	Surveillance; survey
TES	Test evaluation survey

Abbreviations

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

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

3.2 Timing of sexual intercourse

Study	Population	Outcomes	Results	Comments	Study type	EL
Wilcox et al. 1995 ³¹	221 women planning pregnancy (625 menstrual cycles)	Single day conception rate from intercourse on day in relation to ovulation	Increased conception rate: days prior to ovulation: 5: CR 0.08 (CR ± SE 0.10 to 0.08) 4: CR 0.17 (CR ± SE 0.16 to 0.06) 3: CR 0.08 (CR ± SE 0.14 to 0.08) 2: CR 0.36 (CR ± SE 0.27 to 0.07) 1: CR 0.34 (CR ± SE 0.31 to 0.06) 0: CR 0.36 (CR ± SE 0.33 to 0.09)	CR = conception rate; SE = standard error	OB	3

3.2 Assessing ovulation to time intercourse: basal body temperature (BBT) charts

Study	Population	Outcomes	Results	Comments	Study type	EL
Bauman et al. 1981 ³⁴	BBT charts: 77 cycles of normal luteal phase length	% of correct identification of time of ovulation	17/77 (22.1%)	Correct identification defined as agreement by all 6 physicians or 5 out of 6 of the physicians; Ovulation confirmed by LH surge and progesterone rise	TES RCR (6 physicians)	2b
Martinez et al. 1992 ³⁵	172 BBT charts from 54 normal cycles (spontaneous and clomifene citrate-stimulated)	% of correct identification of ovulation	True positive rate 90% False negative rate 2%	Ovulation confirmed by daily TVU	TES RCR (3 physicians)	2b
Corson et al. 1986 ³⁶	78 cycles from 45 women (6 CC stimulated)	% of correct identification of ovulation; BBT corresponding with LH	LH test kit : 77/78 (98.7%) BBT: 36/64 (56%)	Ovulation confirmed with serum LH	TES RCR	2b
Templeton et al. 1982 ³⁷	198 cycles in women receiving AID	% of correct identification of ovulation % of BBT nadir coinciding with LH surge	BBT: 65% BBT nadir coinciding with LH surge: 45%	Ovulation confirmed with LH assay; other outcomes included	TES RCR	2b
Guida et al. 1999 ³⁸	140 cycles from 40 women in family planning programme	% of correlation between TVU and urinary LH, BBT in detecting ovulation	Urinary LH 100% BBT 30.4%	Ovulation confirmed with TVU; other outcomes included	TES RCR	2b
Guermandi et al. 2001 ³⁹	101 infertile couples	Sensitivity, specificity and accuracy of urinary LH; BBT	LH: sensitivity 1.0; specificity 0.25; accuracy 0.97 BBT: sensitivity 0.77; specificity 0.33; accuracy 0.74	Ovulation confirmed with TVU	TES RCR	2b
Kopitzke et al. 1991 ⁴⁰	26 patients from infertility clinics	Patients' rating of stress for BBT, LH test, timed intercourse	BBT: 4 out of 10 LH test: 4.5 out of 10 Timed intercourse: 6 out of 10	Other outcomes included: emotional scale from 1 to 10 (1 = not difficult; 10 = extremely difficult)	SV	3

3.3 Alcohol and female fertility

Study	Population	Outcomes	Results	Comments	Study type	EL
Zaadstra et al. 1994 ⁴¹	489 healthy women receiving AID Never drinkers (n = 159) Irregular drinkers (< 10 glasses/week, n = 86) Regular light drinkers (< 10 glasses/week, n = 206) Regular drinkers (> 10 glasses /week, n = 38)	Fecundability hazard ratio (monthly probability of conception)	Non-significant higher fecundability in regular drinkers Irregular drinkers: HR 1.09 (CI 0.75 to 1.57) Regular light drinkers: HR 1.13 (0.84 to 1.52) Regular drinkers: HR 1.18 (CI 0.73 to 1.90)	HR = hazard ratio	CH	2b
Jensen et al. 1998 ⁴²	1596 cycles from 423 women planning a pregnancy; 0 units/week (n = 388) 1–5 units/week (n = 771) 6–10 units/week (n = 283) 11–15 units (n = 102) > 15 units/week (n = 52)	Fecundability OR (odds of conception among exposed group divided by odds among those not exposed)	Decreased fecundability with increased alcohol intake: 1–5 units/week: OR 0.61 (CI 0.40 to 0.93) 6–10 units/week: OR 0.55 (0.36 to 0.85) 11–15 units/week: OR 0.34 (CI 0.22 to 0.52) > 15 units/week: OR 0.66 (CI 0.11 to 1.07)		CH	2b
Olsen et al. 1997 ⁴³	Population survey: 6630 women Pregnancy-based survey: 4035 pregnant women: 0 drinks/month (n = 1145); 120) 8–14 drinks/month (n = 118) 15+ drinks/month (n = 41) missing (n = 163)	Subfecundability in terms of time to pregnancy	No consistent association between alcohol intake and subfecundability B-effect model analysis: significant association between intake of > 8 drinks/week in women: 1–7 drinks/week: B-effect 1.1 (CI 0.9 to 1.3) > 8 drinks/week: B-effect 1.7 (CI 1.3 to 2.4)	Results adjusted	CH	2b
Juhl et al. 2001 ⁴⁴	29844 pregnant women within first 24 weeks of pregnancy: 0 units/week (n = 3679) 0.5–2.0 units/week (n = 12429) 2.5–7.0 units/week (n = 10910) 7.5–14.0 units/week (n = 2368) > 14.0 units/week (n = 316) missing (n = 142)	Subfecundability in terms of time to pregnancy	Slightly longer time to pregnancy in non-drinkers Modest association between high drinkers and time to pregnancy: 0 drinks/week: OR 1.18 (CI 1.12 to 1.25) 0.5–2.0 drinks/week: OR 1.00 2.5–7.0 drinks/week: OR 0.93 (CI 0.90 to 0.97) 7.5–14.0 drinks/week: OR 0.88 (CI 0.82 to 0.94) > 14.0 drinks/week: OR 1.00 (CI 0.85 to 1.18)	ORs adjusted	CH	2b

3.3 Alcohol and female fertility (continued)

Study	Population	Outcomes	Results	Comments	Study type	EL
Hakim et al. 1998 ⁴⁵	98 healthy volunteers (536 cycles): Non-drinkers (n = 147) 1–12 g/week (n = 168) 13–90 g/week (n = 185) > 91 g/week (n = 36)	Rate of conception	Reduced rate of conception: Significant negative dose relationship between conception and use of alcohol: non-drinker: OR 1.0; 1–12 g/week: OR 0.43 (CI .25 to 0.76); 13–90 g/week: OR 0.40 (CI 0.21 to 0.77); = /> 91 g/week: OR 0.65 (CI 0.20 to 2.15)	ORs adjusted	CH	2b
Joesoef et al. 1993 ⁴⁶	2817 fertile women recently delivered: 0 drinks/week (n = 1742) 1–2 drinks/week (n = 388) 3–5 drinks/week (n = 341) >5 drinks/week (n = 346)	Mean time to pregnancy	No dose relationship 0 drinks/week: RR 1.0 1–2 drinks/week: RR 1.1 (CI 0.9 to 1.2) 3–5 drinks/week: RR 1.0 (0.9 to 1.1) > 5 drinks/week: RR 1.0 (CI 0.9 to 1.10)	RRs adjusted	CH	

3.3 Alcohol and male fertility

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Brzek 1987 ⁵⁰	168 men: 80 alcohol abusers at alcohol clinic; 88 controls at sexology clinic	Alcohol abusers: treatment for alcohol abuse	Pretreatment semen parameters: volume, density, count and motility Post-treatment semen parameters: azoospermia (in 9 alcohol abusers)	Alcohol abusers: significant more subnormal finding in ejaculate volume and sperm motility Significant decrease and subnormal findings in sperm count and motility Azoospermia reversed at 3 months after treatment for alcohol abuse	Incomplete data	CH	2b
Marshburn et al. 1989 ⁵¹	446 men from infertility clinic: 388 non-drinkers; 108 drinkers (> 1.5 fl oz liquor/day)		Semen parameters: volume, density, motility, abnormality	No significant effect in drinkers	Other variables included	CH	2b
Dunphy et al. 1991 ⁵²	258 couples at infertility clinic (204 men were drinkers, 1 to > 20 units a week)		Semen parameters: not specified	No significant association between alcohol intake and semen parameters No significant association between amount consumed/week by male and fertility outcomes in normal and abnormal female partners	Follow-up for 32 months Incomplete data	CH	2b
Odereid et al. 1992 ⁵³	239 men for fertility investigations: < 5 mg alcohol /month (n = 56) 5–200 mg/month (n = 77) > 200 mg/month (n = 106)		Semen quality: concentration, motility	No clear reduction in sperm quality associated with increased alcohol use		CH	2b

3.4 Smoking and female fertility

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Hughes et al. 1996 ⁵⁶	A. 13 studies (fertile and infertile women): 4 cohorts 5 surveys 4 case-control B. 7 cohort studies: (women undergoing IVF/GIFT) C. 7 studies: 1 cohort 3 surveys 3 case-control	Ex-smokers and smokers	A. Natural conception B. Conception C. Spontaneous miscarriage	Negative association: A. OR 0.33 to 1.0 B. OR 0.57 (CI 0.42 to 0.78) C. OR 0.83 to 1.8		SR	2b
Augood et al. 1998 ⁵⁵	12 studies: 8 cohorts; 4 case-control	Ever-smokers and never smokers	Infertility defined as: 12 months of unprotected intercourse without conception	Significant difference: OR 1.60 (CI 1.34 to 1.91) in smokers Cohorts: OR 1.42 (CI 1.27 to 1.58) in smokers Case-controls: OR 2.27 (CI 1.28 to 4.02) in smokers	Different definitions of infertility used; heterogeneous populations No analysis on 'dose'	SR	2b
Hughes et al. 2000 ⁶⁵	94 Infertile women smokers at first visit to infertility clinic 110 pregnant women smokers	A 3 to 5-minute scripted intervention and booklet specific to the 'stage-of-change' in the smoking continuum versus standard care: advice on impact of smoking on fertility and pregnancy	Delta 'stage-of-change' Rate of maintained cessation at 12 months post follow-up	Infertile women: both interventions effective: mean delta of 'stage-of-change' = +0.28; maintained cessation: from 4% to 24% Pregnant women: Neither intervention nor control effective: mean delta of 'stage-of-change' = -0.62; maintained cessation: from 19% to 18%	Computer-generated randomisation: using numbered, opaque and sealed envelopes Exhaled carbon monoxide monitoring used to validate exposure to cigarettes Follow-up of 12 months only No analysis on 'dose'	RCT	1b

3.4 Smoking and male fertility

Study	Population	Outcomes	Results	Comments	Study type	EL
Vine et al. 1994 ⁵⁷	21 studies of cross-sectional design Smokers and non-smokers	Qualitative and quantitative assessment of sperm density	Smokers: Sperm density: 13% to 17% less than non-smokers (CI 8.0 to 21.5%) In 12 studies with available data (< 10; ≥ 10 cigarettes/day) no strong dose-response relationship between number of cigarettes smoked/day and sperm density	Men from infertility clinic included in 13 studies Normal men in 8 studies	MA	2b
Merino et al. 1998 ⁵⁸	358 men at infertility clinic: 197 smokers, 161 non-smokers 197 smokers: Group A: 1–10 cigarettes/day (n = 57) Group B: 11–20 cigarettes/day (n = 115) Group C: > 20 cigarettes/day (n = 25)	Semen parameters: volume, sperm count, viability and normal forms	Significant poorer in smokers Significant differences in grade A forward progressive motility in group C compared with group A		CH	2b
Zhang et al. 2000 ⁵⁹	301 men: 191 smokers and 110 non-smokers at infertility clinic Amount smoked: Light: 1–10 cigarettes/day (n = 58) Medium: 11–20 cigarettes/day (n = 68) Heavy: > 20 cigarettes/day (n = 65) Duration of smoking: Short-term: 1–10 years (n = 148) Long-term: 11–20 years (n = 43)	Semen parameters: semen volume, sperm density, viability, motility and morphology	Significantly lower in smokers than in non-smokers No significant differences in semen quality between light, medium and short-term smokers compared with non-smokers Significantly lower semen parameters in heavy and long-term smokers compared with non-smokers	Also case-control study within this study	CH	2b
Trummer et al. 2002 ⁶⁰	1104 men with infertility: 478 smokers; 109 ex-smokers; 517 non-smokers	Semen parameters: concentration, morphology, motility	No difference between non-smokers, smokers and ex-smokers	No analysis on 'dose'	CH	2b
Marshburn et al. 1989 ⁵¹	446 men from infertility clinic: 294 non-smokers; 152 smokers	Semen parameters: volume, density, motility, abnormality	Significance reduction in ejaculate volume in smokers; No difference in density, motility and abnormality	No analysis on 'dose'	CH	2b
Dunphy et al. 1991 ⁶¹	330 men in infertility clinic: non-smokers (n = 194); smokers: 1–5/day (n = 32) 6–10/day (n = 26) 11–20/day (n = 53) > 20/day (n = 25)	Semen parameters: motility	No significant association between smoking and semen parameters	Insufficient data	CH	2b

3.4 Passive smoking and female fertility

Study	Population	Outcomes	Results	Comments	Study type	EL
Hull et al. 2000 ⁶⁴	8407 women planning pregnancy	Time taken to conceive for > 6 months and > 12 months	<p>Significant delay in conception:</p> <p>In active female smokers: > 6 months, adjusted OR 1.23 (CI 0.98 to 1.49) > 12 months: adjusted OR 1.54 (CI 1.19 to 2.01)</p> <p>In women exposed to passive smoking: > 6 months: adjusted OR 1.17 (CI 1.02 to 1.37) > 12 months: adjusted OR 1.14 (CI 0.92 to 1.42)</p>		CH	2b
Jensen et al. 1998 ⁶³	430 couples with no history of fertility problems: female smokers (n = 127) female non-smokers (n = 303)	Fecundability odds ratio for smoking women exposed in utero	<p>Decreased fecundability:</p> <p>For female smoker exposed in utero: OR 0.53 (CI 0.31 to 0.91) For female non-smokers exposed in utero: OR 0.70 (CI 0.48 to 1.03) For female smoker not exposed in utero: OR 0.67 (CI 0.42 to 1.06) For male non-smokers exposed in utero: OR 0.68 (CI 0.48 to 0.97)</p>	Follow-up for 6 menstrual cycles or till pregnancy occurred	CH	2b

3.5 Caffeine and female fertility

Study	Population	Outcomes	Results	Comments	Study type	EL
Wilcox et al. 1988 ⁶⁹	104 healthy women planning a pregnancy	Fecundability ratio (FR): probability of conception in a menstrual cycle)	Decreased fecundability ratio in high caffeine drinkers: FR 0.59 (CI 0.40 to 0.87) Dose-response effect present	1 cup coffee = 100 mg caffeine; Low caffeine: < 3150 mg/month High caffeine: > 3150 mg/month	CH	2b
Christianson et al. 1989 ⁷⁰	6303 pregnant women: < 1 cup/day (n = 2154) 1-3 cups/day (n = 2639) 4-6 cups/day (n = 998) > 7 cups/day (n = 512)	Difficulty in becoming pregnant	More difficult in high caffeine drinkers: < 3 cups/day < 1 cup/day: RR 1 1-3 cups/day: RR 1.20; 4-6 cups/day: RR 1.88; > 7 cups/day: RR 1.96 (no CI available)		CH	2b
Joesoef et al. 1990 ⁷¹	2817 fertile women	Fecundability ratio	Little/no adverse effect: < 500 mg/month: FR 1 501-3000 mg/month: FR 1.07 (CI 0.95 to 1.21) 3001-5000 mg/month: FR 1.01 (CI 0.89 to 1.15) 5001-7000 mg/month: FR 1.01 (CI 0.88 to 1.15) > 7000 mg/month: FR 1.03 (CI 0.92 to 1.16)	1 cup coffee = 100 mg caffeine	CH	2b
Olsen 1991 ⁷²	10886 pregnant women	Subfecundability (time to pregnancy >1 year)	No adverse effect: 0-3 cups/day: OR 1.0 4-7 cups/day: OR 1.05 (CI 0.87 to 1.27) ≥ 8 cups/day: OR 0.98 (CI 0.70 to 1.37)	Tea and coffee consumption 1 serving coffee = 14-489 mg caffeine 1 serving tea = 8-107 mg caffeine	CH	2b
Hatch et al. 1993 ⁷³	1909 women at prenatal clinic Non-drinkers (n = 404) 1-150 mg/day (n = 1006) 151-3000 mg/day (n = 388) = />3001 mg/day (n = 111)	Delayed conception of > 12 cycles	Increased risk of delayed conception: Non-drinkers: OR 1.00 1-150 mg/day: OR 1.39 (CI 0.90 to 2.13) 151-3000 mg/day: OR 1.88 (CI 1.13 to 3.11) ≥ 3001 mg/day: OR 2.24 (CI 1.06 to 4.73)	5-oz cup = 107 mg caffeine	CH	2b
Florack et al. 1994 ⁷⁴	259 women workers < 3 cups/day (n = 48) 3-7 cups/day (n = 133) ≥ 7 cups/day (n = 78)	Fecundability odds ratio	Increased fecundability in moderate caffeine intake: 3-7 cups/day: OR 1.8 (CI 1.1 to 3.1) ≥ 7 cups/day: OR 1.2 (CI 0.7 to 2.1)	1 cup coffee = 100 mg caffeine	CH	2b

3.5 Caffeine and female fertility (continued)

Study	Population	Outcomes	Results	Comments	Study type	EL
Alderete et al. 1995 ⁷⁵	787 non-smoking pregnant women: Non-drinkers (n = 268) 1–3 cups/day (n = 335) > 3 cups/day (n = 184)	Time to pregnancy	No decrease in time to pregnancy: Non-drinkers: OR 1.0 1–3 cups/day: OR 1.3 (CI 0.7 to 2.5) >3 cups/day: OR 1.0 (CI 0.5 to 1.7)		CH	2b
Stanton et al. 1995 ⁷⁶	1430 parous women	Delayed conception of > 12 cycles	Delayed conception in high caffeine intake Non-drinkers: OR 1.0 1–150 mg/day: OR 0.91 (CI 0.64 to 1.29) 151–300 mg/day: OR 0.92 (CI 0.59 to 1.42) ≥ 301 mg/day: OR 1.44 (CI 0.85 to 2.44)	1 cup coffee = 100 mg caffeine	CH	2b
Bolumar et al. 1997 ⁷⁷	3146 women from population registers: 0–100 mg/day (n = 521) 101–300 mg/day (n = 1227) 301–500 mg/day (n = 7991) > 501 mg/day (n = 599)	Subfecundability (time to pregnancy > 1 year)	Increased time to pregnancy: 0–100 mg/day: OR 1.0 101–300 mg/day: OR 1.02 (CI 0.77 to 1.36) 301–500 mg/day: OR 1.01 (CI 0.74 to 1.37) > 501 mg/day: OR 1.45 (CI 1.03 to 2.04)	1 cup coffee = 130 mg caffeine	CH	2b
Curtis et al. 1997 ⁷⁸	1277 couples: 2444 pregnancies Non-drinkers (n = 89); 1–100mg/day (n = 675); 101–300mg/day (n = 833); 301–500mg/day (n = 549); >500md/day (n = 297)	Fecundability odds ratio	No dose–response effect: Non-drinkers: OR 1.0 1–100 mg/day: OR 1.11 (CI 0.90 to 1.36) 101–300 mg/day: OR 1.14 (CI 0.93 to 1.40) 301–500 mg/day: OR 1.04 (CI 0.85 to 1.29) > 500 md/day: OR 1.11 (CI 0.89 to 1.39)	1 cup coffee = 100 mg caffeine	CH	2b
Caan et al. 1998 ⁷⁹	187 women planning a pregnancy	Risk of pregnancy within 12 cycles	No adverse effect: ≤ 10.4 mg/day: OR 1.0 10.5–106.8 mg/day: OR 1.08 (CI 0.65 to 1.81) > 106.8 mg/day: OR 1.09 (CI 0.63 to 1.89)	Small sample 1 regular coffee = 104 mg caffeine	CH	2b
Jensen et al. 1998 ⁸⁰	423 healthy couples from national mailing : 1596 cycles	Fecundability odds ratio	No adverse effect: 0–299 mg/day: OR 1.0 300–699 mg/day: OR 0.88 (CI 0.60 to 1.31) > 700 mg/day: OR 0.63 (CI 0.25 to 1.60)	1 cup coffee = 100 mg caffeine	CH	2b
Hakim et al. 1998 ⁴⁵	98 healthy volunteers	Conception rate	Decreased conception rate: 0–25 mg/day: OR 1.0 26–100 mg/day: OR 1.13 (CI 0.51 to 2.49) 101–300 mg/day: OR 0.48 (CI 0.26 to 1.35) ≥ 301 mg/day: OR 0.83 (CI 0.34 to 2.01)	1 coffee drink = 100 mg caffeine Small sample	CH	2b

3.5 Caffeine and male fertility

Study	Population	Outcomes	Results	Comments	Study type	EL
Marshburn et al. 1989 ⁵¹	446 men from infertility clinic: non-coffee drinkers (n = 166) 1–2 cups/day (n = 198) ≥ 4 cups/day (n = 82)	Semen quality: volume, density, motility, abnormality	Significant increase in sperm density: non-drinkers: 76.7 (10E6/ml) 1–2 cups/day: 89.1(10E6/ml) ≥ 4 cups/day: 81.4 (10E6/ml) Significant increase in abnormality: non-drinkers: 28% 1–2 cups/day: 28% ≥ 4 cups/day: 31%	Other outcomes included	CH	2b

3.6.1 Obesity and female fertility

Study	Population	Outcomes	Results	Comments	Study type	EL
Jensen et al. 1999 ⁸²	10,903 pregnant women at prenatal clinic BMI (kg/m ²) < 20 (n = 3706) 20–25 (n = 6091) ≥ 26 (n = 1106)	Fecundability in terms of time to pregnancy	Significant lower fecundability ratio: Women with BMI > 25 kg/m ² : OR 0.77 (CI 0.70 to 0.84) compared with BMI 20–25 kg/m ²	Other variables studied Adjusted for duration and regularity of menstrual cycles and others	CH	2b
Bolumar et al. 2000 ⁸³	4035 pregnant women at prenatal clinic BMI (kg/m ²) < 20 (n = 677) 20.0–24.9 (n = 1446) 25.0–29.9 (n = 295) ≥ 30.0 (n = 78)	Delayed conception	No association: Non-smoking women with BMI ≥ 30 kg/m ² : OR 0.79 (CI 0.25 to 2.48) compared with BMI 20.0–24.9 kg/m ² Significant increase in risk: Smoking women with BMI ≥ 30 kg/m ² : OR 1.70 (CI 1.01 to 2.83)	Other variables studied Adjusted for duration and regularity of menstrual cycles and others	CH	2b
Zaadstra et al. 1993 ⁸⁴	489 healthy women undergoing AID Waist–hip ratio BMI (kg/m ²): < 20 (n = 104) 20–25 (n = 303) 25–30 (n = 60) ≥ 30 (n = 22)	Conception rates as hazard ratio (HR)	Non-significant hazard ratio: BMI 19 kg/m ² : HR 0.84(CI 0.75 to 1.25) BMI 22.3 kg/m ² : HR 1.00 BMI 26.4 kg/m ² : HR 0.94 (CI 0.78 to 1.14) BMI 33.1 kg/m ² : HR 0.43 (CI 0.17 to 1.09)	Adjusted Significant decrease in pregnancy rates with higher waist–hip ratio 3 years of follow-up	CH	2b

3.6.1 Obesity and male fertility

Study	Population	Outcomes	Results	Comments	Study type	EL
Kort et al. 2003 ⁸⁹	30 semen samples from men with mean BMI (SEM) of 26.9 (+0.62)	DNA fragmentation Index (DFI)	Significant correlation between BMI and DFI An increase in BMI beyond 25 is associated with a increase in the DFI of sperm		OB (abstract)	3
Kort et al. 2003 ⁹⁰	52 semen samples from men with mean BMI (\pm SEM) of 27.5 (\pm 0.49)	Number of normal-motile sperm	Significant inverse relationship between BMI and number of normal-motile sperm Normal BMI: normal-motile sperm 18.6 x 10 ⁶ cells Overweight: normal-motile sperm 3.6 x 10 ⁶ cells Obese: normal-motile sperm 0.7 x 10 ⁶ cells		OB (abstract)	3

3.6.1 Weight reduction and female fertility

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Guzick et al. 1994 ⁸⁵	12 obese anovulatory women: Programme (n = 6) Waiting list (n = 6) No significance difference between the 2 groups at baseline 'obese': 130–200% of ideal body weight	A 12-week weight loss programme versus on waiting list	Weight loss Detection of ovulation by serum progesterone	Significant weight loss: On programme: 16 kg On waiting list: no change Ovulation: On programme: 4/6 (67%) On waiting list: 1/6 (17%)	Randomisation method not clear Small sample Other outcomes included	RCT	1b
Clark et al. 2000 ⁸⁶	171 obese women with infertility history > 1 year: group programme (n = 87) standard programme (n = 84) 2 groups similar in age and length of infertility 'obese': BMI > 29 kg/m ² < 45 kg/m ²	Group programme (weekly meeting for 2 hours for support, exercise, advice on diet) versus standard programme (usual clinical approach) for 6 months	Weight loss Pregnancy at 18 months	Significant weight loss: Group programme: 4.7 kg Standard programme: 1.3 kg Significant Increase in pregnancy rates: Group programme: 53/87 (61%) Standard programme: 18/84 (21.4%)	Randomisation method not clear; Ovulation status not clear Other outcomes included	RCT (abstract)	1b

3.6.2 Low body weight and female fertility

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Wentz 1980 ⁹²	24 women with primary and secondary amenorrhoea		Estimated % of body fat loss	Loss of over 30% body fat	Other outcomes included	DE	3
Knuth et al. 1977 ⁹³	39 women with amenorrhoea due to loss of weight: 24 with anorexia nervosa, 15 undiagnosed	Encouraged to put on weight	Weight gain Ovulation resumption	Significant mean weight gain of 3.6 kg exceeding weight at baseline 14/39 (36%) resumed ovulation		CH	2b
Bates et al. 1982 ⁹⁴	47 women with simple weight loss: Group A: 29 with unexplained infertility Group B: 18 (4 diagnosed with anorexia nervosa) with menstrual dysfunction	Dietitian-instructed weight gaining regime	Weight gain Absence of menstrual cycle Pregnancy rates	Mean weight gain: Group A: 8.2 lb (SD 0.8) Group B: 9.8 lb (SD 1.3) Menstrual cycle: Group A: pre-regimen 3/29 (10%); post-regimen 0/26 (0%) Group B: pre-regimen 16/18 (89%); post-regimen 1/10 (10%) Pregnancy rates: Group A only: 19/26 (73%)	Dropout rates: Group A 3/29 (10%) Group B 8/18 (44%) Other outcomes included: Simple weight loss: 85–95% of ideal body weight Severe weight loss: < 85% of ideal body weight	CH	2b

3.7 Tight fitting underwear and male fertility

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Tiemessen et al. 1996 ¹⁰⁰	20 healthy men of proven fertility aged 25–50 years: 11 in 'loose-tight' group 9 to 'tight-loose' group No data on baseline comparison	'Loose-tight' group: 6 months' wear of loose underwear (boxers shorts), followed by 6 months of tight-fitting underwear 'Tight-loose' group: 6 months' wear of tight-fitting underwear, followed by 6 months of loose underwear	Sperm parameters every 2 weeks	Significant impairment: Sperm count 310%/ml: Tight: 46.0 (14.7–119.2) Loose: 89.5 (17.8–173.0) Motile sperm 310%/ml: Tight: 17.4 (0.3–36.2) Loose: 53.1 (0.5–47.0) Progressively motile sperm: Tight: 6.9 (310%/ml) Loose: 17.4(310%/ml)	Computer-generated randomisation of order of wear Study dropout rate 11/20 (55%)	RCT	1b

3.8 Occupational agents on male and female fertility

Summarised in Tables 3.1 and 3.2.

3.9 Prescribed drug use and female fertility

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Priddy et al. 1990 ¹⁵⁸	41 volunteers	NSAID (indomethacin, azapropazone, bromfenac) (n = 30) versus placebo (n = 10)	Preovulatory follicular fluid	NSAID use: Significant inhibition of ovulation	Randomisation by computer code	RCT	1b
Killick et al. 1987 ¹⁵⁹	46 cycles from 20 healthy women	NSAID (indomethacin, azapropazone) versus placebo; 1st 46 cycles as control	Production of luteinised unruptured follicles (LUFs)	NSAID use: Significant increase in LUFs	Randomisation by computer code hCG given to induce follicle rupture	RCT DBC	1b
Grodstein et al. 1993 ¹⁶¹	4430 women: 597 ovulatory infertility; 3833 controls		Ovulatory infertility	Use of > 6 months: Thyroid preparation: RR 2.3 (CI 1.5 to 3.5) Antidepressants: RR 2.9 (CI 0.9 to 8.3) Pain relievers: RR 1.4 (CI 0.9 to 2.2) Tranquilisers: RR 1.6 (CI 0.7 to 3.10) Use of > 2 years: Tranquilisers: RR 2.9 (CI 0.8 to 11) Antidepressants: RR 4.3 (CI 0.7 to 26) Asthma medication before age 21: RR 2.5 (CI 1.0 to 5.9)	Self-reported use	CCS	3
Meirow et al. 2001 ¹⁶³	168 cancer patients: acute myelocytic leukaemia (n = 47) non-Hodgkin's lymphoma (n = 36) Hodgkin's (n = 47) breast cancer (n = 38)	Combination chemotherapy	Pre- and post-treatment ovarian function	Combination chemotherapy: Ovarian failure: 34%, OR 3.98 Ovarian failure rates: acute myelocytic leukaemia: 15% non-Hodgkin's: 44% Hodgkin's: 32% Breast cancer: 50%	One group only	OB	3

3.9 Prescribed drug use and male fertility

Study	Population	Outcomes	Results	Comments	Study type	EL
Van Thiel et al. 1979 ¹⁶⁴	7 fertile men on cimetidine 21 controls not on cimetidine	Sperm concentration	Cimetidine use: Significant reduction in mean sperm count of 43% after cimetidine	Small sample size Other outcomes included	CH	2b
Marmor 1995 ¹⁶⁵	11 studies on sulphasalazine in patients with inflammatory bowel disease	Sperm parameters: counts, motility and morphology	Sulphasalazine use: report of low sperm counts, motility and morphology	Effects fully reversible on withdrawal of sulphasalazine	RV CA	3
Beeley 1984 ¹⁶⁷	Discussion paper on drug-induced sexual function and infertility	Sexual function and infertility	Use of betablockers' diuretics, psychotropic drugs: impotence and loss of libido		RV	4
Shalet 1997 ¹⁶⁸	Discussion paper	Sperm parameters	Use of chemotherapy (cyclophosphamide): azoospermia		RV	4
Fody et al. 1985 ¹⁶⁶	Discussion paper	Spermatogenesis	Large dose of androgens: oligospermia		RV	4

3.9 Recreational drug use and female fertility

Study	Population	Outcomes	Results	Comments	Study type	EL
Mueller et al. 1990 ¹⁷⁰	300 women: 150 at infertility clinic; 150 controls	Ovulatory infertility Tubal infertility	Marijuana use: RR 1.7 (CI 1.0 to 3.0) Cocaine use: ovulatory infertility RR 0.6 (CI 0.3 to 1.3) Marijuana use: RR 1.3 (CI 0.5 to 3.3) Cocaine use: tubal infertility RR 11.1 (CI 1.7 to 0.8)		CCS	3

3.9 Recreational drug use and male fertility

Study	Population	Outcomes	Results	Comments	Study type	EL
Knuth et al. 1989 ¹⁷²	82 men: 41 taking anabolic steroids; 41 not taking any drugs	Sperm parameters: concentration, motility, morphology	Anabolic steroids use: % of subjects with sperm counts below normal Anabolic steroids: 24/41 (59%) Non-use: 5/41 (12%) Significant reduction in sperm motility and sperm impairment with anabolic steroid use	Other outcomes included	CH	2b
Torres-Calleja et al. 2001 ¹⁷³	30 body builders: 15 taking anabolic steroids; 15 not taking anabolic steroids	Sperm parameters: concentration, morphology	Anabolic steroid use: significant reduction in sperm count and normal morphology	Small sample size Other outcomes included:	CH	2b
Bracken et al. 1990 ¹⁷¹	Men attending infertility clinic: 189 cases; 283 controls	Sperm parameters	Cocaine use: Low sperm count if used in last 2 years: OR 2.1 (CI 1.0 to 4.6) Low sperm motility if used for > 5 years: OR 2.0 (CI 1.0 to 4.1)		NCC	3

3.10 Complementary therapy

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Regg et al. 1997 ¹⁷⁴	40 men with oligospermia: Oral Y-virilin (n = 20) Placebo (n = 20) Sperm counts comparable at baseline, no information in age and diagnosis	Oral Y-virilin versus placebo twice a day for 6 months	Sperm parameters Conception rates	Significant higher sperm count in Y-virilin group No change in sperm density Conception rates: Oral Y-virilin: 4/20 (20%) Placebo: 1/20 (5%)	Demographic data not available: age, fertility history etc. Randomisation methods unclear No clarification on double-blinding Small sample Ingredients of Y-virilin: shatavari, palash, ashwaganfha, jeevanti, pimpali etc.	DBRP	1b
Scott et al. 1998 ¹⁷⁵	64 men at infertility clinic: Selenium only (n = 16) Selenium + vitamin (n = 30) Placebo (n = 18) No difference in pre-treatment sperm motility between the 3 groups	Selenium versus selenium + vitamin versus placebo 1 tablet daily for 3 months	Sperm parameters Partner pregnancy	Significant increased sperm motility in selenium, selenium + vitamin group No difference in sperm density Pregnancy: Selenium and selenium + vitamin: 5/46 (11%) Placebo: 0 (0%)	Block randomisation blinded using a numeric code Other outcomes included	RCT	1b
Bergman et al. 2000 ¹⁷⁶	67 women: 37 with oligomenorrhoea; 30 with amenorrhoea Phyto Hypophyson® L (n = 33): 16 menorrhoea; 17 oligomenorrhoea Placebo (n = 34): 14 menorrhoea; 20 oligomenorrhoea	50 drops of Phyto-Hypophyson® L versus placebo 3 times a day	Spontaneous menstruation Pregnancy rates Take-home baby rate	Spontaneous menstruation: significant improvement only in oligomenorrhoea as a group Pregnancy rates: non-significant improvement: Phyto Hypophyson® L: 7/16 (44%) versus placebo: 8/14 (57%) (amenorrhoea group) Take-home baby rate: significant improvement: Phyto Hypophyson® L: 14/17(82%) versus placebo: 9/20 (45%) (oligonorrhoea group)	Phyto-Hypophyson® L: an agnus-cactus containing complex Placebo-controlled Methods of randomisation, allocation concealment and blinding unclear 6 months follow-up Drop out rate: 14% Data unclear	RCT	1b

3.10 Complementary therapy (continued)

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Gerhard et al. 1999 ¹⁷⁷	77 infertile women: Homeopathic treatment (n = 43) Conventional treatment (n = 34)	Homeopathic versus conventional treatment	Pregnancy rates Live birth rates	Pregnancy rates non-significant: Homeopathic treatment: 10/30 (33.3%; CI 18% to 53%) Conventional treatment: 12/21 (57%; CI 34% to 77%) Live birth rates non-significant: Homeopathic treatment: 9/30 (30%); Conventional treatment: 11/21 (52%)	Homeopathic treatment: Sepia, pulsatilla, thuja, phosphor etc. Conventional treatment: IVF, Clomifene-hCG; FSH, etc. Methods of randomisation, allocation concealment and blinding unclear Patients allowed to 'change' group Dropout rate: 34%	RCT	1b
Cha et al. 2001 ¹⁷⁸	199 women aged 26–46 years undergoing IVF-ET in Korea: intercessory prayer (n = 100) No intercessory prayer (n = 99) Stratified by: age, length of infertility, type of infertility, number of previous attempts	Distant intercessory prayer versus No intercessory prayer throughout IVF-ET period Intercessory prayer for conception by prayer groups in US, Canada and Australia IVF-ET patients treated with identical protocol: GnRH agonist and gonadotrophins until 3 follicles mature, ET 3 days after retrieval	Pregnancy rates	Significant difference: intercessory prayer: 44/88 (50%) no intercessory prayer: 21/81 (26%) Term pregnancy rates: intercessory prayer: 46.6% no intercessory prayer: 22.2% Adjusted OR for pregnancy: 3.3 (CI 1.6 to 6.6)	Prayer groups sent pictures of patients Double-blind Computerised randomisation by 2 independent statisticians in 2 countries Code available at completion of study Patients and investigators were blinded	RCT	1b

3.11 Folate supplementation

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Lumley et al. 2002 ¹⁷⁹	6425 women planning pregnancy Various countries 4 RCTs	Periconceptional supplementation with daily folic acid + multivitamins versus trace elements Folic acid + multivitamins versus folic acid versus multivitamins Multivitamins versus placebo	Neural tube defects	Significant reduction with folic acid: RR 0.28 (CI 0.13 to 0.58) No significant reduction with multivitamins alone: RR 0.61 (CI 0.26 to 1.45)	Dose of folic acid (0.36–4.0 mg)	SR	1a

3.12 Rubella screening

Study	Population	Outcomes	Results	Study type	EL
Bayer et al. 1991 ¹⁸⁵	324 infertile patients at clinic	% of rubella non-immunity	27/324 (11.4%)	CHR	3
Fawzy et al. 1998 ¹⁸⁶	281 infertile women prior to IVF	% of rubella non-immunity	3/152 (2%)	CHR	3
Leader et al. 1984 ¹⁸⁷	1283 infertile couples at clinic	% of rubella non-immunity	109/1283 (8.5%)	CR	3
Ron-El et al. 1992 ¹⁸⁸	187 infertile couples prior to IVF	% of rubella non-immunity	11/187 (6%)	CHR	3

3.13 Cervical screening

Study	Population	Outcomes	Results	Study type	EL
Fawzy et al. 1998 ¹⁸⁶	102 infertile women prior to IVF	% of abnormal smear	13/102 (12.7%)	CHR	3
Ron-El et al. 1992 ¹⁸⁸	122 infertile couples prior to IVF	% of cervical intra-epithelial dysplasia	6/122 (5%)	CHR	3

4.1 Information giving

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Ellis et al. 1979 ²²⁹	56 patients on discharge from hospital	Written information (n = 30) versus verbal information (n = 26) on diagnosis, general advice, drug treatment, prognosis, follow-up arrangements	Mean scores of the 2 groups	Significant better response from group given written information	General medical patients	CSNR	2a
Laffont et al. 1994 ²³⁰	117 women for 2nd IVF; 101 male partners		Patients' perceived support and needs in IVF treatment	Factors that would improve knowledge and passage through IVF, provision of: Booklets about practical issues: 52% Video about IVF: 28% Booklets on psychological issues of IVF: 37% Bibliography about IVF: 26%	Other outcomes included	CH	2b

4.1 Information giving: patient satisfaction

Study	Population	Outcomes	Results	Comments	Study type	EL
Sabourin et al. 1991 ²²⁴	385 couples at infertility clinic	Patient satisfaction with information given at admission, and at 6 and 12 months	Moderately satisfied with information received about effects of medical treatment	Response rate 205/385 (53%) at 12 months	QS	3
Halman et al. 1993 ²²⁵	185 couples receiving infertility treatment	Patient satisfaction and advice to specialists	Patient advice to specialists to 'share information, explain treatment options and taking time to answer questions': ~ 30%	Other outcomes included	QS	3
Sundby et al. 1994 ²²⁶	361 women at infertility clinic	Patient satisfaction with information given	Dissatisfied with the medical information and communication about infertility: 30-40%	Response rate 262/361 (73%) Other outcomes included	QS	3
Souter et al. 1998 ²²⁰	1366 women in infertility clinic	Patient satisfaction with information given	Given information: 257/784 (33%) Would like more literature: 603/771 (78%) Suggested 'more written information' would improve the service: 59/598 (10%)	Response rate 806/1366 (59%) Other outcomes included	QS	3
Owens et al. 1984 ²¹⁹	501 members of National Association for the Childless	% of patients who said that doctors provide full information about testing and treatment	~ 41%	Response rate 77% Other outcomes included	QS	3
Hammarberg et al. 2001 ²²⁷	211 women after IVF	Satisfaction with information provided	Majority 'satisfied' or 'very satisfied'	Response rate 55% Other outcomes included	QS	3

4.1 Couple-centred management and care

Study	Population	Outcomes	Results	Comments	Study type	EL
Bromham et al. 1998 ²²¹	265 couples (hospital and 3 self-help groups)	% of clinics where couple were seen together	35%	Response rate 82/265 (31%) Other outcomes included	QS	3
Owens et al. 1984 ²¹⁹	501 members of National Association for the Childless	% of patients who experienced couple involvement in consultation process	~70%	Response rate 77% Other outcomes included	QS	3
Souter et al. 1998 ²²⁰	1366 women at infertility clinic	Patient satisfaction when being seen with partner	When seen with partner: significantly more satisfied 89% Without partner 83%	Response rate 806/1366 (59%) Other outcomes included	QS	3
Souter et al. 1997 ²²²	500 GP principals	Opinions in seeing couples together as part of infertility management	Agreed 90% Arranged to see both partners together 66%	Response rate 414/500 (83%) Other outcomes included	QS	3

4.2 Effect of stress on female fertility

Study	Population	Outcomes	Results	Comments	Study type	EL
Hjollund et al. 1998, 1999 ^{247;248}	393 couple planning a pregnancy: 1475 cycles 297 couple planning a pregnancy: 1159 cycles	Probability of conception	High stress score: OR 0.6 (CI 0.4 to 1.0) compared with low stress scores High job strain: OR 0.9 (CI 0.5 to 1.5) compared with low job strain	Stress measured using the 12-item General Health Questionnaire at every cycle Job strain questionnaire used Other outcomes included	CH	2b
Fenster et al. 1999 ²⁴⁹	246 women from California Women's Reproductive Health Study	Anovulation	High stress job: OR 1.34 (CI 0.35 to 4.28) compared with no stress job	Job stress measurement by Karasek 1986 Other outcomes included Large CIs	CH	2b

4.2 Effect of stress on male fertility

Study	Population	Outcomes	Results	Comments	Study type	EL
Poland et al. 1986 ²⁵⁰	53 semen donors: 31 medical students during exam months ; 22 non-students	Semen quality	Medical students: Significant elevation of sperm count and quality when compared with non-students	Potential confounders	CH	2b
Fenstere al 1997 ²⁵¹	157 men in California Women's Reproductive Health Study: 12 men experienced bereavement; 145 men did not	Evaluation of stress: stressful jobs, life events, bereavement Semen quality	Bereavement group: significant reduction in straight-line velocity and % of progressively motile sperm compared with non-bereavement group	Job stress measurement by Karasek 1986 Other outcomes included Confounders adjusted	CH	2b

4.2 Effect of counselling

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Domar et al. 2000 ²⁷⁰	184 women trying to conceive for 1–2 years Cognitive behavioural therapy (n = 56) Support group (n = 65) Routine care (n = 63) Baseline data comparable between 3 groups	Cognitive behavioural therapy versus support versus routine care Intervention: 10 weekly sessions of: Cognitive behavioural therapy: relaxation, cognitive restructuring, emotional expression, nutrition/diet information Support: update on treatments, discussion on feelings, impact of infertility on relationship etc. Routine care: usual care	Viable pregnancy rate at 1 year	Significant increase in pregnancy rates in both cognitive behavioural therapy and support versus the routine care group: Cognitive behavioural therapy: 26/47 (55%) Support: 26/48 (54%) Routine care: 5/25 (20%)	All patients to keep monthly fertility medication and treatment diary Changing groups (from CBT to support) mid-study Dropout: CBT 9/56 Support 17/65 Routine care 38/63 Study assessor-blind Intention-to-treat	RCT	1b

4.2 Effect of counselling (continued)

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Domar et al. 2000 ²⁶⁹	184 women trying to conceive for 1–2 years Cognitive behavioural therapy (n = 56) Support group (n = 65) Routine care (n = 63) Baseline data comparable between 3 groups	Cognitive behavioural therapy versus support versus routine care Intervention: 10 weekly sessions of: cognitive behavioural therapy: relaxation, cognitive restructuring, emotional expression, nutrition/diet information Support: update on treatments, discussion on feelings, impact of infertility on relationship etc. Routine: usual care	Psychological assessment at baseline, 6 and 12 months Instruments: – Profile of Mood Scale – State Trait Anxiety Inventory – Beck Depression Inventory – Hamilton Rating Scale for Depression – Rosenberg Self-Esteem Scale – Marital Distress Scale – Health Promoting Lifestyle Profile – Stress Management Scale	At 6 months: Significant improvement in cognitive behavioural therapy and support groups versus routine care in: Stress Management Scale, State Trait Anxiety Inventory, Marital Distress Scale, Profile of Mood Scale Significant improvement in cognitive behavioural therapy versus support group in Health Promoting Lifestyle Profile, Stress Management Scale At 12 months: Significant improvement in cognitive behavioural therapy versus support group in Hamilton Rating Scale for Depression Significant improvement in cognitive behavioural therapy versus routine care in Health Promoting Lifestyle Profile, Stress Management Scale	Changing groups (from cognitive behavioural therapy to support) mid-study Patients remaining at 6 months: Cognitive behavioural therapy (n = 20) Support (n = 29) Routine care (n = 14) Patients remaining at 12 months: cognitive behavioural therapy (n = 7) Support (n = 11) Routine care (n = 2) High dropout rates Assessor- blind Intention-to-treat	RCT	Ib
Connolly et al. 1993 ²⁷²	82 couples receiving first IVF Information (n = 45) Information and counselling (n = 37)	Information versus information with counselling Information: oral and written information on procedures and course of IVF Information and counselling: Information as above plus discussion of IVF, interpersonal and psychosexual considerations, coping etc.	Psychological state at baseline, before treatment cycle and at end of cycle Instruments: – General Health Questionnaire – State Trait Anxiety Inventory – Self-esteem Scale – Profile of Mood Scale – IVF Stress Inventory – Self-assessment Scale – Satisfaction with Counselling	No significant differences between information versus information and counselling For both groups: decrease in State Trait Anxiety Inventory; increase in General Health Questionnaire	Methods of randomisation, allocation concealment and blinding of outcomes assessment unclear	RCT	Ib

4.3 Specialist and generalist care

Study	Population	Outcomes	Results	Comments	Study type	EL
Bromham et al. 1988 ²²¹	265 couples (hospital and 3 self-help groups)	Patients' satisfaction with service received in general gynaecology clinic	Dissatisfaction frequently expressed (no quantitative data)	Response rate – 82/265 (31%) Other outcomes included	QS	3
Souter et al. 1998 ²²⁰	1366 women at infertility clinic	Patient satisfaction in attending a dedicated infertility clinic versus gynaecology clinic	Infertility clinic: significantly more satisfied 533/601 (89%) General gynaecology clinic: 145/178 (81%)	Response rate 806/1366 (59%) Other outcomes included	QS	3

5.1 Semen analysis

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Opsahl et al. 1996 ²⁸⁶	Semen analyses from 209 men with primary and secondary infertility	One versus two/three analysis versus andrological evaluation	False negatives and sensitivity based on first sample results	Multiple samples (3): False negatives 11/106 (10.4%) Sensitivity 95/106 (89.4%) First sample falsely identified normal as abnormal 9/106 (8.5%) Multiple sample falsely identified normal as abnormal 2/106 (2%)	Normal and abnormal semen parameters based on WHO criteria	TES CH	2b
WHO 2000 ²⁸⁵					Two samples of semen should be collected for initial evaluation	EO	4

5.2.1 Assessing ovulation: serum progesterone

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Hull et al. 1982 ³⁰⁷	212 untreated cycles in 113 infertile women including 21 untreated singleton conception cycles	Serum progesterone level versus 'gold standard'	Single measurement of mean serum progesterone level in 21 untreated conception cycles	40.7 nmol/l (CI 28 to 53 nmol/l) (range 28 to 53 nmol/l) 28 nmol/l proposed as the lowest limit	Conception cycles measurement as proof of ovulation 1 ng/ml = 3.18 nmol/l	TES	2b
Wathen et al. 1984 ³⁰⁹	79 women with regular menstruation		Serum progesterone in follicular phase and luteal phase	20 nmol/l proposed as the lowest limit	Mid-luteal phase values derived from follicular phase measurements	TES	2b
Abdulla et al. 1983 ³⁰⁸	Untreated cycles from 68 women 40 conception cycles		Mean plasma progesterone levels in conception cycle and follicular rupture	55.2 nmol/l (range 12.2 to 92.2 nmol/l) 38 nmol/l proposed as lowest limit)	Follicular rupture confirmed by laparoscopy	TES	2b
ESHRE 1996 ²¹¹				16nmol/l for a minimum of 5 days to a single value of 32 nmol/l suggested as indication of ovulation		EO	4

5.2.2 Assessing ovulation: prolactin

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Vanrell 1983 ³¹⁵	130 infertile but ovulatory women and no galactorrhea undergoing evaluation of luteal function		Serum prolactin measurement	Raised serum prolactin: 15/130 (11.5%); 1/15 (6.6%) with inadequate luteal phase Normal serum prolactin: 115/130 (88.5%); 20/115 (17.4%) with inadequate luteal phase		OB	3
Laufer et al. 1995 ³¹⁶	98 ovulatory women aged 25–43 years with tubal infertility undergoing IVF	Serum prolactin versus reference lab normal values	Serum prolactin measurement	Significantly higher level: 7/98 (7.1%, CI 2.9% to 14%)	Other outcomes measured: TSH Analysis also stratified by age	OB	3
Varkopoulou et al. 1993 ³¹⁷	292 patients from infertility clinic		Serum prolactin levels	Serum prolactin > 600 miu: 33/292 (11.3%) Hyperprolactinaemia: 11/292 (3.8%)		OB	3
Glazener et al. 1987 ³¹⁸	188 infertile women aged 18–41 years with normal menstrual cycle, thyroid-stimulating hormone and FSH		Serum prolactin levels Progesterone and cumulative conception rates	No significant association Serum prolactin levels range: < 200 miu/l to > 800 miu/l	12 months follow-up	OB	3
Stratford et al. 1999 ³¹⁹	315 infertile women		Serum prolactin levels Prevalence of raised serum prolactin (> 500 miu)	Serum prolactin levels range: 77 to 1629 miu/l 2/315 (0.63%) with menstrual dysfunction 20/315 (6.3%) with serum prolactin of 500–800 miu ovulatory	Normal ovulation occurs when PRL < 800 miu	OB	3

5.2.3 Assessing ovulation: ovarian reserve

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Navot et al. 1987 ³²⁸	51 women aged over 35 with unexplained infertility Baseline characteristics similar	Clomifene citrate challenge test (CCCT)	Rate of diminished ovarian reserve as indicated by FSH level of ≥ 26 miu/ml Conception rate Miscarriage rate	Diminished ovarian reserve: 18/51 (35%) Conception rate: significantly lower in diminished ovarian reserve: Ovarian reserve: Diminished: 1/18 (5.6%) Adequate: 14/33 (42%) Miscarriage rate: Ovarian reserve: Diminished: 0/1 (0%) Adequate: 4/14 (29%)	47 women treated with hMG and hCG for ovulation induction	CH	2b
Levi et al. 2001 ³³³	9802 infertile patients (10,874 basal FSH measurements)		Rate of diminished ovarian reserve: (FSH ≥ 14.2 iu/l) Conception rate Pregnancy loss Live birth rate	Diminished ovarian reserve: 1034/9802 (10.5%) Conception rate: diminished ovarian reserve 28/1034 (2.7%); adequate ovarian reserve, no data Pregnancy loss significantly higher in diminished ovarian reserve for all age groups Diminished ovarian reserve: 20/28 (71.4%) < 35 years: 4/7 (57.1%) 35–40 years: 7/11 (63.6%) > 40 years: 9/10 (90%) Adequate ovarian reserve: < 35 years: 16.4% 35–39 years: 13.7% > 40 years: 33.2% Live birth rate: diminished ovarian reserve: 8/28 (0.8%); adequate ovarian reserve, no data	28 conceptions: 12 IVF 9 spontaneous 6 with COH/IUI 1 clomifene citrate/IUI	RCR	3

5.2.3 Assessing ovulation: ovarian reserve (continued)

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Scott et al. 1993 ³²⁶	236 infertile women from unselected general infertility population (excluding women with previous tests, referral or for reversal of sterilisation)	Clomifene citrate challenge test	Incidence of abnormal test (if FSH > 10miu/ml) Pregnancy rate	Abnormal CCCT: 23/236 (10%) Pregnancy rate: Abnormal CCCT: 2/23 (8.7%) < 30 years 0/2 (0%) 30–34 years 1/5 (2%) 35–39 years 1/7 (14%) > 40 years 0/9 (0%) Normal CCCT: 92/213 (43%) < 30 years 34/59 (58%) 30–34 years 31/67 (46%) 35–39 years 25/61 (41%) > 40 years 2/26 (7.7%)	Age-related pregnancy rate decline in both groups	CH	2b
Scott et al. 1995 ³²⁷	588 women aged 19–46 years from a general infertile population (excluding tubal disease, peritoneal adhesive disease, male factor)	Clomifene citrate challenge test	Incidence of abnormal test Pregnancy rate	Abnormal CCCT: 83/588 (14%) Pregnancy rate: Abnormal CCCT: 4/83 (4.8%) ≤ 30 years 0/5 (0%) 31–33 years 2/11 (18%) 34–36 years 1/22 (4.5%) 37–39 years 1/21 (4.8%) ≥ 40 years 0/24 (0%) Normal CCCT: 245/505 (48.5%) ≤ 30 years 61/92 (66%) 31–33 years 85/150 (56.7%) 34–36 years 20/48 (42.6%) 37–39 years 33/85 (38.3%) ≥ 40 years 3/30 (10%)	Age-related pregnancy rate decline in both groups	RRR	3

5.2.4 Assessing ovulation: thyroid function

Study	Population	Outcomes	Results	Comments	Study type	EL
Conway et al. 1985 ³⁴⁶	447 infertile women aged 18-46, with normal menstrual cycle	Measurement of TSH	Normal level: 441/447 (98.7%) Abnormal level: 6/447 (1.3%)	Other outcomes measured: FSH Prolactin progesterone	OB	3
Strickland et al. 1990 ³⁴⁷	210 infertile women (62 with ovulation disorder)	Measurement of TSH Incidence of subclinical hypothyroidism	Normal level: 202/210 (96%); 55/202 (27%) with ovulation disorder Abnormal level: 8/210 (3.8%); 7/8 (87.5%) with ovulation disorder Incidence of subclinical hypothyroidism 7/62 (11.3%) of women with ovulation disorder	Other outcomes measured: prolactin	OB	3
Shalev et al. 1994 ³⁴⁸	444 infertile women (114 with ovulatory dysfunction)	Measurement of TSH Incidence of subclinical hypothyroidism	Normal TSH level: 441/444 (99%) Abnormal level: 3/444 (0.67%) Incidence of subclinical hypothyroidism 1/444 (0.23%); 1/114 (0.88%) with ovulatory dysfunction	Other outcomes measured: Free T4	OB	3
Laufer et al. 1995 ³⁴⁶	98 ovulatory women aged 25-43 with tubal infertility undergoing IVF	Measurement of TSH	Normal TSH level: 94/98 (96%) Significantly abnormal level: 4/98 (4.1%, CI 1.1% to 10.1%) 3 with >4.6 uIU/ml 1 with <0.6 uIU/ml	Other outcomes measured: prolactin Analysis stratified by age	OB	3
Stratford et al. 2000 ³⁴⁹	472 women attending infertility clinic	Measurement of TSH	Normal TSH level: 448/472 (95%) Abnormal level: 24/472 (5.1%) 13 with high TSH, 9/13 (69%) ovulatory 7 with low TSH, 6/7 (86%) ovulatory Documentation of signs and symptoms poor		OB	3

5.2.5 Assessing endometrial biopsy in treatment of luteal phase defect effect of treatment for luteal phase defect

Study	Population	Intervention	Outcomes	Results	Study type	EL
Karamardian et al. 1992 ³⁵⁴	1 RCT 3 comparative studies 19 case series studies	Progesterone versus no treatment Progesterone, clomifene versus no treatment Progesterone,, clomifene, FSH, bromocriptine etc	Risk of pregnancy Pregnancy rates	Risk of pregnancy non-significant, RR 1.9 (CI 0.4 to 8.1) No significant benefit Pregnancy rates: no significant benefit with large CIs	SR	Ib-3

5.3 Chlamydia trachomatis: incidence

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Scholes et al. 1996 ³⁶⁴	2607 women identified from data base of Group Health Cooperative Scheme, aged 18-24 years Screening: (n = 1009) Usual care: (n = 1598) Exclusion: married, pregnant, cervical ectopy Baseline characteristics comparable	Women invited for screening (2 cervical samples tested) versus usual care (attend as needed) Women testing positive were treated	Incidence of pelvic inflammatory disease confirmed by medical records Rates expressed as per 10,000 woman-months	Screening: 9 cases Usual care: 33 cases Rates: screening: 8; usual care: 18 Adjusted RR 0.44 (CI 0.20 to 0.90)	Screening group: 645/1009 (64% tested, 7% positive and treated) 12 month follow-up Response rate: 76% Method of randomisation and allocation concealment unclear Data extractors 'blind' Intention-to-treat analysis	RCT	Ib

5.3 Chlamydia trachomatis: screening techniques

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Skulnick et al. 1994 ³⁶⁶	993 women attending women's unit, aged 15–50 years	PCR and EIA versus endocervical swabs	Sensitivity Specificity PPV NPV	Higher sensitivity in PCR Sensitivity/specificity PCR: 84.6/99.2% EIA: 61.5/99.7% PPV/NPV: PCR: 57.9/99.8% EIA: 72.7/99.5%	True positive PCR confirmed by PCR for major outer membrane protein	TES	2b
Schachter et al. 1995 ³⁶⁷	4043 women attending clinics for sexually transmitted disease	LCR on first catch urine versus cervical and urethral cell culture	Sensitivity Specificity Positive predictive value Negative predictive value	High sensitivity and specificity for LCR on FCU Sensitivity/specificity LCR on FCU: 88.2/100.0% Cervical cell culture: 67.1/100.0% Cervical and urethral cell culture: 74/100% PPV/NPV: LCR on FCU: 100.0/99.1% Cervical cell culture: 100.0/97.6% Cervical and urethral cell culture: 100.0/98.1%	2812 women had second cell culture on urethra and cervix True positive LCR confirmed by direct fluorescent antibody or by LCR for major outer membrane protein	TES	2b
Ridgway et al. 1995 ³⁶⁸	600 women attending genitourinary clinic	Cervical and urine LCR versus cervical and urethral culture	Sensitivity Specificity	High sensitivity and High specificity for LCR Sensitivity/specificity Cervical LCR: 81%/100% Urine LCR: 69.6%/99.8% PPV/NPV: cervical LCR 100.0/97.2% Urine LCR: 98.2/95.6% Cervical and urine LCR Combined: sensitivity 91.1% cervical and urine LCR	True positive LCR confirmed by LCR for major outer membrane protein	TES	2b

5.4 Assessing tubal damage: hysterosalpingography, laparoscopy and hysterosalpingo-contrast-sonography

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Collins 1988 ³⁰⁶	18 comparative studies	HSG versus laparoscopy	Sensitivity Specificity	HSG: Sensitivity: 0.76 Specificity: 0.83 (no CI) Likelihood ratio: positive test: 4.47 negative test: 0.29		MA	2b
Swart et al. 1995 ³⁷⁵	20 comparative studies including 4179 patients with infertility	HSG versus laparoscopy and dye in detecting tubal patency and peritubal adhesions	Sensitivity Specificity	HSG: Low sensitivity: 0.65 (CI 0.50 to 0.78) High specificity: 0.83 (CI 0.77 to 0.88) Likelihood ratio: positive test: 3.82 negative test: 0.42 Based on point estimates of homogeneous subgroups in 3 studies where HSG and laparoscopy were evaluated independently	Overall point estimated not calculated due to heterogeneity Different types of cannula used	MA	2b
Dijkman et al. 2000 ³⁸⁶	100 infertile women	HyCoSy versus HSG versus laparoscopy/dye in detecting tubal patency	Kappa statistics agreement between tests in detecting tubal patency Likelihood ratio (LR)	Similar between HyCoSy and HSG: LR: kappa 0.07 (CI -0.03 to -0.16) HyCoSy and lap: LR for absence of tubal patency: 2.9 (CI 1.4 to 8.6) LR for presence of tubal patency: 0.75 (CI 0.51 to 1.1) HSG and laparoscopy: LR for absence of tubal patency: 3.6 (CI 2.1 to 6.2) LR for presence of tubal patency: 0.39 (CI 0.22 to 0.67)	Results of first 50 procedures omitted from analysis to allow for 'inexperience' (learning curve)	RCT	Ib

5.4 Assessing tubal damage: hysterosalpingography and hysterosalpingo-contrast-sonography

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Ayida et al. 1996 ³⁸⁷	66 infertile women HyCoSy (n = 34) HSG (n = 32)	HyCoSy versus HSG to assess patient acceptability and tolerance	Examination of tubal patency and uterine cavity Report of pain and analgesia	Patent tubes diagnosed: HyCoSy: 60% (39/65) HSG: 55/64 (86%) Uterine pathology: HyCoSy: 12% (4/34) HSG: 9% (3/32) Ovarian pathology: HyCoSy: 14/68 (20%) HSG: 0% No significant differences in the frequency and severity of pain and analgesia requirement in the 2 groups	Methods of randomisation and allocation unclear Both HyCoSy and HSG performed by same gynaecologist	RCT	Ib
Boudghene et al. 2001 ³⁸⁸	23 women referred for HyCoSy prior to HSG	Infoson-enhanced HyCoSy versus saline HyCoSy versus HSG	No of correct diagnosis of tubal patency	Significant difference in number of patent tubes diagnosed: Infoson™ (MBI, San diego, CA)-enhanced HyCoSy: 20/22 (91%) Adjusted: 87.6% Saline HyCoSy: 12/24 (50%) Adjusted: 53% Patent tubes detected by HSG: 30/46 (65%)	Small sample Multicentred 'Sequential design' Methods of randomisation and allocation unclear Blind assessment by 2 radiologists	RCT	Ib

5.4 Assessing tubal damage: fertiloscopy and falloposcopy

No appropriate tables available. Please see text (Chapter 5, Section 5.4)

5.4 Tubal flushing: unexplained infertility

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Johnson et al. 2003 ³⁹⁶	8 RCTs (1706 participants)	<p>Tubal flushing with oil-soluble contrast media (OSCM) versus no treatment</p> <p>Tubal flushing with oil-soluble contrast media versus tubal flushing with water-soluble contrast media (WSCM)</p> <p>Tubal flushing with oil-soluble contrast media plus water-soluble contrast media versus water-soluble contrast media</p>	<p>Pregnancy rates</p> <p>Live birth rates</p> <p>Miscarriage rates</p> <p>Ectopic pregnancy</p> <p>Infection</p> <p>Post-procedure bleeding</p>	<p>Pregnancy rates: significant improvement with OSCM versus no intervention: OR 3.57 (CI 1.76 to 7.23)</p> <p>Live birth rates:</p> <p>Significant improvement with OSCM versus WSCM: OR 1.49 (CI 1.05 to 2.11)</p> <p>Pregnancy rates: no significant improvement with OSCM versus WSCM, OR 1.23 (CI 0.95 to 1.60)</p> <p>No significant differences with OSCM versus WSCM in:</p> <p>Miscarriage rates: OR 0.82 (CI 0.41 to 1.64)</p> <p>Ectopic pregnancy: OR 0.49 (CI 0.10 to 2.42)</p> <p>Infection: OR 0.37 (CI 0.11 to 1.21)</p> <p>Post-procedure bleeding significantly lower with OSCM: OR 0.06 (CI 0.04 to 0.11)</p> <p>No significant differences with OSCM + WSCM versus WSCM:</p> <p>Pregnancy rate: OR 1.16 (CI 0.78 to 1.70)</p> <p>Live birth rate: OR 1.06 (CI 0.64 to 1.77)</p> <p>Miscarriage rate: OR 1.14 (CI 0.53 to 2.48)</p> <p>Ectopic pregnancy rate: OR 0.54 (CI 0.08 to 3.45)</p>	Statistical heterogeneity	SR	1a

5.5 Assessing uterine abnormalities: hysteroscopy

Study	Population	Intervention	Outcomes	Results	Study type	EL
Golan et al. 1996 ³⁹⁹	464 infertile women	HSG versus hysteroscopy in diagnosis of uterine pathology	Sensitivity Specificity Positive predictive value Negative predictive value	HSG: Sensitivity: 98 Specificity: 15 Positive predictive value: 45 Negative predictive value: 95 53% of HSG detected 'filling defects' found by hysteroscopy to be normal 56% of HSG detected 'wall irregularity' found by hysteroscopy to be normal	TES	2b

5.5 Assessing pelvic abnormalities: pelvic ultrasound

Study	Population	Intervention	Outcomes	Results	Study type	EL
Frederick et al. 1991 ⁴⁰³	133 gynaecological patients aged 16–67 years (including patients with infertility)	Bimanual pelvic exam versus TVU versus elective laparoscopy/laparotomy	Sensitivity Specificity Positive predictive value Negative predictive value Test efficiency	Bimanual: Sensitivity: 65.7 Specificity: 92.5 PPV: 77.5 NPV: 87.3 Test efficiency: 84.9 TVU: Sensitivity: 93.8 Specificity: 98.4 PPV: 95.8 NPV: 97.7 Test efficiency: 97.2	TES	2b
Nezhat et al. 1994 ⁴⁰⁴	91 women with pelvic pain aged 17–59 years	Bimanual pelvic exam versus TVU	Detection of normal uterus Concordance between bimanual and TVU In women with endometriosis extended to the uterus and ovaries	No significant difference Bimanual: 43/91 (47%) TVU: 37/91 (41%) Concordance between bimanual and TVU 65% Abnormal TVU in 89%	CS	3
Reuss et al. 1996 ⁴⁰⁵	663 premenopausal women with indications for TVU (pelvic mass, fibroids, abnormal bleeding, adnexal mass)	TVU versus retrospective bimanual and surgical/ histological findings	Detection of normal uterus Intraoperative confirmation	Bimanual: 12/347 (36%) of TVU-diagnosed fibroids 134/190 (70.5%) of TVU-diagnosed adnexal abnormalities TVU: 46/51 (90%) TVU-diagnosed fibroids	OB	3

5.6 Postcoital testing

Study	Population	Intervention	Outcomes	Results	Comments	Study	EL type
Oei et al. 1998 ⁴⁴	444 new couples in infertility clinics, Netherlands PCT (n = 227), no PCT (n = 217) No significant difference in baseline characteristics in: age of woman and man	PCT versus no PCT as part of Infertility investigations	Cumulative pregnancy rates (CPR) at 24 months Number of tests and treatments given	No significant difference in CPR: PCT 49% (CI 42% to 55%); no PCT 48% (CI 42% to 55%) No. of tests given: PCT 528; no PCT 326 Significant difference in no of treatments given: PCT 122 (54%); No PCT 89 (41%)	Central randomisation, sequentially numbered, opaque sealed envelope put in case notes at first visit PCT was carried out in 3 couples in the control group Clinicians blind to secondary outcomes, free to apply tests and treatments as appropriate Analysis based on intention-to-treat basis	RCT	1b

6.1 Medical treatment of antisperm antibodies: male infertility

Study	Population	Intervention	Outcomes	Results	Comments	Study	EL type
Haas et al. 1987 ⁴⁹	43 men with antibody-mediated infertility	3 cycles of methylprednisolone (MP) (n = 24) versus placebo (n = 19)	Semen parameters Pregnancy rate Adverse effects	No significant differences: Pregnancy rate: MP: 3/20 (15%) Placebo: 1/15 (7%) RR 2.25 (CI 0.26 to 19.55) Adverse effects non-specific in the 8 dropouts	Method of randomisation and allocation concealment unclear 4 dropouts in each group 3 months follow-up Small sample Double-blind	RCT	1b

6.1 Medical treatment of antisperm antibodies: male infertility (continued)

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Hendry et al. 1990 ⁴⁵²	43 men with antibodies to spermatozoa	9 months of prednisolone (n = 22) versus placebo (n = 21)	Semen parameters Pregnancy rate Adverse effects (acne, weight gain, dyspepsia, irritability)	No significant difference: Pregnancy rate: significant differences: prednisolone: 9/33 (27%), placebo: 2/27 (7%), RR 3.68 (CI 0.87 to 15.62) Adverse effects: prednisolone: 18/30 (60%), placebo: 5/26 (19%)	Method of randomisation and allocation concealment unclear 16 dropouts (8 in each group) Double-blind crossover	RCT	Ib
Bals-Pratsch et al. 1992 ⁴⁵⁰	20 men with sperm antibodies	3 months of Prednisolone (n = 20) versus Placebo (n = 20)	Semen parameters Pregnancy rate Adverse effects	No significant differences: Pregnancy rate 0 in both groups Adverse effects 7/18 (39%) (non specific, 1 with suspected encephalitis)	Method of randomisation and allocation concealment unclear 3 dropouts (2 in treatment group, 1 in placebo group) Small sample Double-blind crossover	RCT	Ib
Lahteenmaki et al. 1995 ⁴⁵¹	50 men with antisperm antibodies	2 weeks of prednisolone (n = 27) versus placebo (n = 26) prior to IVF	Fertilisation rate/oocyte Pregnancy rate Adverse effects	No significant differences: Fertilisation rate/oocytes: prednisolone: 90/258 (34.9%); placebo: 89/230 (39%) Pregnancy rate: prednisolone: 5/17 (29%); placebo: 6/19 (32%) RR 0.93 (CI 0.35 to 2.51) Adverse effects: 1 in prednisolone group discontinued treatment (dyspepsia) No drug-related adverse effects reported	Method of randomisation and allocation concealment unclear	RCT	Ib
Omu et al. 1996 ⁴⁵³	80 men with antisperm antibodies	Low dose prednisolone (n = 40) versus no treatment (n = 37)	Sperm parameters Live birth rates Adverse effects	Significant differences: Live birth rates: Prednisolone: 7/40 (18%) No treatment: 1/37 (3%) No adverse events reported	Method of randomisation and allocation concealment unclear 12–18 months follow-up	RCT	Ib

6.1 Medical treatment of leucocytospermia: male infertility

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Branigan et al. 1994 ⁴⁵⁷	102 men with leucospermia	No treatment (n = 25) versus antibiotic (n = 25) versus antibiotic and frequent ejaculation (n = 27) versus frequent ejaculation (n = 25)	Resolution of leucocytospermia at 1 month Pregnancy rate	Significant resolution: No treatment: 1/25 (4%) Antibiotic: 10/25 (40%) Antibiotic and frequent ejaculation: 17/25 (68%) Frequent ejaculation: 8/25 (32%) Pregnancy rate: limited data: No treatment: 1/25 (4%) Antibiotic: 2/25 (8%) Antibiotic + frequent ejaculation: 4/25 (16%) Frequent ejaculation: 3/25 (12%)	Block randomisation 3 months follow up	RCT	Ib
Micic et al. 1987 ⁴⁶⁴	120 men with oligoasthenozoospermia and genital infection	Kallikrein + antibiotic (n = 64) versus antibiotic only (n = 56)	Pregnancy rate	Significant improvement in kallikrein plus antibiotic group: Kallikrein plus antibiotic: 21/64 (32%) Antibiotic only: 10/56 (17%)	Methods of randomisation and allocation concealment unclear	RCT	Ib
Comhaire et al. 1986 ⁴⁶¹	33 men with male accessory gland infection (MAGI)	Antibiotic (doxycycline)(n = 20) versus placebo (n = 13)	Pregnancy rate	No significant differences Antibiotic: 2/20 (10%) Placebo: 1/13 (8%)	Methods of randomisation and allocation concealment unclear Partners treated Small sample	RCT	Ib
Vicari 2000 ⁴⁶²	122 men with MAGI	Antimicrobials (doxycycline, ofloxacin)(n = 85) versus no treatment (n = 37)	Pregnancy rate	Significant improvement at 3 months: Antimicrobial: 24/85 (28.2%) No treatment: 2/37 (5.4%) RR 5.22 (CI 1.30 to 20.97)	Computer randomisation Partners treated	RCT	Ib
Harrison et al. 1975 ⁴⁶³	88 couples with T-mycoplasmas	Antibiotic (doxycycline)(n = 30) versus placebo (n = 28) versus no treatment (n = 30)	Pregnancy rate	No significant differences Antibiotic: 5/30 (17%) Placebo: 4/28 (14%) No treatment: 5/30 (17%)	Methods of randomisation and allocation concealment unclear Partners treated	DBRP	Ib

6.1 Medical treatment with anti-oestrogens: male infertility

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Vandekerckhove et al. 1996 ⁴³⁷	11 RCTs (738 participants)	Tamoxifen (tamoxifen) versus placebo or vitamin C (5 RCTs) Clomifene citrate versus placebo or vitamin C (6 RCTs)	Pregnancy rates Adverse effects	Significant benefit: Pregnancy rates: Combined OR 1.54 (CI 0.99 to 2.40) tamoxifen versus placebo: combined OR 1.64 (CI 0.81 to 3.34) Clomifene versus placebo: combined OR 1.48 (CI 0.84 to 2.61) 'Low incidence' of adverse effects	Small sample size overall and limited power Review update in progress	SR	1a
Khan et al. 1996 ⁴³⁸	9 RCTs	Tamoxifen (tamoxifen) versus placebo (3 RCTs) Clomifene citrate versus placebo or vitamin C (6 RCTs)	Pregnancy rates Adverse effects	Non-significant benefit: pregnancy rates: OR 1.6 (CI 0.9 to 2.6) Adverse effects not reported		SR	1a

6.1 Medical treatment with gonadotrophins: male infertility

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Matorras et al. 1997 ⁴³⁶	148 couples undergoing IUI due to male infertility	FSH 150 IU (n = 68) 3 times/week versus no treatment (n = 80) for 8 months	Pregnancy rates/woman Multiple pregnancy	Non-significant higher rate in FSH group Pregnancy rates/woman: FSH: 26/58 (44.8%) No treatment: 29/78 (37.2%) RR 1.21 (CI 0.80 to 1.81) Multiple pregnancy: FSH: 8/26 (30.1%) No treatment: 8/29 (27.6%)	Randomisation following a random number table	RCT	Ib
Kamischke et al. 1998 ⁴³⁵	67 couples with male idiopathic infertility	rhFSH 150 IU daily (n = 34) versus placebo (n = 31) for 12 weeks	Semen parameters Spontaneous pregnancy rates Multiple pregnancy	No significant differences: Spontaneous pregnancy rates: rhFSH :2/34 (5.8%); placebo: 0/31 (0%) Multiple pregnancy: no data	Randomisation by third party Examiners 'blind' Double-blind	DBRP	Ib

6.1 Medical treatment with androgens: male infertility

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Vandekerckhove et al. 1996 ⁴³⁹	9 RCTs (905 participants)	Mesterolone versus placebo or vitamin C Testosterone versus placebo	Pregnancy rates Adverse effects	No significant benefit: Pregnancy rates: OR 1.10 (CI 0.75 to 1.61) Adverse effects 'minor'	Small sample size overall and limited power Review update in progress	SR	1a

6.1 Medical treatment with bromocriptine: male infertility

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Vandekerckhove et al. 1996 ⁴⁴²	4 RCTs (112 participants)	Bromocriptine versus placebo	Pregnancy rates Adverse effects	Non-significant benefit: Pregnancy rates: combined OR 0.70 (CI 0.15 to 3.24) Adverse effects not reported	Small sample size overall and limited power Review update in progress	SR	1a

6.1 Medical treatment with kinin enhancing drugs: male infertility

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Vandekerckhove et al. 2003 ⁴⁴⁰	12 RCTs (768 participants)	Kallikrein versus placebo or no treatment	Pregnancy rates Adverse effects	Non-significant benefit: Pregnancy rates: OR 1.65 (CI 0.98 to 2.77) Adverse effects 'mild and transient'	Small sample size overall and limited power	SR	1a
Yamamoto et al. 1996 ⁴⁴¹	102 patients with idiopathic oligozoospermia	Kallikrein (n = 52) versus placebo (n = 50) for 12 weeks	Pregnancy rates	No significant differences: Kallikrein: 5/52 (9.6%) Placebo: 7/ 50 (14%)	Methods of randomisation and allocation concealment unclear Double-blind	DBRP	1b

6.1 Medical treatment with antioxidants: male infertility

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Kessopoulou et al. 1995 ⁴⁴³	30 healthy men with high levels of ROS generation in semen	Vitamin E (n = 15) versus placebo (n = 15) for 3 months	In vitro and in vivo sperm function by zona binding test Pregnancy rate Adverse effects	Significant improvement in sperm functions Pregnancy rate: no significant differences: Vitamin E :1/15 (7%) Placebo: 2/15 (13%) No adverse effects reported	Randomisation by manufacturer Small sample Other outcomes assessed Double-blind, crossover after 1-month 'washout'	DBRP	Ib
Suleiman et al. 1996 ⁴⁴⁴	87 men from infertility clinic	Vitamin E (n = 52) versus placebo (n = 35) for 6 months	Lipid peroxidation in semen and sperm motility by MDA concentration Pregnancy rate Miscarriage	Significant decrease MDA levels in Vit E group Pregnancy rate: significant improvement Vitamin E: 11/ 52 (21%) Placebo: 0/32 (0%) Miscarriage 2/11 (18%)	Methods of randomisation and allocation concealment unclear Other outcomes assessed Double-blind	DBRP	Ib
Rolf et al. 1999 ⁴⁴⁵	31 men with asthenozoospermia	Vitamin C + E (n = 15) versus placebo (n = 16)	Sperm parameters Pregnancy rate	No significant differences: No pregnancies in either group	Randomisation and allocation code held by pharmacy Double-blind	DBRP	Ib
Lenzi et al. 1993 ⁴⁴⁶	20 infertile men with dyspermia associated with varicocele or germ-free genital tract inflammation	Glutathione intramuscularly versus placebo for 2 months	Sperm parameters by CASA Pregnancy rate	Significant improvement with glutathione Pregnancy rate not reported	Methods of randomisation, allocation concealment and blinding unclear Double-blind, crossover after 2-month 'washout' period	DBRP	Ib

6.1 Medical treatment with mast-cell blockers: male infertility

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Yamamoto et al. 1995 ⁴⁴⁸	50 men with severe oligozoospermia	Mast-cell blocker (tranilast) (n = 25) versus placebo (n = 25) for 3 months	Semen parameters Pregnancy rate Adverse effect	Significant improvement With alpha-blocker Pregnancy rate: Mast-cell blocker: 6/21 (28.6%) Placebo: 0/25 (0%) Severe drowsiness on mast cell blocker group	Methods of randomisation, allocation concealment and blinding unclear 4/25 (16%) attrition in treatment group due to adverse effect 1 year follow up Single-blind	RCT	1b

6.1 Medical treatment with alpha-blockers: male infertility

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Yamamoto et al. 1995 ⁴⁴⁷	31 men with infertility	alpha-blocker (bunazosin) (n = 16) versus placebo (n = 15) for 6 months	Semen parameter Pregnancy rate Adverse effects	Significant improvement With alpha-blocker Pregnancy rate: no significant differences: alpha-blocker: 4/16 (25%) Placebo: 1/15 (6.7%) RR 3.75 (CI 0.47 to 29.87) Adverse effects: nasal obstruction and dizziness	Methods of randomisation, allocation concealment and blinding unclear Double-blind	DBRP	1b

6.2 Surgical treatment of varicoceles: male infertility

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Evers et al. 2003 ⁴⁶⁸	7 RCTs	Surgical ligation or embolisation versus no or delayed treatment	Pregnancy rates	No significant effect: Combined RR 1.04 (CI 0.62 to 1.75), random effect model Combined RR 1.01 (CI 0.73 to 1.40), fixed effect model	Clinical heterogeneity No data yet from ongoing WHO trial since 1997 3 versions of results from WHO multicentre trials excluded	SR	1a

7.1 Ovulation induction in ovulatory disorders: clomifene citrate and placebo

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Hughes et al. 2001 ⁴⁸⁵	279 infertile oligo-ovulatory women with hypothalamic-pituitary failure and dysfunction (hypogonadotrophic and normogonadotrophic) 4 crossover RCTs	Clomifene citrate 10 to 250 mg versus placebo	Ovulation rates Clinical pregnancy rate per treatment cycle	Ovulation rates: Clomifene 50–250 mg daily versus placebo: OR 6.82 (CI 3.92 to 11.85) Clomifene 10 mg daily versus placebo: OR 1.29 (CI 0.48 to 3.49) When combined: OR 4.6 (CI 2.84 to 7.45) Clinical pregnancy rate per treatment cycle: clomifene 10–100 mg versus placebo: OR 3.41 (CI 1.23 to 9.48)	Heterogeneity introduced as different dose of CC used in 1 study BBT used to determine ovulation in 3 studies Limitation of crossover design	SR	1a

7.1 Ovulation induction in ovulatory disorders: clomifene citrate and tamoxifen

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Gerhard et al. 1979 ⁴⁸⁷	48 women with various types of menstrual disorder 30 received pre-treatment with clomifene citrate	Tamoxifen (? dose) Versus daily clomifene citrate 100 mg	Ovulation rate (as determined by BBT and serum progesterone) for 20 patients who received tamoxifen and clomifene alternately Pregnancy rate (for 31 patients) Adverse effects of ovarian enlargement	No significant difference: Ovulation rate: Tamoxifen: 70% Clomifene: 50% Pregnancy rate: Tamoxifen: 3/31 (9.6%) Clomifene: 4/31 (13%) Ovarian enlargement: Tamoxifen: 20% Clomifene: 40%	Heterogeneous group Method of randomisation and allocation concealment unclear Group number unclear	RCT	2a
Messinis et al. 1982 ⁴⁸⁹	46 women aged 18–36 years with anovulatory infertility (30 with oligomenorrhea, 14 with secondary amenorrhea. All had normal FSH and prolactin + other factors) 30 women with no pre-treatment of clomifene 16 received pre-treatment	First cycle of daily tamoxifen 20 mg or clomifene 50 mg versus second cycle of daily clomifene 50 mg versus tamoxifen 20 mg	Ovulation rate (as determined by BBT and serum progesterone)	No significant difference: Tamoxifen: 56.2 (50/89 cycles) Clomifene: 62.9 (56/89 cycles) OR 0.76 (CI 0.40 to 1.44) No severe adverse effects	Heterogeneous group Method of randomisation and allocation concealment unclear Alternate allocation of randomised treatment cycle of tamoxifen and clomifene Gradual increase in clomifene and tamoxifen dosage if ovulation failed	RCT	1b

7.1 Ovulation induction in ovulatory disorders: clomifene citrate and tamoxifen (continued)

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Buvat et al. 1987 ^{48b}	66 infertile women with eugonadal anovulation (n = 26) or luteal phase deficiency (n = 40)	Clomifene versus tamoxifen	Pregnancy rates at 9 months Twin pregnancy rates Miscarriage rates Adverse effects (not specified) Pregnancy rates at 6 months	No significant difference: Pregnancy at 9 months: Clomifene 80% Tamoxifen 80% Twin pregnancy rate: Clomifene 1/19 (5%) Tamoxifen 1/11 (9%) Miscarriage rates: Clomifene 2/19 (11%) Tamoxifen 4/11 (36%) Adverse effects: Similar in both groups Clomifene 20% Tamoxifen 17% Pregnancy rates at 6 months: Significant differences: In LPD patients: Clomifene 40% Tamoxifen 11%	Methods of randomisation and allocation concealment unclear Numbers in each group not available	RCT	Ib
Suginami et al. 1993 ^{49b}	20 nomoprolactinaemic anovulatory women	Daily clomifene citrate 100 mg (n = 10) (57 cycles) versus daily clomifene citrate 50 mg plus 20 mg tamoxifen (n = 10) (56 cycles)	Ovulation/treated rate Pregnant/treated rate Pregnant/ovulatory cycle rate	Significant improvement with clomifene + tamoxifen Ovulation/treated rate: Clomifene+ tamoxifen 42/56 (75%) Clomifene 25/57 (43.9%) RR 1.71 (CI 1.23 to 2.38) Pregnant/treated rate: Clomifene + tamoxifen 3/47 (6.4%) Clomifene 1/48 (2.1%) Pregnant/ovulatory cycle rate: Non-significant difference: Clomifene + tamoxifen 3/35 (8.6%) Clomifene 1/21 (4.8%) RR 1.80 (CI 0.20 to 16.21) No remarkable adverse effects	Withdrawal bleeding induced before treatment Method of randomisation and allocation concealment unclear Ovulation rate (as determined by BBT and serum progesterone) Crossover trial design	RCT	Ib

7.1 Ovulation induction in ovulatory disorders: clomifene citrate and tamoxifen (continued)

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Boostanfar et al. 2001 ⁴⁸⁶	86 anovulatory women under 40 years	Daily clomifene citrate 50 mg (n = 47) versus daily tamoxifen 20mg (n = 48)	<p>Ovulation rate (as determined by serum progesterone)</p> <p>Pregnancy</p> <p>Cumulative pregnancy rate/ovulatory cycle</p> <p>Multiple gestation</p> <p>Adverse effect of ovarian enlargement</p>	<p>No significant difference</p> <p>Ovulation rate: Tamoxifen: 50/113 (44.2%) Clomifene: 41/91 (45.1%) OR 0.97 (CI 0.53 to 1.75)</p> <p>Pregnancy: Tamoxifen: 10/46 (22%) Clomifene: 6/40 (15%)</p> <p>Cumulative pregnancy rate/ovulatory cycle: tamoxifen: 20% Clomifene 14.6%</p> <p>Multiple gestation: none in either group</p> <p>Ovarian enlargement: none in either group</p>	<p>Withdrawal bleeding induce before treatment</p> <p>Gradual increase in clomifene and tamoxifen dosage if ovulation failed</p> <p>Method of randomisation and allocation concealment unclear</p>	RCT	Ib

7.1 Ovulation induction in unexplained infertility: clomifene citrate

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Hughes et al. 2003 ⁵⁰³	6 RCTs (177 participants with unexplained infertility)	Clomifene citrate (50–100 mg daily) versus placebo versus no treatment (IUI/AIH)	Pregnancy rates/woman Pregnancy rates/cycle Spontaneous miscarriage (3 RCTs) Crude twin pregnancy rate (2 RCTs) OHSS	Significant differences in pregnancy rates in clomifene group: Pregnancy rates/woman OR 2.37 (CI 1.22 to 4.62) Pregnancy rates/cycle OR 2.5 (CI 1.35 to 4.62) Spontaneous miscarriage no difference (insufficient power): 5/28 (18.6%) Crude twin pregnancy rate 3/38 (7.9%) OHSS: none reported	Cross-over design in 4 RCTs Included RCTs of poor quality 27 women with mild endometriosis hCG given to clomifene patients to trigger ovulation	SR	1a
Fujii et al. 1997 ⁵⁰⁴	33 women with unexplained infertility	Clomifene citrate 50 mg daily (n = 18) versus no treatment (n = 15) (timed intercourse)	Pregnancy rates/woman Pregnancy rates/cycle Spontaneous miscarriage Live birth/pregnancy	Significant differences in clomifene group: Pregnancy rates/woman: Clomifene: 4/14 (22%) No treatment: 11/15 (73%) OR 0.10 (CI 0.01 to 0.64) Pregnancy rates/cycle: Clomifene: 4/66 (6%) No treatment: 11/52 (21%) Spontaneous miscarriage: No significant difference: Clomifene: 1/4 (25%) No treatment: 3/11 (27%) Live birth/pregnancy: Clomifene: 3/4 (75%) No treatment: 8/11 (73%)	Observations terminated and clomifene stopped by 7 women due to 'anti-oestrogenic effect'	QR	1b–2a

7.2 Ovulation induction in ovulatory disorders: metformin and clomifene citrate

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Lord et al. 2003 ⁵⁰⁵	15 RCTs (997 participants) PCOS 4 trials PCOS with obesity 4 trials PCOS with clomifene citrate resistance 6 trials PCOS with clomifene citrate sensitivity 1 trial	Metformin versus metformin +clomifene versus placebo/no treatment	Ovulation rates Clinical pregnancy rates/woman Miscarriage (1 trial only) Multiple pregnancy rate (1 trial only) Adverse effects (nausea, vomiting) Gastrointestinal disturbances	Significant improvement: Ovulation rates: Metformin versus placebo OR 3.88 (CI 2.25 to 6.69) Metformin + clomifene versus clomifene: OR 4.41 (CI 2.37 to 8.22) Clinical pregnancy rates/woman: Metformin versus placebo (no significance): OR 2.76 (CI 0.85 to 8.98) Metformin + clomifene versus clomifene: OR 4.88 (CI 2.46 to 9.67) Miscarriage: Clomifene + metformin versus clomifene + placebo: 2 versus 0 Multiple pregnancy rate: 0 versus 0 Adverse effects: Metformin versus placebo: OR 3.91 (CI 0.98 to 15.64) Gastrointestinal disturbances: OR 4.62 (CI 1.71 to 12.51)	Sensitivity analysis showed results stability in relation to: trial methodology, obesity, treatment duration, doses of metformin and ethnicity	SR	1a
Costello et al. 2003 ⁵⁰⁶	12 RCTs 2 cohort studies 16 uncontrolled descriptive studies	Metformin versus placebo versus metformin + clomifene citrate Metformin prior to FSH versus FSH versus metformin + IVF	Ovulation rates Pregnancy rates	Significant improvement in metformin +clomifene for clomifene-resistant PCOS: Ovulation rate: RR 4.0 (CI 1.6 to 4.1) Pregnancy rate: RR 2.2 (CI 1.5 to 3.0) Metformin prior to FSH versus FSH versus metformin + IVF: Insufficient data for interpretation	Women included unselected and clomifene-resistant PCOS Limited data	SR	1a

7.3 Ovulation induction in ovulatory disorders: ovarian drilling

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Farquhar et al. 2002 ⁵⁰⁸	A: 4 RCTs (303 women with CC-resistant PCOS) B: 1 RCT (10 women) C: 1 RCT (40 women)	A: Laparoscopic ovarian drilling (electrocautery, CO ₂ laser vaporisation) versus gonadotrophins (pure FSH/hMG) B: Unilateral versus bilateral ovarian drilling C: Second-look laparoscopy with adhesiolysis versus expectant management	Cumulative pregnancy rate/woman after 12 months Miscarriage rate Multiple pregnancy rate Pregnancy rate	Non significant differences: A: Cumulative pregnancy rate: OR 1.42 (CI 0.84 to 2.42) A: Miscarriage rate: OR 0.61 (CI 0.17 to 2.16) Significantly reduced in ovarian drilling: A: Multiple pregnancy rate: OR 0.16 (CI 0.03 to 0.98) B, C: Pregnancy rate: no significant difference	Overall quality of trials was poor in reporting method of randomisation, allocation concealment, blinding, attrition rates, follow-up period and data availability etc	SR	1a
Muenstermann et al. 2000 ⁵¹¹	18 women with PCOS BMI > 29 kg/m ² 21 cycles	GnRH-a + oral contraceptive for 6 months (n = 8; 21 cycles) versus ovarian laser diathermy (n = 10; 20 cycles)	Ovulation cycles Pregnancy rates Miscarriage rates Live birth rates	No significant differences: Ovulation cycles: GnRH-a + oral contraceptive: 14/21 (67%) Laser diathermy: 14/20 (70%) Pregnancy rates: GnRH-a + oral contraceptive: 5/8(63%) Laser diathermy: 5/10(50%) RR 0.8 (CI 0.4 to 1.8) No miscarriages Live birth rates: GnRH-a + oral contraceptive: 29% Laser diathermy: 36%	Alternate randomisation	QR	1b
El-Saeed et al. 2000 ⁵⁰⁹	40 patients aged 22–31 years, with clomifene citrate-resistant PCOS	Laparoscopic ovarian drilling with 'fine' needle' (n = 23) versus laparoscopic ovarian drilling with 'thick' needle (n = 17)	Adhesions at second-look laparoscopy Mean score of adhesions	Significant difference: Adhesions at second-look laparoscopy: 'Fine' needle: 12/23 (52%) 'Thick' needle: 15/17 (88%) No significant difference in mean score of adhesions	Method of randomisation and RCT allocation concealment unclear Second-look laparoscopy 3–4 weeks after surgery 'Fine' needle: 3–5 mm, depth 10 mm 'Thick' needle: 6–9 mm, depth 5mm		1b

7.4 Ovulation induction in ovulatory disorders: gonadotrophins (rFSH versus uFSH)

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Bayram et al. 2002 ⁵¹⁴	4 RCTs (554 women with PCOS)	A: rFSH versus uFSH (3 RCTs) B: rFSH regimens: chronic low dose versus conventional (1 RCT)	Ovulation rates Pregnancy rates Multiple pregnancy rates Miscarriage rates OHSS rates	A: No significant differences: Ovulation rates: OR 1.19 (CI 0.78 to 1.80) Pregnancy rates: OR 0.95 (CI 0.64 to 1.41) Multiple pregnancy rates: OR 0.44 (CI 0.16 to 1.21) Miscarriage rates: OR 1.26 (CI 0.59 to 2.70) OHSS rates: OR 1.55 (CI 0.50 to 4.84) B: No significant differences: Ovulation rates: OR 0.95 (CI 0.43 to 2.06) Pregnancy rates: OR 1.62 (CI 0.64 to 4.07) Multiple pregnancy rates: OR 0.59 (CI 0.07 to 5.12)	Insufficient data rFSH used: Gonal-F® (Serono); Puregon R® (Organon) uFSH used: Metrodin R®	SR	1a

7.5 Ovulation induction in in vitro fertilisation: gonadotrophins (hMG versus uFSH)

Study	Population	Intervention	Outcomes	Results	Study type	EL
Daya et al. 1995 ⁵¹⁵	8 RCTs Women undergoing IVF cycles	FSH (\pm GnRHa) versus hMG (\pm GnRHa)	Clinical pregnancy rates/cycle Clinical pregnancy rates/cycle reaching oocyte retrieval Clinical pregnancy rates/ cycle reaching embryo transfer Miscarriage Multiple pregnancy OHSS	Significant increase with uFSH: Clinical pregnancy rates/cycle OR 1.71 (CI 1.12 to 2.62) Clinical pregnancy rates/cycle reaching oocyte retrieval OR 1.69 (CI 1.10 to 2.59) Clinical pregnancy rates/cycle reaching embryo transfer OR 1.70 (CI 1.10 to 2.62) Miscarriage, multiple pregnancy, OHSS: insufficient data	SR	1a
Agarwal et al. 2000 ⁵¹⁶	11 RCTs Woman undergoing IVF cycles	FSH (\pm GnRHa) versus hMG (\pm GnRHa)	Clinical pregnancy rates/cycle	Significant with FSH: No GnRHa protocol: OR 2.8 (CI 1.01 to 7.72) Short GnRHa protocol non-significant: OR 1.72 (CI 0.85 to 3.50) Long GnRHa protocol non-significant: OR 0.77 (CI 0.58 to 1.05)	SR	1a

7.5 Ovulation induction in in vitro fertilisation: gonadotrophins (rFSH and uFSH)

Study	Population	Intervention	Outcomes	Results	Study type	EL
Van Wely et al. 2003 ⁵¹⁷	8 RCTs (2377 participants)	hMG (\pm GnRHa) versus rFSH (\pm GnRHa)	<p>No GnRHa protocol:</p> <p>Ongoing pregnancy/live birth rate/woman</p> <p>Clinical pregnancy rate/woman</p> <p>Miscarriage rate/woman</p> <p>Multiple pregnancy rate/woman</p> <p>Short GnRHa protocol:</p> <p>Clinical pregnancy rate/woman</p> <p>Multiple pregnancy rate/woman</p> <p>Cycle cancellation</p> <p>OHSS</p> <p>Long GnRHa protocol:</p> <p>Ongoing pregnancy/live birth rate/woman</p> <p>Miscarriage rate/woman</p> <p>Multiple pregnancy rate/woman</p> <p>Cycle cancellation</p> <p>OHSS</p>	<p>No GnRHa protocol – no significant difference:</p> <p>Ongoing pregnancy/live birth rate/woman: 17% versus 22% OR 0.73 (CI 0.26 to 2.10)</p> <p>Clinical pregnancy rate/woman: 23% versus 24%, OR 0.94 (CI 0.35 to 2.53)</p> <p>Miscarriage rate/woman: 5.7% versus 1.9% OR 3.2 (CI 0.3 to 33.7)</p> <p>Multiple pregnancy rate/woman: 5.7% versus 9.3%, OR 0.62 (CI 0.13 to 2.97)</p> <p>Short GnRHa protocol – no significant difference:</p> <p>Clinical pregnancy rate/woman: 28% versus 25%, OR 1.11 (CI 0.77 to 1.60)</p> <p>Multiple pregnancy rate/woman, 18% versus 14%, OR 1.35 (CI 0.61 to 3.01)</p> <p>Cycle cancellation: 7.1% versus 9.5%, OR 0.73 (CI 0.41 to 1.32)</p> <p>OHSS: none</p> <p>Long GnRHa protocol – no significant difference:</p> <p>Ongoing pregnancy/live birth rate/woman: OR 1.27 (CI 0.98 to 1.64)</p> <p>Miscarriage rate/woman: OR 1.18 (CI 0.63 to 2.20)</p> <p>Multiple pregnancy rate/woman: OR 1.46 (CI 0.98 to 2.16)</p> <p>Cycle cancellation: OR 0.89 (CI 0.51 to 1.52)</p> <p>OHSS: OR 1.60 (CI 0.60 to 4.3)</p> <p>Borderline significance:</p> <p>Clinical pregnancy rate/woman: OR 1.28 (CI 1.00 to 1.64)</p>	SR	1a

7.5 Ovulation induction in in vitro fertilisation: gonadotrophins (uFSH and rFSH; urinary gonadotrophins versus rFSH)

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Daya 2003 ⁵¹⁸	18 RCTs (3421 cycles)	r-FSH ± GnRHa versus uFSH ± GnRHa Long GnRHa protocol prior to FSH in 17 studies	Clinical pregnancy rate/cycle Clinical pregnancy rate/oocyte retrieval Clinical pregnancy rate/embryo transfer Ongoing/delivered pregnancy rate/cycle Multiple pregnancy rate Spontaneous miscarriage rate OHSS	Significant increase with rFSH Clinical pregnancy rate/cycle: OR 1.21 (CI 1.04 to 1.42) RD 3.7% with rFSH Clinical pregnancy rate/oocyte retrieval: OR 1.18 (CI 1.00 to 1.39) RD 3.4% with rFSH Clinical pregnancy rate/embryo transfer: OR 1.17 (CI 1.00 to 1.37) RD 3.4% with rFSH Ongoing/delivered pregnancy rate/cycle: OR 1.29 (CI 1.08 to 1.54) No significant differences: Multiple pregnancy rate OR 0.82 (CI 0.59 to 1.13) Spontaneous miscarriage rate OR 0.80 (CI 0.56 to 1.13) OHSS: 2% versus 1.4% RR 1.50 (CI 0.88 to 2.58)	Other outcomes included	SR	1a
Larizgoitia 2000 ⁵¹⁹	8 RCTs (1703 participants)	rFSH versus uFSH/hMG/unpurified FSH (rFSH versus uFSH: 4 RCTs, rFSH versus hMG/unpurified FSH 2 RCTs, rFSH versus high-purity uFSH)	Ongoing pregnancy rate (mean)	No significant difference: 25% versus 21% (17.7% increase in rate with rFSH)	Limitation in methods of review	SR	1a

7.5 Ovulation induction in in vitro fertilisation: gonadotrophins (uFSH and rFSH; urinary gonadotrophins versus rFSH) (continued)

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Al-Inany et al. 2003 ⁵²⁰	20 RCTs (4610 cycles)	rFSH + long GnRHa protocol versus urinary gonadotrophins (hMG, uFSH-P, uFSH high-purity) + long GnRHa protocol	Clinical pregnancy rate/cycle (subgroup analysis)	No significant difference: OR 1.07 (CI 0.94 to 1.22) rFSH versus hMG: OR 0.81 (CI 0.63 to 1.05) rFSH versus FSH-P: OR 1.24 (CI 0.98 to 1.58) rFSH versus FSH-HP: OR 1.14 (CI 0.94 to 1.40) rFSH versus u-gonadotrophins (excluding drug co-sponsored trials): OR 1.20 (CI 0.79 to 1.83) rFSH versus u-gonadotrophins (sponsored trials only): OR 1.06 (CI 0.92 to 1.21)	Sensitivity analysis showed results stability in relation to: influence of drug companies and publication bias	SR	1a

7.5 Ovulation induction in in vitro fertilisation: gonadotrophins (rFSH versus urinary-derived gonadotrophins)

Study	Population	Intervention	Outcomes	Results	Study type	EL
Alvino et al. 1995 ⁵³¹	60 women undergoing IVF	rFSH (n = 30) versus uFSH (n = 30)	Clinical pregnancy rate/cycle OHSS (n)	No significant difference: Clinical pregnancy rate/cycle: rFSH: 8/30 (27%) uFSH: 6/30 (20%) RR 1.33 (CI 0.53 to 3.38) OHSS: rFSH: 2 uFSH: 1	RCT	Ib
Hedon et al. 1995 ⁵⁴¹	90 women undergoing IVF	rFSH (n = 57) versus uFSH (n = 33)	Clinical pregnancy rate/cycle Ongoing pregnancy rate/cycle No of OHSS	No significant difference: Clinical pregnancy rate/cycle: rFSH: 20/57 (35%) uFSH: 9/33 (27.25%) RR 1.29 (CI 0.67 to 2.49) Ongoing pregnancy rate/cycle: rFSH: 17/57 (30%) uFSH: 6/33 (18%) RR 1.64 (CI 0.72 to 3.75) OHSS: rFSH:3 uFSH: 2	RCT	Ib
Out et al. 1995 ⁵⁴⁶	981 women undergoing IVF	rFSH (n = 585) versus uFSH (n = 396)	Clinical pregnancy rate/cycle Ongoing pregnancy rate/cycle OHSS (n)	No significant difference: Clinical pregnancy rate/cycle: rFSH: 171/585 (29%) uFSH: 100/396 (25%) RR 1.16 (CI 0.94 to 1.43) Ongoing pregnancy rate/cycle: rFSH: 129/585 (22%) uFSH: 72/396 (18%) RR 1.21 (CI 0.94 to 1.57) OHSS: rFSH: 19 uFSH: 8	RCT	Ib

7.5 Ovulation induction in in vitro fertilisation: gonadotrophins (rFSH versus urinary-derived gonadotrophins) (continued)

Study	Population	Intervention	Outcomes	Results	Study type	EL
RHFSG 1995 ⁵⁴⁷	123 women undergoing IVF	rFSH (n = 60) versus uFSH (n = 63)	Clinical pregnancy rate/cycle Live birth rate/cycle OHSS (n)	No significant difference: Clinical pregnancy rate/cycle: rFSH: 12/60 (20%) uFSH: 10/63 (15.8%) RR 1.26 (CI 0.59 to 2.70) Live birth rate/cycle: rFSH: 9/60 (15%) uFSH: 8/63 (12.6%) RR 1.18 (CI 0.49 to 2.86) OHSS: rFSH: 0 uFSH: 0	RCT	Ib
Bergh et al. 1997 ⁵³³	233 women undergoing IVF	rFSH (n = 119) versus uFSH (n = 114)	Clinical pregnancy rate/cycle Live birth rate/cycle OHSS (n)	No significant difference: Clinical pregnancy rate/cycle: rFSH: 53/119 (45%) uFSH: 42/114 (37%) RR 1.21 (CI 0.88 to 1.65) Live birth rate/cycle: rFSH: 40/119 (34%) uFSH: 36/114 (32%) RR 1.06 (CI 0.74 to 1.54) OHSS: rFSH: 6 uFSH: 2	RCT	Ib
Berger et al. 1999 ⁵³²	148 women (165 cycles) undergoing IVF	rFSH (n = 89) versus uFSH (n = 76)	Clinical pregnancy rate/cycle	No significant difference: Clinical pregnancy rate/cycle: rFSH: 23/89 (25.8%) uFSH: 16/76 (21%) RR 1.23 (CI 0.70 to 2.15) OHSS not reported	RCT (abstract)	Ib
Ghosh et al. 1999 ⁵³⁹	47 women undergoing IVF	rFSH (n = 22) versus uFSH (n = 25)	Clinical pregnancy rate/cycle OHSS (n)	No significant difference: Clinical pregnancy rate/cycle: rFSH: 6/22 (27%) uFSH: 5/25 (20%) RR 1.36 (CI 0.48 to 3.86) OHSS: rFSH: 0 uFSH: 2	RCT (abstract)	Ib

7.5 Ovulation induction in in vitro fertilisation: gonadotrophins (rFSH versus urinary-derived gonadotrophins) (continued)

Study	Population	Intervention	Outcomes	Results	Study type	EL
Hoomans et al. 1999 ⁵⁴²	165 women undergoing IVF	rFSH (n = 83) versus uFSH (n = 82)	Clinical pregnancy rate/cycle OHSS (n)	No significant difference: Clinical pregnancy rate/cycle: rFSH: 32/83 (38.5%) uFSH: 27/82 (33%) RR1.17 (CI 0.78 to 1.77) OHSS: rFSH: 1 uFSH: 2	RCT	Ib
Kornilov et al. 1999 ⁵⁴³	137 women undergoing IVF	rFSH (n = 28) versus uFSH (n = 109)	Clinical pregnancy rate/cycle	No significant difference: Clinical pregnancy rate/cycle: rFSH: 18/28 (64.3%) uFSH: 51/109 (46.7%) RR 1.37 (CI 0.98 to 1.93) OHSS not reported	RCT	Ib
Franco et al. 2000 (11730)	120 women undergoing IVF	rFSH (n = 60) versus uFSH (n = 60)	Clinical pregnancy rate/cycle OHSS (n)	No significant difference: Clinical pregnancy rate/cycle: rFSH: 22/60 (36.7%) uFSH: 19/60 (31.7%) RR 1.16 (CI 0.70 to 1.91) OHSS: rFSH: 0 uFSH: 0	RCT	Ib
Frydman et al. 2000 ⁵³⁷	278 women undergoing IVF	rFSH (n = 139) versus uFSH (n = 139)	Clinical pregnancy rate/cycle Ongoing pregnancy rate/cycle Live birth rate/cycle OHSS (n)	No significant difference: Clinical pregnancy rate/cycle: rFSH: 32/139 (23%) uFSH: 38/139 (27.3%) RR0.84 (CI 0.56 to 1.27) Ongoing pregnancy rate/cycle: rFSH: 25/139 (18%) uFSH: 25/139 (18%) RR 1.00 (CI 0.61 to 1.65) Live birth rate/cycle: rFSH: 36/139 (26%) uFSH: 35/139 (25.2%) RR 1.03 (CI 0.69 to 1.54) OHSS: rFSH: 7 uFSH: 3	RCT	Ib

7.5 Ovulation induction in in vitro fertilisation: gonadotrophins (rFSH versus urinary-derived gonadotrophins) (continued)

Study	Population	Intervention	Outcomes	Results	Study type	EL
Germond et al. 2000 ⁵³⁸	75 women undergoing IVF	rFSH (n = 35) versus uFSH (n = 40)	Clinical pregnancy rate/cycle	No significant difference: Clinical pregnancy rate/cycle: rFSH: 16/35 (45.7%) uFSH: 10/40 (25%) RR 1.93 (CI 0.96 to 3.49) OHSS not reported	RCT (abstract)	Ib
Lenton et al. 2000 ⁵⁴⁵	155 women undergoing IVF	rFSH (n = 80) versus uFSH (n = 75)	Clinical pregnancy rate/cycle Live birth rate/cycle OHSS (n)	No significant difference: Clinical pregnancy rate/cycle: rFSH: 27/80 (33.8%) uFSH: 24/75 (32%) RR 1.05 (CI 0.67 to 1.66) Live birth rate/cycle: rFSH: 27/80 (33.8%) uFSH: 20/75 (26.7%) RR 1.27 (CI 0.78 to 2.06) OHSS: rFSH: 7 uFSH: 6	RCT	Ib
Nardo et al. 2002 ⁵²⁹	110 women undergoing IVF	rFSH (n = 75) versus uFSH (n = 35)	Clinical pregnancy rate/cycle Live birth rate/cycle OHSS (n)	No significant difference: Clinical pregnancy rate/cycle: rFSH: 18/75 (24%) uFSH: 4/35 (11.4%) RR 2.10 (CI 0.77 to 5.74) Live birth rate/cycle: rFSH: 12/75 (16%) uFSH: 4/35 (11.4%) RR 1.40 (CI 0.49 to 4.03) OHSS: rFSH: 3 uFSH: 2	RCT	Ib

7.5 Ovulation induction in in vitro fertilisation: gonadotrophins (rFSH versus urinary-derived gonadotrophins) (continued)

Study	Population	Intervention	Outcomes	Results	Study type	EL
Schats et al. 2000 ⁵⁴⁸	496 women undergoing IVF	rFSH (n = 247) versus uFSH (n = 249)	Clinical pregnancy rate/cycle Live birth rate/cycle OHSS (n)	No significant difference: Clinical pregnancy rate/cycle: rFSH: 62/247 (25.1%) uFSH: 50/249 (20.1%) RR 1.25 (CI 0.90 to 1.74) Live birth rate/cycle: rFSH: 56/247 (22.7%) uFSH: 43/249 (17.3%) RR 1.31 (CI 0.92 to 1.87) OHSS: rFSH: 7 uFSH: 2	RCT	Ib
Gordon et al. 2001 ⁵⁴⁰	69 women undergoing IVF	rFSH (n = 39) versus uFSH (n = 30)	Clinical pregnancy rate/cycle Live birth rate/cycle	No significant difference: Clinical pregnancy rate/cycle: rFSH: 11/39 (28.2%) uFSH: 4/30 (13.3%) RR 2.12 (CI 0.75 to 5.99) Live birth rate/cycle: rFSH: 9/39 (23%) uFSH: 2/30 (6.7%) RR 3.46 (CI 0.81 to 14.85) OHSS not reported	RCT	Ib
Ng et al. 2001 ⁵⁴⁴	40 women undergoing IVF	rFSH (n = 20) versus uFSH (n = 20)	Clinical pregnancy rate/cycle	No significant difference: rFSH: 4/20 (20%) uFSH: 5/20 (25%) RR 0.80 (CI 0.25 to 2.55) OHSS not reported	RCT	Ib
Westergaard et al. 2001 ⁵⁴⁹	379 women undergoing IVF	rFSH (n = 190) versus uFSH (n = 189)	Clinical pregnancy rate/cycle Live birth rate/cycle	No significant difference: Clinical pregnancy rate/cycle: rFSH: 65/190 (34.2%) uFSH: 75/189 (39.7%) RR 0.86 (CI 0.66 to 1.21) Live birth rate/cycle: rFSH: 53/190 (28%) uFSH: 67/189 (35.5%) RR 0.79 (CI 0.58 to 1.06) OHSS not reported	RCT	Ib

7.5 Ovulation induction in in vitro fertilisation: gonadotrophins (rFSH versus urinary-derived gonadotrophins) (continued)

Study	Population	Intervention	Outcomes	Results	Study type	EL
Dickey et al. 2002 ⁵³⁴	177 women undergoing IVF	rFSH (n = 119) versus uFSH (n = 58)	Clinical pregnancy rate/cycle Ongoing pregnancy rate/cycle Live birth rate/cycle OHSS (n)	No significant difference: Clinical pregnancy rate/cycle: rFSH: 18/58 (31%) uFSH: 45/119 (27.8%) RR 0.82 (CI 0.52 to 1.28) Ongoing pregnancy rate/cycle: rFSH: 17/58 (29.3%) uFSH: 44/119 (37%) RR 0.79 (CI 0.50 to 1.26) Live birth rate/cycle: rFSH: 14/58 (24.1%) uFSH: 37/119 (31.15%) RR 0.78 (CI 0.46 to 1.32) OHSS: rFSH: 0 uFSH: 6	RCT	Ib
EISG 2002 ⁵³⁵	727 women undergoing IVF	rFSH (n = 354) versus uFSH (n = 373)	Clinical pregnancy rate/cycle Ongoing pregnancy rate/cycle OHSS (n)	No significant difference: Clinical pregnancy rate/cycle: rFSH: 76/354 (21.5%) uFSH: 95/373 (25.5%) RR0.84 (CI 0.65 to 1.10) Ongoing pregnancy rate/cycle: rFSH: 73/354 (20.6%) uFSH: 87/373 (23.3%) RR0.88 (CI 0.67 to 1.16) OHSS: rFSH: 18 uFSH: 26	RCT	Ib

7.5 Ovulation induction in in vitro fertilisation: gonadotrophins (rFSH versus urinary-derived gonadotrophins) (continued)

Study	Population	Intervention	Outcomes	Results	Study type	EL
Kilani et al. 2003 ⁵³⁰	100 women undergoing IVF	rFSH (n = 50) versus uFSH (n = 50)	Clinical pregnancy rate/cycle Live birth rate/cycle OHSS (n)	No significant difference: Clinical pregnancy rate/cycle: rFSH: 28/50 (56%) uFSH: 30/50 (60%) RR 0.93 (CI 0.67 to 1.30) Live birth rate/cycle: rFSH: 22/50 (44%) uFSH: 24/50 (48%) RR 0.92 (0.60 to 1.40) OHSS: rFSH: 1 uFSH: 2	RCT	Ib

7.6 Ovulation induction in ovulatory disorders: gonadotrophins (uFSH versus hMG)

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Nugent et al. 2002 ⁵¹³	14 RCTs (388 participants)	<p>A) FSH versus hMG (\pm concomitant GnRH-a): 7 RCTs</p> <p>B) Gonadotrophins versus gonadotrophins+GnRH-a: 2 RCTs</p> <p>C) Gonadotrophins: pulsatile versus IMI: 3 RCTs</p> <p>D) Daily versus alternate day: 1 RCT</p> <p>E) Step-up versus Standard protocol: 1 RCT</p>	<p>Ovulation rates/cycle</p> <p>Pregnancy rates/cycle</p> <p>Miscarriage rates/pregnancy</p> <p>Multiple pregnancy rates/pregnancy</p> <p>Overstimulation rates/cycle</p> <p>OHSS rates/cycle</p>	<p>A) FSH versus hMG (\pm concomitant GnRH-a):</p> <p>No significant difference:</p> <p>Ovulation rates/cycle: OR 0.75 (CI 0.52 to 1.07)</p> <p>Pregnancy rates/cycle: OR 0.89 (CI 0.53 to 1.49)</p> <p>Miscarriage rates/pregnancy: OR 0.85 (CI 0.24 to 2.95)</p> <p>Multiple pregnancy rates/pregnancy: OR 0.62 (CI 0.11 to 3.58)</p> <p>Overstimulation rates/cycle: OR 0.85 (CI 0.40 to 1.81)</p> <p>Significant reduction:</p> <p>Overstimulation rates/cycle: OR 0.33 (CI 0.16 to 0.65)</p> <p>When GnRH-a used: OR 0.84 (CI 0.26 to 2.68)</p> <p>When GnRH-a not used: OR 0.20 (CI 0.08 to 0.46)</p> <p>B) Gonadotrophins versus gonadotrophins+GnRH-a:</p> <p>No significant differences in ovulation, pregnancy, miscarriage and multiple pregnancy rates: (insufficient data)</p> <p>Significantly higher in FSH/hMG+GnRH-a:</p> <p>Overstimulation rates/cycle: OR 3.15 (CI 1.48 to 6.70)</p> <p>Non-significantly higher in FSH/hMG+GnRH-a:</p> <p>OHSS rate: OR 1.41 (CI 0.50 to 3.95)</p> <p>C) Gonadotrophins: pulsatile versus IMI:</p> <p>D) Daily versus alternate day:</p> <p>E) Step-up versus Standard protocol:</p> <p>No significant differences in ovulation, pregnancy, miscarriage, multiple pregnancy, overstimulation and OHSS rates: (insufficient data)</p>	<p>Trials generally of small to moderate sample size and poor methodological quality with insufficient information on: randomisation, allocation concealment, definitions, timing and dosage of interventions etc.</p> <p>GnRH-a used: buserelin by nasal insufflation</p>	SR	1a

7.6 Ovulation induction in ovulatory disorders: gonadotrophins (uFSH versus hMG) (continued)

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Hughes et al. 2002 ⁵⁵⁵	3 RCTs	GnRH-a/hMG/FSH versus hMG/FSH	Pregnancy rates Moderate to severe OHSS rates	No significant difference: Pregnancy rates: OR 1.50 (CI 0.72 to 3.12) Moderate to severe OHSS rates: OR 1.40 (CI 0.50 to 3.92)	Trials of small sample size and poor methodological quality with insufficient information on: allocation concealment and inclusion criteria, dose regimes and mode of administration etc.	SR	1a
Vegetti et al. 1998 ⁵⁵⁶	20 women with clomifene citrate-resistant PCOS aged 26 to 32 years; BMI < 25 kg/m ²	Pure FSH in stepwise low-dose with GnRH-a pre-treatment (n = 10) versus Pure FSH in stepwise low-dose without GnRH-a pre-treatment (n = 10)	Ovulation/woman Pregnancy/woman Cycle cancellation/woman due to multifollicular response	Significant differences: Ovulation/woman: FSH in stepwise low-dose with GnRH-a pre-treatment: 2/10 (20%) FSH in stepwise low-dose without GnRH-a pre-treatment: 9/10 (90%), RR 0.22 (CI 0.06 to 0.78) Pregnancy/woman: FSH in stepwise low-dose with GnRH-a pretreatment: 0 (0%) FSH in stepwise low-dose without GnRH-a pretreatment: 5/10 (50%) Non-significant: Cycle cancellation/woman due to multifollicular response: FSH in stepwise low-dose with GnRH-a pretreatment: 5/10 (50%) FSH in stepwise low-dose without GnRH-a pretreatment: 1/10 (10%), RR 5.00 (CI 0.7 to 35.5)	Computer-generated randomisation, allocation concealment unclear Women treated for a single cycle only Metrodin HP withdrawn (DoH 10/2/03)	RCT	1b

7.7 Ovulation induction in in vitro fertilisation: gonadotrophin-releasing hormone analogues

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Hughes et al. 1992 ⁵⁵⁷	17 RCTs (11 RCTs, 6 quasi-RCTs) 2480 cycles)	A: GnRHa protocol versus no GnRHa protocol (10 RCTs) B: Short GnRHa protocol versus long GnRha protocol (7 RCTs)	A: Clinical pregnancy rate in IVF, GIFT, ET Cancellation rate B: Clinical pregnancy rate Cancellation rate Overall miscarriage rate Multiple pregnancy rate OHSS	A: Significant increase in clinical pregnancy rates with GnRHa protocol: IVF: OR 1.80 (CI 1.33 to 2.44) GIFT: OR 2.37 (CI 1.24 to 4.51) ET: OR 1.40 (CI 1.01 to 1.95) Significant reduction in cycle cancellation rate with GnRHa protocol: OR 0.33 (CI 0.25 to 0.44) B. No significant difference: Clinical pregnancy rate: OR 0.90 (CI 0.65 to 1.23) Cancellation rate OR 1.13 (CI 0.71 to 1.80) Overall miscarriage rate OR 0.84 (CI 0.41 to 1.73) Multiple pregnancy rate OR 2.56 (CI 0.95 to 6.91) OHSS Insufficient relevant data		SR	1a
Daya 2001 ⁵⁵⁸	26 RCTs	A: Long GnRHa protocol versus short GnRHa protocol versus ultrashort GnRHa protocol B: Long GnRHa protocol versus short GnRHa protocol C: Long GnRHa protocol versus ultrashort GnRHa protocol	Clinical pregnancy rate /cycle when commenced in: follicular phase, luteal phase Clinical pregnancy rate/cycle	A. Significant increase with long GnRHa protocol: Clinical pregnancy rate/cycle: OR 1.32 (CI 1.10 to 1.57) when commenced in follicular phase: OR 1.54 (CI 1.11 to 2.13) when commenced in luteal phase: OR 1.21 (CI 0.98 to 1.51) B. Long GnRHa protocol versus short GnRHa protocol: Significant increase in clinical pregnancy rate /cycle: OR 1.27 (CI 1.04 to 1.56) C. Long GnRHa protocol versus ultrashort GnRHa protocol: Significant increase in clinical pregnancy rate /cycle: OR 1.47 (CI 1.02 to 2.12)		SR	1a

7.7 Ovulation induction in in vitro fertilisation: gonadotrophin-releasing hormone analogues (continued)

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Albuquerque et al. 2003 ⁵⁵⁹	6 RCTs (552 women)	High-dose GnRHa protocol (depot) versus low-dose GnRHa	Clinical pregnancy rate/woman Pregnancy rate/embryo transfer Ongoing/delivered pregnancy rate/cycle Multiple pregnancy rate Miscarriage rate Severe OHSS incidence	No significant difference: Clinical pregnancy rate/woman: 75/263 (28.5%) versus 88/289 (30.4%) OR 0.94 (CI 0.65 to 1.37) Pregnancy rate/embryo transfer: 75/229 (32.7%) versus 88/263 (32.5%) OR 1.01 (CI 0.69 to 1.49) Ongoing/delivered pregnancy rate/cycle: 45/195 (23%) versus 51/197 (25.8%), OR 0.85 (CI 0.54 to 1.36) Multiple pregnancy rate: 6/20 (30%) versus 8/26 (30.7%), OR 0.95 (CI 0.27 to 3.39) Miscarriage rate: 9/55 (16.3%) versus 9/60 (15%), OR 1.17 (CI 0.43 to 3.15) Severe OHSS incidence: 2/77 (2.5%) versus 3/78 (3.8%), OR 0.72 (CI 0.14 to 3.74)	Other outcomes assessed	SR	1a
Wong et al. 2001 ⁵⁶⁰	9 RCTs (1014 women)	Intranasal GnRHa protocol versus other GnRHa protocols (long, short)	Clinical pregnancy rate/embryo transfer Cycle cancellation Fertilisation rate	No significant differences: Clinical pregnancy rate /embryo transfer: 32% versus 30%, OR 0.93 (CI 0.57 to 1.51) Cycle cancellation: 5% versus 6%, OR 0.88 (CI 0.44 to 1.79) Fertilisation rate: 77% versus 72%, OR 1.04 (CI 0.94 to 1.15)		SR	1a

7.7 Ovulation induction in in vitro fertilisation: antagonists

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Al-Inany et al. 2003 ⁵⁶¹	5 RCTs (1796 participants)	Fixed protocol of GnRH antagonist versus long protocol GnRH agonist	Clinical pregnancy rate/woman Clinical pregnancy rate/oocyte retrieval Clinical pregnancy rate/embryo transfer Multiple pregnancy rate Cycle cancellation rate Spontaneous miscarriage rate Severe OHSS	Significantly lower in GnRH antagonist: Clinical pregnancy rate/woman: OR 0.79 (CI 0.63 to 0.99) Clinical pregnancy rate/oocyte retrieval: OR 0.77 (CI 0.61 to 0.96) Clinical pregnancy rate/embryo transfer: OR 0.76 (CI 0.60 to 0.97) No significant difference: Cycle cancellation rate: OR 0.74 (CI 0.48 to 1.16) Spontaneous miscarriage rate: OR 0.88 (CI 0.56 to 1.40) No significant difference: Severe OHSS OR 1.03 (CI 0.52 to 2.04) Significant reduction: Severe OHSS: OR 0.67 (CI 0.18 to 1.25)	Other outcomes included	SR	1a
Ludwig et al. 2001 ⁵⁶²	7 RCTs	GnRH antagonist protocol versus GnRH agonist (long) protocol	Clinical pregnancy rate/embryo transfer Ongoing pregnancy rate/embryo transfer OHSS rate	Significant lower in GnRH antagonists: Clinical pregnancy rate/embryo transfer: OR 0.85 (CI 0.71 to 1.02) Ongoing pregnancy rate/embryo transfer: OR 0.81 (CI 0.65 to 1.01) No significant difference: OHSS rate: OR 0.49 (CI 0.21 to 1.12)		SR	1a

7.8 Ovulation induction in ovulation disorders: adjuvant growth hormone

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Homburg et al. 1995 ⁵⁶⁹	30 women with Clomifene-resistant PCOS	GnRH-a + hMG + growth hormone (n = 15) versus GnRH-a + hMG + placebo (n = 15)	Ovulation rate Clinical pregnancy rate Miscarriage rate Live birth rate Multiple pregnancy rate OHSS rate	No significant differences Ovulation rate: Growth hormone: 14/15 (93%) Placebo: 14/15 (93%) Clinical pregnancy rate: Growth hormone: 4/15 (26%) Placebo: 3/15 (20%) Miscarriage rate: Growth hormone: 2/15 (13%) Placebo: 2/15 (13%) Live birth rate: Growth hormone: 1/15 (7%) Placebo: 2/15 (13%) Multiple pregnancy rate: GH: 1/15 (7%) Placebo: none OHSS: Growth hormone: none Placebo: none	Computer randomisation Allocation concealment and blinding unclear Other outcomes included Small sample	DBRP	Ib
Jacobs et al. 1992 ⁵⁷⁰	16 women with amenorrhoea (5 post-surgery microprolactinoma; 5 hypogonadotrophic hypogonadism, 1 Kallmann syndrome; 5 PCOS)	hMG + growth hormone (n = 8) versus hMG + placebo (n = 8)	No. of hMG ampoules used Duration of treatment Ovulation rate Pregnancy rate	No. of hMG ampoules used: significant reduction Duration of treatment: significant reduction Ovulation rate similar: Growth hormone: 7/8 (88%) Placebo: 8/8 (100%) Pregnancy rate: GH: 2/8 (25%) Placebo: 1/8 (13%)	'Blinded' randomisation Other outcomes included Small sample Supported by Novo Nordisk	RCT	Ib

7.9 Ovulation induction in ovulatory disorders: pulsatile gonadotrophin-releasing hormone (1)

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Bayram et al. 2002 ⁵⁷⁴	3 RCTs and 1 non-RCT Women with PCOS	Pulsatile GnRH versus hMG Pulsatile GnRH (after 3 weeks' pretreatment with GnRH-a) versus pulsatile GnRH only Pulsatile GnRH +FSH versus FSH only Pulsatile GnRH (after 6–10 weeks of GnRH-a) versus pulsatile GnRH (after 3–6 weeks of oral contraceptive)	Ovulation rates Pregnancy rates Multiple pregnancy rates Miscarriage rates OHSS rates	Clinical significance of results is limited due to small number and sample size of trials	Overall quality of trials was poor: very small sample, methods of randomisation and allocation concealment unclear Insufficient data; short cycles, short follow-up; pre-crossover data not available, and 1 trial funded by Ferring Co.	SR	1a–3
	12 uncontrolled case series (clomifene-resistant PCOS) 6 uncontrolled case series (unselected for clomifene resistance)	Pulsatile GnRH	Total ovulation rates/cycle Total pregnancy rates/woman Total miscarriage rates/woman	Non RCTs: Total ovulation rates/cycle: 42% Total pregnancy rates/woman: 22% Total miscarriage rates/woman: 37%	Non-RCTs Heterogeneous population		

7.9 Ovulation induction in ovulation disorders: pulsatile gonadotrophin-releasing hormone (2)

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Balen et al. 1994 ⁵⁷¹	200 anovulatory women (103 clomifene-resistant PCOS; 77 hypogonadotrophic hypogonadism; 20 weight-related amenorrhoea)	pGnRH (sc/iv/im) and gonadotrophins	Cumulative pregnancy rates Live birth rates Miscarriage rates Multiple pregnancy rates OHSS rates/cycles	After 12 cycles of treatment: Cumulative pregnancy rates: PCOS: 73.2% Hypogonadotrophic hypogonadism: 82.1% Weight-related amenorrhoea: 95% Live birth rates: PCOS: 62.4% Hypogonadotrophic hypogonadism: 65.4% Weight-related amenorrhoea: 85.3% Miscarriage rates: PCOS: 15.5% Hypogonadotrophic hypogonadism: 22.9% Weight-related amenorrhoea: 32.3% Multiple pregnancy rates significantly greater in PCOS: PCOS: 17.9% Hypogonadotrophic hypogonadism: 3.6% (CI 5.12 to 23.36) Weight-related amenorrhoea: 3.2% (CI 4.35 to 24.92) OHSS rates/cycles: PCOS: 3/603 (0.5%)	Multiple pregnancy rates fell after introduction of transvaginal ultrasound	CA RCR	3
Filicori et al. 1994 ⁵⁷³	292 anovulatory women (600 cycles) (73 PHA; 57 OHH; 39 MFO; 85 PCO; 38) OHA	pGnRH iv preceded by GnRH-a	Ovulation rates/cycle Pregnancy rates/cycle Multiple pregnancy rates Miscarriage rates OHSS rates	Ovulation rates/cycle: 75% Pregnancy rates/cycle: 23% Multiple pregnancy rates: 3.8% (none after GnRH-a) Miscarriage rates: 30% (45% in PCO) OHSS: none	PHA = primary hypogonadotrophic amenorrhoea OHH = other hypogonadotrophic hypogonadism MFO = multifollicular ovary OHA = other hyperandrogenic anovulation	CA	3

7.9 Ovulation induction in ovulation disorders: pulsatile gonadotrophin-releasing hormone (2) (continued)

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Braat et al. 1991 ⁵⁷²	48 women with normogonadotrophic and hypogonadotrophic amenorrhoea (244 cycles)	pGnRH iv	Cumulative pregnancy rates Mean pregnancy rate/cycle Multiple pregnancy rates/cycle Miscarriage rates OHSS rates	After 12 cycles of treatment: Cumulative pregnancy rates 93% Mean pregnancy rate/cycle 22.5% (CI 16.4% to 28.65) Multiple pregnancy rates/cycle 5/244 (2%) Miscarriage rates: 14.5% OHSS: none	Life-table analysis	CA RCR	3
Martin et al. 1993 ⁵⁷⁵	71 women with hypogonadotrophic amenorrhoea (229 cycles)	pGnRH iv versus hMG	Cumulative pregnancy rates Ovulation rates/cycle Multiple pregnancy rates/cycle Miscarriage rates OHSS rates	After 6 cycles of treatment: Cumulative pregnancy rates: pGnRH : 96% hMG: 72% Ovulation rates/cycle: pGnRH : 29% hMG: 25% Non-significant: Multiple pregnancy rates/cycle pGnRH: 8.3% (all twins) hMG: 14.8% (75% triplets or higher order) Miscarriage rates: pGnRH : 23.8% hMG: 16.6% OHSS: none	Life-table analysis	CH	2b

7.10 Ovulation induction in ovulation disorders: dopamine

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Webster et al. 1994 ⁵⁷⁶	495 women with prolactinaemic amenorrhoea aged 15–45 years	Cabergoline 0.5–1.0 mg twice/week (n = 223) versus bromocriptine 2.5–5 mg twice/day (n = 236)	Normalisation of prolactin Ovulation and pregnancy rate Adverse effects (dizziness, headache, nausea, fatigue, constipation)	Significant difference: Normalisation of prolactin: Cabergoline: 186/223 (83%) Bromocriptine: 138/236 (59%) RR 1.45 (CI 1.28 to 1.64) Ovulation and pregnancy rate: Cabergoline: 72% Bromocriptine: 52% Adverse effects: CAB: 151/223 (68%) Bromocriptine: 184/236 (78%) RR 0.87 (CI 0.78 to 0.97)	Computer-generated randomisation	DBRCT	Ib
Pascal-Vigneron et al. 1995 ⁵⁷⁷	118 women with prolactinaemic amenorrhoea	Cabergoline 1 mg twice/week (n = 60) versus bromocriptine 2.5 to 5 mg twice/day (n = 58)	Normalisation of prolactin Ovulation and pregnancy rate Adverse effect Gastrointestinal symptoms	Significant difference: Normalisation of prolactin: Cabergoline: 56/60 (93.3%) Bromocriptine: 27/58 (52%) RR 2.0 (CI 1.51 to 2.66) Ovulation and pregnancy rate: Cabergoline: 43/60 (71.6%) Bromocriptine: 28/58 (48.2%) RR 1.48 (CI 1.09 to 2.02) Adverse effects: Cabergoline: 32/60 (53.3%) Bromocriptine: 38/58 (65.5%) RR 0.81 (CI 0.60 to 1.10) Gastrointestinal symptoms: Cabergoline: 22/60 (36.6%) Bromocriptine: 49/58 (84.5%) RR 0.43 (CI 0.31 to 0.62)		DBRCT	Ib

7.10 Ovulation induction in ovulation disorders: bromocriptine

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Hughes et al. 2003 ⁵⁷⁸	3 RCTs (127 participants)	Bromocriptine versus placebo	Pregnancy rates/woman	No significant difference: OR 1.12 (CI 0.48 to 2.57)	Double-blind, 1 trial crossover	SR	1a

7.12 Ovulation induction agents and cancer

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Rossing et al 1994 ⁵⁰²	3837 women evaluated for infertility	<p>Comparison of rate of ovarian tumour in general population</p> <p>Comparison of rate of ovarian tumour in women who had taken clomifene citrate and women who had not taken clomifene citrate with a subcohort of 135 women as control</p> <p>Comparison of rate of ovarian tumour in women who had taken human chorionic gonadotrophin</p>	Ovarian cancer incidence (standardised incidence ratio, SIR)	<p>Borderline malignant ovarian tumour: 11 cases observed 4.4 cases expected SIR 2.5 (CI 1.3 to 4.5)</p> <p>9/11 cases of ovarian tumours had taken clomifene: adjusted RR 2.3 (CI 0.5 to 11.4) for gravid and nulligravid women</p> <p>5/9 cases of ovarian tumours had taken clomifene citrate for 12 or > 12 cycles: RR 11.1 (CI 1.5 to 82.3)</p> <p>6/11 cases of ovarian tumours had ovulation abnormalities: RR 1.8 (CI 0.5 to 6.1)</p> <p>3/11 cases of ovarian tumours in women who had taken human chorionic gonadotrophin: adjusted RR 1.0 (CI 0.2 to 4.3)</p>		CH OB	2b-3
Doyle et al. 2002 ⁵²¹	5556 women treated in fertility clinic, aged 20-40 years: Nulliparous 60% Parous 38% Unknown 2%	Comparison between ovarian stimulation (S) and no ovarian stimulation (NS)	Cancer incidence (standardised incidence ratio)	<p>Breast: S – 116 (CI 84 to 185) NS – 115 (CI 57 to 205) RR 0.95 (CI 0.47 to 1.92)</p> <p>Uterus: S – 121 (CI 25 to 353) NS – 168 (CI 4 to 937) RR 0.72 (CI 0.06 to 8.62)</p> <p>Ovary: S – 84 (CI 23 to 215) NS – 167 (CI 20 to 605) RR 0.59 (CI 0.12 to 3.00)</p> <p>Cervix: S – 41 (CI 8 to 119) NS – 0 (CI 0 to 170) RR (-)</p> <p>Others: S – 114 (CI 92 to 141) NS – 0.92 (CI 0.43 to 1.94) RR 0.92 (CI 0.43 to 1.94)</p> <p>All cancers: S – 114 (CI 92 to 141) NS – 120 (CI 78 to 178) RR 0.93 (CI 0.57 to 1.49)</p>	0.6% lost to follow-up Follow up 7.5 years after first clinic visit Limited study power due to low incidence of these rarer tumours	CH	2b

8.1 Tubal surgery

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Watson et al. 2003 ⁶³⁸	8 RCTs (547 participants): 14 non-RCTs (1623 participants)	Magnification with microscope versus Loupes Microsurgery versus macrosurgery CO ₂ laser versus electrosurgery Salpingostomy + prosthesis versus salpingostomy without prosthesis Salpingostomy techniques Fibrin sealant Open adhesiolysis versus no treatment	Pregnancy rates (total, intrauterine, term) Miscarriage Ectopic pregnancy Tubal patency Adhesions Morbidity	No significant differences in pregnancy rates: CO ₂ laser versus electrosurgery: OR 1.04 (CI 0.65 to 1.67) Laser salpingostomy versus diathermy salpingostomy: OR 1.30 (CI 0.77 to 2.19) Magnification with microscope versus Loupes: OR 0.75 (CI 0.26 to 2.15) Other outcomes from non-RCTs: insufficient data	Participants included proximal and distal tubal diseases, and reversal of sterilisation Cautious interpretation of results from non-RCTs	SR	1a
Johnson et al. 2003 ⁶³⁹	5 RCTs (588 participants)	Hydrotubation versus no hydrotubation Hydrotubation with steroids versus antibiotics versus dextran Second-look laparoscopy with adhesiolysis versus no treatment	Live birth rate Pregnancy rates Miscarriage Ectopic pregnancy Tubal patency Infections	No significant differences in pregnancy rates: Live birth rate: hydrotubation versus no hydrotubation: OR 1.12 (CI 0.57 to 2.21) Hydrotubation with steroids versus no steroids: OR 1.10 (CI 0.74 to 1.64) Hydrotubation with antibiotics versus no antibiotics: OR 0.67 (CI 0.30 to 1.47) Hydrotubation with dextran versus no dextran: OR 0.65 (CI 0.37 to 1.14) Second-look laparoscopy with adhesiolysis versus no treatment: OR 0.96 (CI 0.44 to 2.07)	Participants included tubal diseases and ovarian drilling Insufficient evidence due to underpowered studies of poor quality	SR	1a

8.2 Tubal catheterisation and cannulation

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Honore et al. 1999 ⁶⁴⁸	10 cohort studies of selective salpingography + catheterisation (482 women) 4 observational studies of hysteroscopic cannulation (133 women)	Selective salpingography + catheterisation versus hysteroscopic cannulation for proximal tubal obstruction	Pregnancy rates	Significant association Selective salpingography + catheterisation: 103/482 (21%) Hysteroscopic cannulation: 65/133 (49%), OR 3.52 (CI 2.30 to 5.37)	No untreated group Spontaneous pregnancy rate not known	SR	2b-3

8.3 Uterine surgery: leiomyoma

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Seracchioli et al. 2000 ⁶⁵⁵	131 women with at least one large myoma	laparoscopic (n = 56) versus abdominal (n = 59) myomectomy	Pregnancy rate Miscarriage rate Ectopic pregnancy Live births Preterm delivery rate Postoperative outcomes: drop in Hb, fever, hospital stay	No significant differences Pregnancy rate: Laparoscopic: 30/56 (54%) Abdominal: 33/59 (56%) Miscarriage rate: Laparoscopic: 6/30 (20%) Abdominal: 4/33 (12%) Ectopic pregnancy: Laparoscopic: 1 Abdominal: 0 Live births: Laparoscopic: 20 Abdominal: 27 Preterm delivery rate: Laparoscopic: 1/20 (5%) Abdominal: 2/27 (7%) Postoperative outcomes significantly higher in abdominal group	Randomisation by use of total random digits 12 months of follow-up	RCT	Ib

9.1 Medical treatment: endometriosis

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Hughes et al. 2001 ⁶⁶⁶	16 RCTs (participants with endometriosis of all AFS stages)	Danazol versus medroxyprogesterone versus gonadorelin analogues versus placebo versus no treatment	Clinical pregnancy rates	No significant difference: Ovulation suppression agents versus placebo /no treatment OR 0.83 (CI 0.5 to 1.39) All agents versus danazol OR 1.20 (CI 0.85 to 1.68)	Other outcomes assessed	SR	1a
Harrison et al. 2000 ⁶⁶⁷	96 infertile women with laparoscopy-confirmed endometriosis	MPA for 3 months (n = 48) versus placebo (n = 48)	Pregnancy rates	No significant difference: Medroxyprogesterone: 0/48 (0%) Placebo: 3/48 (6%)	Other outcomes assessed	RCT	1b

9.1 Medical treatment: unexplained infertility

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Hughes et al. 2003 ⁶⁷⁰	2 RCTs (68 participants with unexplained infertility)	Danazol 200mg daily versus placebo	Pregnancy rates	No significant benefit: OR 2.57 (CI 0.53 to 12.46)	Small sample size, underpowered One pregnancy excluded in placebo group in 1 RCT	SR	1a

9.2 Surgical treatment: endometriosis

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Jacobson et al. 2002 ⁶⁷¹	2 RCTs (444 participants with minimal and mild endometriosis)	Laparoscopic ablation/resection versus Diagnostic laparoscopy	Ongoing pregnancy and live birth rate	Significant increase with surgery: OR 1.64 (CI 1.05 to 2.57)	The larger trial showed significant effect but not the smaller trial	SR	1a

9.2 Post-surgery medical treatment: endometriosis

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Parazzini et al. 1994 ⁶⁸³	75 patients with unexplained infertility and stage 3 or 4 endometriosis	Post-laparotomy nasal nafarelin (n = 36) versus placebo nasal spray (n = 39)	Pregnancy rates (within a year)	Non-significant difference: Nafarelin spray: 7/36 (19%) Placebo spray: 7/39 (18%) OR 1.10 (CI 0.30 to 4.07)	Computer-generated randomisation, blinded to patients and investigators Other outcomes assessed Clinical heterogeneity	RCT	Ib
Vercellini et al. 1999 ⁶⁸⁰	267 women with mild to severe endometriosis	Post-surgery s/c goserelin depot (n = 133) versus expectant management (n = 134)	Pregnancy rates	Non-significant difference: OR 0.58 (CI 0.23 to 1.48)	Centralised treatment allocation with computer-generated randomisation Non-blind Other outcomes assessed 152 women desired pregnancy	RCT	Ib
Bianchi et al. 1999 ⁶⁸²	77 women with stage 3 to 4 endometriosis	Post-surgery danazol (n = 36) versus expectant management (n = 41)	Pregnancy rates	Non-significant difference: Danazol: 6/11 (55%) Expectant management: 8/16 (50%) OR 1.20 (CI 0.20 to 7.38)	Computer-generated randomisation Non-blind 27 women desired pregnancy	RCT	Ib
Busacca et al. 2001 ⁶⁸¹	89 women with stage 3 to 4 endometriosis	Post-laparoscopy GnRHa depot (n = 44) versus expectant management (n = 45)	Pregnancy rates Cumulative pregnancy rate (at 18 months)	Non-significant difference: GnRHa depot: 5/15 (33%) Expectant management: 6/15 (40%) OR 0.83 (CI 0.32 to 2.15)	Computer-generated randomisation Non-blind 30 women desired pregnancy	RCT	Ib

9.2 Surgical treatment: ovarian endometrioma

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Beretta et al. 1998 ⁶⁷⁵	64 women with advanced stages of endometriosis	Laparoscopic cystectomy (n = 32) versus laparoscopic drainage and coagulation (n = 32)	Pregnancy rates	Significant benefit with cystectomy: Cystectomy: 6/9 (67%) Drainage/coagulation: 4/17 (24%) OR 2.83 (CI 1.01 to 7.50)	Computer-generated randomisation Blinding unclear Other outcomes assessed	RCT	Ib

10 Intrauterine insemination: male infertility

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Ford et al. 1997 ⁶⁸⁴	10 RCTs (2082 cycles in couples with male infertility)	Unstimulated or stimulated IUI versus ICI/natural timed intercourse	Pregnancy rate/cycle	Significant differences: IUI: 70/1073 (6.5%) ICI/natural timed intercourse: 31/1009 (3.1%) R 2.20 (CI 1.43 to 3.39)	Ovarian stimulation with gonadotrophins	SR	1a
Cohlen et al. 2003 ⁶⁸⁵	17 RCTs (3755 cycles in couples with male infertility)	Unstimulated or stimulated IUI versus natural timed intercourse	Pregnancy rate/cycle	Significant differences: Unstimulated OR 2.5 (CI 1.6 to 3.9) Stimulated OR 2.2 (CI 1.4 to 3.6) No significant difference: Stimulated IUI versus unstimulated IUI OR 1.8 (CI 0.98 to 3.3)	Clinical heterogeneity Ovarian stimulation with clomifene citrate and gonadotrophins	SR	1a
Goverde et al. 2000 ⁶⁸⁶	258 couples with idiopathic (n = 181) or male subfertility (n = 77)	6 cycles each of unstimulated IUI (n = 86; 338 cycles) versus stimulated IUI (n = 85; 355 cycles) versus IVF (n = 87; 270 cycles)	Pregnancy rate/cycle Multiple pregnancy rate	No significant difference: Pregnancy rate/cycle: IUI alone: 25/338 (7.4%) Stimulated IUI: 31/355 (8.7%) IVF: 33/270 (12.2%) Multiple pregnancy rate: IUI alone: 4% (1 twin) Stimulated IUI: 29% (9 twins) IVF: 21% (1 triplets, 6 twins)	No of embryo transferred: Maximum of 2 in women aged ≤ 35 years Maximum of 3 in women > 35 years	RCT	1b
Zreik et al. 1999 ⁶⁸⁷	54 couples (141 cycles) with male factor, anovulation and unexplained infertility Male factor (n = 7)	hCG-timed IUI (n = 27) versus LH-timed IUI (n = 25)	Clinical pregnancy rate/cycle	No significant difference: hCG-timed IUI: 3/71 (4.23%) LH-timed IUI: 3/70 (4.3%) RR 1.01 (CI 0.21 to 4.86) In 7 couples with male factor: hCG-timed IUI: 12.5% LH-timed IUI: 0%	Computer-generated randomisation Clinical heterogeneity Ovarian stimulation with clomifene citrate Cross-over trial	RCT	1b

10 Intrauterine insemination: endometriosis

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Tummon et al. 1997 ⁶⁹⁸	103 women (311 cycles) with minimal/mild endometriosis	FSH + IUI (n = 53; 127 cycles) versus no treatment (n = 50; 184 cycles)	Live birth rates/woman Multiple pregnancy rate/woman OHSS	Significant difference: Live birth rates/woman: FSH +IUI 14/53 (26%) no treatment 4/50 (8%) RR 3.3 (CI 1.2 to 9.4) NNT 6 (CI 3 to 28) Multiple pregnancy rate/woman: 3/14 (21%) 2 twins 1 triplet OHSS: none reported	Randomisation by random numbers concealed in sealed opaque envelopes No crossover	RCT	Ib
Fedele et al. 1992 ⁶⁹⁹	49 women with stage I & 2 endometriosis	Buserelin or hMG or hCG +IUI x 3 cycles (n = 24) versus expectant treatment (n = 25)	Live birth rates/woman Multiple pregnancy rate Miscarriages OHSS	No significant difference: Live birth rates/woman: Buserelin or hCG or hMG 7/24 (29%) expectant treatment 5/25 (20%) RR 1.5 (CI 0.5 to 4.0) Multiple pregnancy rate: 3/9 (33.3%) 2 twins 1 quadruplets 1 miscarriage in each group OHSS: 5 cases	Randomisation according to randomisation list – unclear Small sample	RCT	Ib

10 Intrauterine insemination: endometriosis (continued)

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Nulsen et al. 1993 ⁷⁰⁰	119 couples with male factor (n = 20), unexplained (n = 21) and endometriosis-related infertility (n = 57) and other (n = 21)	hMG +IUI (n = 58) versus LH-timed IUI (n = 61) on an alternating basis For endometriosis patients: hMG +IUI (n = 127 cycles) versus LH-timed IUI (n = 96 cycles) on an alternating basis	Pregnancy rate Multiple pregnancy Miscarriage rate OHSS Pregnancy rate/cycle	Significant higher in hMG group Pregnancy rate: hMG + IUI 11/58 (19%) IUI 0/61 (0%) NNT 5 (CI 4 to 14) Multiple pregnancy: hMG +IUI 18.2% (all twins) Miscarriage rate: hMG +IUI 24.2% OHSS: none reported Pregnancy rate/cycle: hMG +IUI 15/127 (11.8%) IUI 2/96 (2.1%) RR 5.1 (CI 1.1 to 22.5)	Method of randomisation unclear	RCT	Ib

10 Intrauterine insemination in unexplained infertility: oral or injectable ovulation induction agents

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Athallah et al. 2003 ⁶⁹³	5 RCTs (231 couples with unexplained infertility) 4 parallel design; 1 crossover	Oral ovulation induction agents (anti-oestrogens) versus injectable ovulation induction agents (gonadotrophins) Clomifene citrate versus hMG (3 trials) Clomifene citrate versus urinary gonadotrophins (1 trial) Clomifene citrate versus rFSH (1 trial)	Live births/couple excluding co-intervention trials Live births/couple including co-intervention trials Pregnancy rates/couple: excluding co-intervention trials; including co-intervention trials Miscarriage: excluding co-intervention trials; including co-intervention trials Multiple birth: excluding co-intervention trials; including co-intervention trials OHSS Cycle cancellation	No significant differences: Live births/couple excluding co-intervention trials: OR 0.06 (CI 0.00 to 1.15) Live births/couple including co-intervention trials: OR 0.40 (CI 0.15 to 1.08) Pregnancy rates/couple: excluding co-intervention trials: OR 0.33 (CI 0.09 to 1.20) Significant reduction with oral agents: Pregnancy rates/couple including co-intervention trials: OR 0.41 (CI 0.17 to 0.80) Miscarriage: excluding co-intervention trials: OR 0.11 (CI 0.00 to 2.84) Miscarriage including co-intervention trials: OR 0.61 (CI 0.09 to 4.01) Multiple birth: excluding co-intervention trials not reported No significant difference: Multiple birth including co-intervention trials: OR 1.08 (CI 0.16 to 7.03) OHSS not reported Cycle cancellation not reported	Co-intervention with hCG triggers in 3 trials Insufficient power due to small sample size of trials reviewed	SR	1a

10 Intrauterine insemination in unexplained infertility: fallopian sperm perfusion

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Trout et al. 1999 ³⁹⁷	5 RCTs (610 cycles) Patients with unexplained infertility	FSP versus IUI (after undergoing ovarian stimulation with clomifene citrate + gonadotrophins or gonadotrophins only)	Pregnancy rates/cycle	Significant improvement in FSP group diagnosed with unexplained infertility: OR 1.9 (CI 1.2 to 3)	Patients with different diagnosis of infertility included	MA	1a
Sadek et al. 1998 ⁷⁰⁴	96 patients with different causes of infertility (100 cycles) (32 patients with unexplained infertility)	FSP (n = 50 cycles) versus IUI (n = 50 cycles) (after undergoing ovarian stimulation with clomifene citrate + gonadotrophins or gonadotrophins only)	Pregnancy rates/cycle Deliveries Twins/cycle Triplets/cycle Abortions/cycle	No significant differences in unexplained infertility: Pregnancy rates/cycle: FSP: 25% IUI: 3/14 (21.4%) No significant differences in all groups Pregnancy rates/cycle: FSP: 8/50 (16%) IUI: 6/50 (18%) Deliveries: FSP: 7/8 (87.5%) IUI: 8/9 (88.9%) Twins/cycle: FSP: 1/8 (12.5%) IUI: 2/9 (22.2%) Triplets/cycle: FSP: 1/8 (12.5%) IUI: 0 (0%) Abortions/cycle: FSP: 1/8 (12.5%) IUI: 1/9 (11.1%)	Block randomisation Patients with different diagnosis of infertility included	RCT	1b

10 Intrauterine insemination in unexplained infertility: fallopian sperm perfusion (continued)

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Ricci et al. 2001 ⁷⁰³	65 women with unexplained infertility undergoing COH (132 cycles)	FSP (n = 66 cycles) versus IUI (n = 66 cycles)	Ongoing pregnancy rate/woman Ongoing pregnancy rate/cycle Miscarriage Ectopic pregnancy Twins Triplets	Significant improvement with FSP Ongoing pregnancy rate/woman: FSP: 14/33 (42.4%) IUI: 5/32 (15.6%) RR 2.72 (CI 1.11 to 6.66) Ongoing pregnancy rate/cycle: FSP: 14/66 (21.2%) IUI: 5/66 (7.6%) RR 2.80 (CI 1.07 to 7.33) Non-significant differences: Miscarriage: FSP: 1/16 (6.3%) IUI: 1/6 (16.6%) Ectopic pregnancy: FSP: 1/16 (6.3%) IUI: 0/6 (0%) Twins: FSP: 2/16 (12.5%) IUI: 1/6 (16.7%) Triplets: FSP: 1/16 (6.3%) IUI: 0/6 (0%)	Randomisation by random number generator	RCT	Ib

10 Intrauterine insemination in unexplained infertility: fallopian sperm perfusion (continued)

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Soliman et al. 1999 ⁷⁰⁵	38 women with unexplained infertility undergoing COH (118 cycles)	FSP with 4 ml sperm suspension (n = 36 cycles) versus FSP using FAST system (n = 32 cycles) versus IUI + FSP with 1 ml sperm suspension (n = 50 cycles)	Pregnancy rate /cycle Abortion Multiple pregnancy OHSS per cycle	<p>Significant difference:</p> <p>Pregnancy rate /cycle: FSP with 4 ml sperm suspension: 14/36 (39%) FSP using FAST system: 13/32 (41%) IUI + FSP with 1 ml sperm suspension: 9/50 (18%) RR 2.21 (CI 1.14 to 4.27)</p> <p>No significant differences:</p> <p>Abortion: FSP with 4 ml sperm suspension: 1/14 (7%) FSP using FAST system: 2/13 (15%) IUI + FSP with 1 ml sperm suspension: 1/9 (11%)</p> <p>Multiple pregnancy: FSP with 4 ml sperm suspension: 4/14 (28%) FSP using FAST system 4/13 (31%) IUI + FSP with 1 ml sperm suspension: 1/9 (11%)</p> <p>OHSS per cycle: FSP with 4 ml sperm suspension: 1/36 (2.7%) FSP using FAST system: 0/32 (0%) IUI + FSP with 1 ml sperm suspension: 1/50 (2%)</p>	<p>Randomisation by random number generator</p> <p>No significant difference between FSP with 4 ml sperm and FSP using FAST</p> <p>Single blind (patient)</p>	RCT	Ib

10 Intrauterine insemination in unexplained infertility: gonadotrophins

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Hughes 1997 ⁶⁹¹	22 RCTs (5214 cycles) Women with unexplained infertility	FSH/IUI versus FSH/timed intercourse (8 RCTs)	Pregnancy rate	Significant improvement with FSH/IUI: OR 2.37 (CI 1.43 to 3.90) FSH: OR 2.35 (CI 1.87 to 2.94) IUI: OR 2.82 (CI 2.18 TO 3.66) Male factor: OR 0.48 (CI 0.37 to 0.61) Endometriosis: OR 0.45 (CI 0.27 to 0.76)	Clinical heterogeneity	SR	1a
Zeyneloglu et al. 1998 ⁶⁹⁰	7 RCTs (431 cycles) Women with unexplained infertility	Gonadotrophins/IUI versus gonadotrophins only	Pregnancy rate	Significant improvement with gonadotrophins/IUI: OR 1.84 (CI 1.30 to 2.62)		SR	1a
Ford et al. 1997 ⁶⁸⁴	7 RCTs (934 cycles) Women with unexplained infertility	IUI versus timed intercourse versus ICI +gonadotrophins (4 trials) +CC (2 trials) + no stimulation (3 trials)	Pregnancy rate	No significant differences overall: OR 1.5 (CI 1.0 to 2.2) Significant improvement with gonadotrophins in IUI/Timed intercourse/ICI: RR 2.17 (CI 1.10 to 4.28; NTT 11 CI 7 to 58)		SR	1a

10 Intrauterine insemination in unexplained infertility: gonadotrophins (continued)

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Guzick et al. 1999 ^{68b}	932 couples with unexplained infertility (4676 cycles) Similar baseline characteristics	IUI + FSH (n = 231) versus IUI (n = 234) versus ICI + FSH (n = 234) versus ICI (n = 233)	Pregnancy rate/cycle Live births Miscarriage Ectopic pregnancy Multiple pregnancies: quadruplets, triplets, twins OHSS Cycle cancellation	Significant differences: Pregnancy rate/cycle: IUI + FSH: 56/618 (33%) IUI: 35/717 (18%) ICI + FSH: 26/637 (19%) ICI: 14/706 (10%) OR 3.2 (CI 2.0 to 5.3) (IUI+FSH versus ICI) Live births: OR 1.7 (CI 1.2 to 2.6) (IUI+FSH versus IUI) Miscarriage: IUI: 28; IUI+FSH: 41 ICI: 17; ICI+FSH: 31 Ectopic pregnancy: IUI: 6; IUI+FSH: 22 ICI: 4; ICI+FSH: 5 Multiple pregnancies: IUI: 2; IUI+FSH: 4 ICI: 0; ICI+FSH: 1 Quadruplets: IUI+FSH: 2 ICI+FSH: 1 Triplets: IUI+FSH: 3 ICI+FSH: 1 Twins: IUI+FSH/ICI+FSH: 17/18 OHSS: IUI+FSH/ICI+FSH: 6 Cycle cancellation: IUI: 98; ICI: 119 IUI+FSH: 32; ICI+FSH: 43	Randomisation using a permuted-block procedure, stratified according to centre Pregnancy confirmed by hCG levels Follow-up for 4 cycles	RCT	Ib

10 Intrauterine insemination in unexplained infertility: gonadotrophins (continued)

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Sengoku et al. 1999 ⁶⁹⁴	97 couples with unexplained infertility	IUI + Conventional FSH (n = 48) versus IUI + low dose, step-up FSH (n = 49)	Pregnancy rate/woman Miscarriage rate Multiple pregnancy OHSS/woman	No significant difference: Pregnancy rate/woman: RR 1.02 (CI 0.39 to 2.69) Miscarriage rate: RR 1.0 (CI 0.08 to 13.02) Multiple pregnancy: RR 2.0 (CI 0.23 to 17.34) Significant difference in conventional FSH+IUI: OHSS/woman: RR 3.32 (CI 1.16 to 9.56)	Randomisation by random numbers in sealed opaque envelopes Pregnancy confirmed by gestational sac on ultrasound Evaluation of first cycle	RCT	Ib
Sengoku et al. 1994 ⁶⁹⁶	91 couples with unexplained infertility	IUI + hMG (n = 45; 62 cycles) versus IUI + hMG/GnRHa (n = 46; 69 cycles)	Pregnancy rate/cycle Miscarriage rate Multiple pregnancy OHSS/woman Cycle cancellation	No significant difference: Pregnancy rate/cycle: IUI + hMG: 11.3% IUI + hMG/GnRHa: 13% RR 0.87 (CI 0.34 to 2.19) Miscarriage rate, multiple pregnancy, OHSS/woman not reported Cycle cancellation: none	Method of randomisation unclear Pregnancy confirmed by gestational sac on ultrasound Evaluation of first cycle	RCT	Ib
Hughes et al. 1998 ⁶⁹⁵	63 women with unexplained infertility (89%), endometriosis (6%), tubal factors (5%)	3 low-dose FSH: FSH 2 ampoules versus FSH 4 ampoules versus FSH 6 ampoules	Ovulation rate/cycle Pregnancy rate/cycle OHSS/woman Cycle cancellation Overall fecundity rate	No significant difference: Ovulation rate/cycle: FSH x 2 ampoules: 82% FSH x 4 ampoules: 81% FSH x 6 ampoules: 79% Pregnancy rate/cycle: FSH x 2 ampoules: 5.4% FSH x 4 ampoules: 0% FSH x 6 ampoules: 0% OHSS/woman: none Cycle cancellation: none Overall fecundity rate 1.8%	Computer-generated randomisation via numbered opaque envelopes Ovulation confirmed by serum progesterone levels 7 days post-hCG	RCT	Ib
Cantineau et al. 2003 ⁷⁰¹	3 RCTs (386 participants, 580 cycles)	Single IUI versus double IUI (following ovarian stimulation)	Pregnancy rate/cycle	No significant difference: OR 1.45 (CI 0.78 to 2.70)	Patients with different diagnosis of infertility including unexplained infertility	SR	1a

10 In vitro fertilisation: unexplained infertility

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Pandian et al. 2003 ⁶⁹⁷	5 RCTs	IVF versus expectant management (1 trial) IVF versus IUI (1 trial) IVF versus IUI + ovarian stimulation (1 trial) IVF versus GIFT (2 trials)	Pregnancy rate/woman Live birth rate/woman Multiple pregnancy rate/woman OHSS/woman Clinical pregnancy rate	No significant differences: Pregnancy rate/woman: IVF versus expectant management: OR 0.30 (CI 0.02 to 3.67) Live birth rate/woman: IVF versus IUI: OR 1.96 (CI 0.88 to 4.36) Live births rate/woman: IVF versus IUI + ovarian stimulation: OR 1.15 (CI 0.55 to 2.42) IVF versus IUI no ovarian stimulation: OR 1.96 (CI 0.88 to 4.4) Multiple pregnancy rate/woman: OR 0.63 (CI 0.27 to 1.47) OHSS/woman: OR 1.53 (CI 0.25 to 9.49) Clinical pregnancy rate/woman: IVF versus GIFT: OR 0.24 (CI 1.08 to 4.22) Multiple pregnancy rate/woman: OR 6.25 (CI 1.70 to 23) OHSS: OR 0.39 (CI 0.02 to 9.87)	Clinical heterogeneity Trials reviewed of poor design, underpowered and using different definitions of unexplained infertility	SR	1a

11.1 In vitro fertilisation: selected diagnosis of infertility

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Jarrell et al. 1993 ⁷¹³	399 women with infertility	Immediate IVF (n = 205 couples) versus delayed IVF (n = 194 couples)	Clinical pregnancy rate Live births	Significant difference: Clinical pregnancy rate: IVF: 33/190 (17%) No IVF: 13/163 (8%) RR 2.43 (CI 1.18 to 5.07) Live births: IVF: 22/190 (12%) No IVF: 8/163 (5%) RR 2.36 (CI 1.03 to 5.66)	Randomisation using random number table Intention-to-treat Withdrawal: IVF: 45/205 (22%) No IVF: 61/194 (31%) Dropout: IVF: 15 No IVF: 31	RCT	Ib
Soliman et al. 1995 ⁷¹⁴	245 couples with all causes of infertility	1 cycle of IVF treatment (n = 127) versus 6-months' wait before IVF treatment (n = 118)	Clinical pregnancy rate Live births	No significant difference: Clinical pregnancy rate: Immediate IVF: 13/127 (10%) Delayed IVF: 8/118 (7%) *RR 1.51 (CI 0.65 to 3.51) Live births: Immediate IVF: 12/127 (9%) Delayed IVF: 6/118 (5%) *RR 1.86 (CI 0.72 to 4.79)	* Intention-to-treat analysis	RCT	Ib
Hughes et al. 2002 ⁷¹²	139 couples with persistent subfertility (at least one patent fallopian tube)	1 cycle of IVF treatment (n = 68) versus 3-months wait before IVF treatment (n = 71)	Live birth rate	Significant difference: IVF: 20/68 (29.4%) Delayed IVF: 1/71 (1.4%)	Mean no of embryos transferred = 2	RCT (abstract)	Ib
Barnhart et al. 2002 ⁷¹⁷	22 non-RCTs (6760 IVF cycles)	IVF in women with endometriosis (n = 2377 IVF cycles) versus IVF in women without endometriosis (n = 4383 IVF cycles)	No. of oocytes retrieved Fertilisation rate Implantation rate Pregnancy rates Multiple pregnancy rate Miscarriage rate	Significant decrease: No. of oocytes retrieved (adjusted OR): 0.92 (CI 0.85 to 0.99) Fertilisation rate: 0.87 (CI 0.85 to 0.88) Implantation rate: 0.86 (CI 0.85 to 0.88) Pregnancy rates: 0.63 (CI 0.51 to 0.77) Multiple pregnancy rate: no data Miscarriage rate: no data		SR	2a

11.1 Surgical treatment prior to in vitro fertilisation: hydrosalpinges

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Johnson et al. 2003 ⁷³⁴	3 RCTs (295 participants with hydrosalpinges) 5 non-RCTs	Surgical treatment (uni- or bilateral laparoscopic salpingectomy and selective salpingostomy-salpingectomy) versus non-surgical management Aspiration of hydrosalpinges, proximal tube cauterly versus no treatment	Live birth + ongoing pregnancy Pregnancy Ectopic pregnancy Miscarriage/pregnancy Treatment complications Implantation/embryo transferred Pregnancy rates	Significant differences: Live birth + ongoing pregnancy: OR 2.13 (CI 1.24 to 3.65) Pregnancy: OR 1.75 (CI 1.07 to 2.86) No significant differences: Ectopic pregnancy: OR 0.42 (CI 0.08 to 2.14) Miscarriage/pregnancy: OR 0.49 (CI 0.16 to 1.52) Treatment complications: OR 5.80 (CI 0.35 to 96.79) Implantation/embryo transferred: OR 1.34 (CI 0.87 to 2.05) Significant increase in pregnancy rates: Aspiration of hydrosalpinges (3 studies) Laparoscopic salpingectomy or tubal cauterly (1 study) No significant difference in pregnancy rates: aspiration of hydrosalpinges (1 study)	Different surgical techniques used Cautious interpretation of results from non-RCTs	SR	1a

11.3 Embryo transfer (ET): number of embryo transfer

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Gerris et al. 1999 ⁷⁸⁸	53 women undergoing fresh IVF/ICSI cycles	1 ET (n = 26) versus 2 ET (n = 27) in a single cycle of treatment	Clinical pregnancy rate/cycle Ongoing pregnancy rate/cycle Multiple pregnancy	Significant difference: Clinical pregnancy rate/cycle: 1 ET: 14/26 (53.8%) 2 ET: 21/27 (77.7%) Ongoing pregnancy rate/cycle: 1 ET: 10/26 (38.4%) 2 ET: 20/27 (74.1%) RR 1.75 (CI 1.06 to 2.89) Multiple pregnancy: 1 ET: 1/10 (10%) 2 ET: 6/20 (30%)	Small sample size Inclusion criteria: age limit, embryo quality	RCT	Ib
Martikainen et al. 2001 ⁷⁹⁰	144 women undergoing IVF/ICSI	1 ET (n = 74) versus 2 ET (n = 70) in a single cycle of treatment	Clinical pregnancy Live birth Multiple pregnancy	No significant difference: Clinical pregnancy: 1 ET: 24/74 (32.4%) 2 ET: 33/70 (47.1%) Live birth: 1 ET: 22/24 (92%) 2 ET: 28/33 (85%) Significant difference: Multiple pregnancy: 1 ET: 1/22 (5%) 2 ET: 11/28 (39%)	Small sample size Inclusion criteria: age limit, embryo quality	RCT	Ib
Lukassen et al. 2002 ⁷⁸⁹	74 women undergoing 1st IVF/ICSI	2 cycles of 1 ET (n = 22) versus 1 cycle of 2 ET (n = 21)	Clinical pregnancy/cycle Multiple pregnancy	No significant difference: Clinical pregnancy/cycle: 1 ET: 6/22 (27.3%) after 1 cycle; 8/22 (36.4%) after 2 cycles 2 ET: 6/21 (28.6%) after 1 cycle Multiple pregnancy: 1 ET: 0/22 2 ET: 2/21	Small sample size Inclusion criteria: age limit, embryo quality Results of 43 cycles available	RCT (abstract)	Ib

11.3 Embryo transfer (ET): number of embryo transfer (continued)

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Vauthier-Brouzes 1994 ⁷⁹²	56 couples undergoing IVF	2 ET (n = 28) versus 4 ET (n = 28)	Clinical pregnancy/cycle Live birth Multiple pregnancy	No significant difference: Clinical pregnancy/cycle: 2 ET: 15/28 (53.5%) 4 ET: 17/28 (60.7%) OR 1.34 (CI 0.46 to 3.87) Live birth: 2 ET: 9/28 (32%) 4 ET: 15/28 (53.5%) OR 2.88 (CI 0.95 to 8.72) Multiple pregnancy: 2 ET: 3/28 (11%) 4 ET: 6/28 (21.4%) OR 2.27 (CI 0.51 to 10.18)	Small sample size	RCT	1b
Staessen et al. 1993 ⁷⁹¹	183 women undergoing 1st IVF Good prognosis women undergoing IVF Age < 37 years, first attempt, good-quality embryos	2 ET (n = 80) versus 3 ET (n = 103)	Ongoing pregnancy rate Multiple pregnancy	No significant difference: Ongoing pregnancy rate: 2ET: 30/80 (37.5%) 3ET: 43/103 (41.7%) OR 1.26 (CI 0.70 to 2.26) Multiple pregnancy: 2ET: 8/80 (10%) 3ET: 21/103 (20.3%) OR 2.17 (CI 0.98 to 4.82)		CSNR	2a

11.6 In vitro fertilisation: effect of alcohol

Study	Population	Outcomes	Results	Comments	Study type	EL
Klonoff-Cohen et al. 2003 ⁸⁰⁰	221 couples with female infertility undergoing IVF or GIFT Women drinkers: 20–40% Men drinkers: 40–60%	Pregnancy rates	Significant increase in risk of not achieving pregnancy Adjusted RR 2.86 (CI 0.99 to 8.24)	Other outcomes included 1 glass of alcoholic beverage = 12 g alcohol	QS	3

11.6 In vitro fertilisation: effect of smoking

Study	Population	Outcomes	Results	Comments	Study type	EL
Klonoff-Cohen et al. 2001 ⁸⁰¹	221 couples undergoing IVF or GIFT Couples never smoked: 22% Couples had smoked: 62%	Pregnancy rate Live birth	Significant risk of not achieving a pregnancy Pregnancy rate women smokers versus non-smokers: adjusted risk 2.71 (CI 1.37 to 5.35) Live birth adjusted risk 2.51 (CI 1.11 to 5.67) Pregnancy rate couples (female or male or both) who smoke versus non-smokers: adjusted risk 2.41 (CI 1.07 to 5.45) Live birth adjusted risk 3.76 (CI 1.40 to 10.03)	Other outcomes included	CH	2b
Feichtinger et al. 1997 ⁸⁰²	8 cohort studies (541 patients; 2314 IVF cycles) Smokers: 690 cycles Non-smokers: 1624 cycles	Pregnancy rate	Significant success in achieving a pregnancy: Non-smokers versus smokers RR 1.79 (CI 1.24 to 2.59)		MA	2b
Zitzmann et al. 2003 ⁸⁰⁵	301 couples undergoing IVF/ICSI (425 cycles) Male smokers: 139 Women smokers: 77	Clinical pregnancy rate	Significant difference: Smokers versus male non-smokers: OR 2.95 (CI 1.32 to 6.59)		CH	2b

11.6 In vitro fertilisation: effect of caffeine

Study	Population	Outcomes	Results	Comments	Study type	EL
Klonoff-Cohen et al. 2002 ⁸⁰⁶	221 couples undergoing IVF or GIFT Mean female caffeine consumption: 106 mg/day in 94% of women Mean male caffeine consumption: 192 mg/day in 88% of men	Live birth rate	Significant association: Caffeine consumption of 0–2 mg/day versus > 2–50 and 50 mg/day adjusted OR 3.1 (CI 1.1 to 9.7)	Other outcomes included One cup of coffee = 100 mg caffeine One cup of tea = 50 mg caffeine	QS	3

11.6 In vitro fertilisation: effect of body weight

Study	Population	Outcomes	Results	Comments	Study type	EL
Wittemer et al. 2000 ⁸⁰⁹	398 couples undergoing IVF/ICSI 236 couples IVF 162 couples ICSI BMI < 20 (n = 77) BMI ≥ 20 < 25 (n = 178) BMI ≥ 25 (n = 70)	Pregnancy rate/cycle Delivery rate/cycle Miscarriage rate/pregnancy Ectopic pregnancy (n)	Significant difference: Pregnancy rate/cycle: BMI < 20: 26% BMI ≥ 20 < 25: 22.5% BMI ≥ 25: 28.6% Delivery rate/cycle: BMI < 20: 20.8% BMI ≥ 20 < 25: 15.2% BMI ≥ 25: 14.3% Miscarriage rate/pregnancy: BMI < 20: 15% BMI ≥ 20 < 25: 27.5% BMI ≥ 25: 35% Ectopic pregnancy: BMI < 20: 1 BMI ≥ 20 < 25: 2 BMI ≥ 25: 3	Long GnRHa protocol used in 332 women Short GnRHa protocol in 50 women No GnRHa protocol in 16 women	CH	2b
Boone 2003 ⁸¹⁰	372 women undergoing IVF (465 IVF cycles) BMI < 20 (underweight) n = 45 cycles BMI 20 ≥ 27.9 (normal weight) n = 315 cycles BMI ≥ 28 (obese) n = 105 cycles	Clinical pregnancy rate	Significant difference: BMI < 20: 35.6% BMI 20 ≥ 27.9: 52.1% BMI ≥ 28: 35.2% Adjusted OR 0.50 (CI 0.24 to 1.05) for BMI < 20 group Adjusted OR 0.53 (CI 0.32 to 0.86) for BMI ≥ 28 group		CH	2b

11.9 Gamete intrafallopian transfer: male infertility

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Leeton et al. 1987 ⁸¹⁵	13 couples with male factor	IVF (n = 7) versus GIFT (n = 6)	Pregnancy rate	No significant difference: IVF: 2/7 (28.5%) GIFT: 2/6 (33%) RR 1.17 (CI 0.23 to 5.95)	Randomisation methods not clear Small sample	RCT	1b

11.9 Gamete intrafallopian transfer: unexplained infertility

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Murdoch et al. 1991 ⁸¹²	59 couples with unexplained infertility for over 3 years	3 cycles of : GIFT (n = 20) versus IUI after OH (n = 20) versus IUI in a spontaneous cycle (n = 19)	Live birth rate/couple Pregnancy rate/cycle Fecundability Cycle cancellation Multiple pregnancy	Significantly higher in GIFT: Live birth rate/couple: GIFT: 6/20 (30%) IUI + OH: 1/20 (5%) IUI spontaneous: 1/19 (5%) Pregnancy rate/cycle: GIFT: 6/40 (15%) IUI + OH: 1/40 (2.5%) IUI spontaneous: 1/41 (2.4%) Fecundability: GIFT: 0.12 (CI 0.02 to 0.20) IUI + OH: 0.018 (CI 0 to 0.05) IUI spontaneous: 0.018 (CI 0 to 0.05) Cycle cancellation: GIFT: 12/42 (28.5%) IUI + OH: 17/40 (42.5%) IUI spontaneous: 13/41 (31.7%) Multiple pregnancy: GIFT: twins 2/6 (33%) Singletons: 4/6 (66%) IUI + OH: 1 twins IUI spontaneous: 1 singleton	Randomisation using a random number sequence	RCT	Ib

11.9 Gamete intrafallopian transfer: unexplained infertility (continued)

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Wessels et al. 1992 ⁸¹³	174 couples with female infertility excluding tubal factors (idiopathic infertility, endometriosis, cervical factors, anovulation, immunologic factors and multifactorial causes; numbers not available)	GIFT (n = 90; 161 cycles) versus conventional treatment (n = 84; 185 cycles)	Pregnancy rate/woman Pregnancy rate/cycle Multiple pregnancy rate Ectopic pregnancy rate In patients with idiopathic infertility: pregnancy rate/cycle	Significantly higher in GIFT: Pregnancy rate/woman: GIFT: 42/90 (46.7%) Conventional: 18/84 (21.4%) Pregnancy rate/cycle: GIFT: 42/161 (26.7%) Conventional: 18/185 (9.7%) Non-significant differences: Multiple pregnancy rate: GIFT: 17.2% Conventional: 10.5% Ectopic pregnancy rate: GIFT: 2.2% Conventional: 0% No significant difference: In patients with idiopathic infertility: pregnancy rate/cycle: GIFT: 23.6% Conventional: 36.8%	Clinical heterogeneity Randomisation using a computer-generated list of random numbers	RCT	Ib
Hogerzeil et al. 1992 ⁸¹⁴	50 couples with unexplained infertility of at least 3 years (n = 23; 39 cycles) or failed AID (n = 27; 48 cycles)	2 cycles of: GIFT (n = 26) versus ovarian stimulation + timed intercourse or timed cervical donor insemination (n = 24)	Pregnancy rate/cycle	No significant difference (in patients with unexplained infertility): GIFT: 2/24 (8%) Ovarian stimulation + timed intercourse: 2/15 (13%) RR 0.63 (CI 0.10 to 3.98)	Methods of randomisation unclear	RCT	Ib

12.3 Ovulation induction in in vitro fertilisation: natural cycles and stimulated cycles

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
MacDougall et al. 1994 ⁸³⁷	30 women for IVF	Clomifene citrate-stimulated cycle (n = 16) versus no treatment (n = 14)	Clinical pregnancy rate/ET Multiple pregnancy rate No. of embryos transferred Cycle cancellation (due to premature LH surge and poor follicular growth)	Non-significant difference: Clinical pregnancy rate/ET: Clomifene: 2/11 (18%) Natural: 0/4 (0%) Multiple pregnancy rate: 2 singletons in clomifene group No. of embryos transferred: Clomifene: 11/16 (69%) Natural: 4/14 (28.6%) RR 2.41 (CI 0.99 to 5.87) Significant difference: Cycle cancellation: Clomifene: 0 Natural: 10	Randomisation using computer-selected numbers	RCT	Ib
Ingerslev et al. 2001 ⁸³⁸	132 couples for IVF	Clomifene citrate cycle (n = 68; 111 cycles) versus natural cycle (n = 64, 114 cycles)	Implantation rate/ET Clinical pregnancy rate/cycle Clinical pregnancy rate/transfer Adverse effects (nausea, hot flushes, mammary tenderness, visual disturbances)	Non-significant difference: Implantation rate/ET: Clomifene: 22/85 (26%) Natural: 4/29 (14%) RR 1.88 (CI 0.71 to 4.99) Significant difference: Clinical pregnancy rate/cycle: Clomifene: 20/111 (18%) Natural: 4/114 (3.5%) RR 5.14 (CI 1.81 to 14.55) Clinical pregnancy rate/transfer: Clomifene: 20/59 (34%) Natural: 4/29 (14%) RR 2.46 (CI 0.92 to 6.53) Adverse effects: CC: 51/111 (46%) Natural: 2/114 (1.7%) RR 26.19 (CI 6.53 to 104.98)	Block randomisation by sealed envelope	RCT	Ib

12.3 Ovulation induction in in vitro fertilisation: natural cycles and stimulated cycles (continued)

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Levy et al. 1991 ⁸³⁹	29 women for IVF-ET	hMG cycle (n = 13, 26 cycles) versus natural cycle (n = 16, 22 cycles)	Clinical pregnancy rate/cycle Cancellation rate No. of embryos transferred Multiple pregnancy rate Adverse effects	Significant difference: Clinical pregnancy rate/cycle: hMG cycle: 6/26 (23%) Natural cycle: 0/22 (0%) Cancellation rate 'higher' in natural cycle (no data) No. of embryos transferred: hMG cycle: 23/26 (88%) Natural cycle: 11/22(50%) RR 1.14 (CI 1.77 to 2.75) Multiple pregnancy rate: no data Adverse effects: no data	Method of randomisation unclear Cycles monitored with ultrasound and E ₂ Ultrasound guided transvaginal follicles aspiration Crossover study	RCT	Ib

12.3 Ovulation induction in in vitro fertilisation: adjuvant growth hormone

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Kotarba et al. 2003 ⁸⁵⁰	6 RCTs	For any diagnosis of infertility: GH + GnRHa/gonadotrophin versus GnRHa/gonadotrophin only For IVF poor responders: GH + GnRHa/gonadotrophin versus GnRHa/gonadotrophin only	Pregnancy/cycle	No significant differences: Any diagnosis: OR 0.97 (CI 0.34 to 2.76) IVF poor responders: OR 2.55 (CI 0.64 to 10.12)	Clinical heterogeneity Small sample size of trials	SR	1a

12.4 Oocyte maturation: human chorionic gonadotrophins

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
ERHCGSG 2000 ⁸⁵⁴	190 women undergoing IVF/ET	rhCG (n = 97) versus uhCG (n = 93)	Mean no. of mature oocytes Clinical pregnancy rate Miscarriage rate Live birth rate OHSS	Significant difference: Mean no. of mature oocytes: 9.4 versus 7.1 No significant difference: Clinical pregnancy rate: 32/97 (33%) versus 23/93 (24.7%) Miscarriage rate: 3/97 (3.1%) versus 0/93 (0%) Live birth rate: 26/97 (27%) versus 21/93 (23%) OHSS: 7/97 (7.2%) versus 6/93 (6.4%)	Randomisation method unclear All women received down regulation and ovarian stimulation with FSH Trial conducted by Ares-Serono Multicentred, double-blind	RCT	Ib
Chang et al. 2001 ⁸⁵⁵	297 women undergoing IVF/ET	rhCG 250 microgrammes (n = 94) versus rhCG 500 microgrammes (n = 89) versus uhCG (n = 92)	Mean no. of mature oocytes Clinical pregnancy rate Live birth rate OHSS	No significant difference: Mean no. of mature oocytes: 13.6 versus 14.6 versus 13.7 Clinical pregnancy rate: 33/94 (35%) versus 32/89 (36%) versus 33/92 (35.9%) Live birth rate: 29/94 (87.9%) versus 27/89 (84.4%) versus 28/92 (84.8%) OHSS: 3/94 (3.2%) versus 8/89 (9%) versus 3/92 (3.1%)	Computer-generated randomisation All women received downregulation and ovarian stimulation with FSH Trial funded by Serono	RCT	Ib

12.5 Ultrasound monitoring in in vitro fertilisation

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Golan et al. 1994 ⁸⁵⁷	114 women undergoing IVF	Ultrasound monitoring (n = 57) versus ultrasound + hormonal determination (n = 57)	Pregnancy rate/embryo transfer OHSS rate	No significant differences: Pregnancy rate/embryo transfer: Ultrasound only: 26.5% Ultrasound + hormonal test: 27.2% OHSS rate: Ultrasound only: 7% Ultrasound + hormonal test: 5.3%	GnRHa and hMG used for ovulation induction	RCT	Ib
Lass et al. 2003 ⁸⁵⁸	297 women undergoing IVF	Oestrogen + ultrasound monitoring (n = 143) versus ultrasound monitoring (n = 145)	Pregnancy rate OHSS rate	No significant differences: Pregnancy rate: Oestrogen + ultrasound: 34.3% Ultrasound only: 31.7% OHSS rate: Oestrogen + ultrasound: 3.4% Ultrasound only: 4.7%	GnRHa and rFSH used for ovulation induction	RCT	Ib

12.6 Prevention of ovarian hyperstimulation syndrome

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Van Wely et al. 2003 ⁵¹⁷	4 RCTs	HMG versus recombinant FSH	OHSS	No significant difference: OR 1.60 (CI 0.60 to 4.3)		SR	1a
Daya et al. 2003 ⁵¹⁸	10 RCTs	Recombinant versus urinary gonadotrophins	OHSS	No significant difference: OR 1.36 (CI 0.79 to 2.33)		SR	1a
D'Angelo et al. 2003 ⁸⁶⁵	2 RCTs	Cryopreservation of all embryos versus 4 albumin <i>Cryopreservation of all embryos versus fresh embryo transfer</i>	OHSS Clinical pregnancy rate	No significant difference: OHSS: Cryo-embryos versus iv albumin: OR 5.33 (CI 0.51 to 56.24) Cryo-embryos versus fresh embryo transfer: OR 0.12 (CI 0.01 to 2.29) Clinical pregnancy rate: Cryo-embryos versus iv albumin: OR 0.06 (CI 0.00 to 1.17) Cryo-embryos versus fresh embryo transfer: OR 1.08 (CI 0.54 to 2.19)		SR	1a
Al-Inany et al. 2003 ⁵⁶¹	5 RCTs	GnRH antagonists versus GnRH agonists	OHSS	Significant difference: OHSS: OR 0.47 (CI 0.18 to 1.25) RR 0.51 (CI 0.22 to 1.18)		SR	1a
Aboulghar et al. 2003 ⁸⁶⁸	5 RCTs	Human albumin versus placebo versus no treatment	OHSS Pregnancy rate	Significant difference: OHSS: OR 0.28 (CI 0.11-0.73) RR 0.35 (CI 0.14 to 0.97) No significant difference: Pregnancy rate: 1.09 (CI 0.65 to 1.83)	For every 18 women at risk of severe OHSS, albumin infusion will save one more case	SR	1a
D'Angelo et al. 2003 ⁸⁶⁴	1 RCT	'Coasting' (withholding gonadotrophins) versus no 'coasting'	OHSS Pregnancy rate	No significant difference: OHSS: OR 0.76 (CI 0.18-3.24) Pregnancy rate OR 0.75 (CI 0.17 to 3.33)		SR	1a

12.7 Analgesia and sedation in oocytes retrieval

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Ng et al. 2001 ⁸⁷⁸	150 women undergoing oocyte retrieval	Paracervical block with sedation (n = 75) versus paracervical block with placebo (n = 75)	Pain levels Pregnancy rate	Significant difference: Pain levels: Sedation: mean score: 43.0 Placebo: mean score: 16.5 No significant difference: Pregnancy rate: Sedation: 18/75 (24%) Placebo: 19/75 (25.3%)	Pain score: 100-mm linear visual analogue scale: 0 = no pain 100 = intolerable	RCT	1b
Thompson et al. 2000 ⁸⁸¹	112 women undergoing oocyte retrieval	Patient-controlled inhalation analgesia (isodesox) (n = 57) versus iv fentanyl (n = 55)	Worse pain score Satisfaction	Significant difference: Worse pain score: Inhalation: 21.1% 4 fentanyl:25.4% No significant difference: Satisfaction: Inhalation: 67% 4 fentanyl:75%	Pain score: 100-mm linear visual analogue scale 0 = no pain 100 = maximum pain	RCT	1b
Ben-Shlomo et al. 1999 ⁸⁸³	50 women undergoing oocyte retrieval	General anaesthesia (n = 25, 84 embryo transfers) versus sedation (n = 25, 88 embryo transfers)	Pregnancy rate/embryo transfer Satisfaction with pain relief	No significant difference: Pregnancy rate/embryo transfer: GA: 5/21 (23.8%) Sedation: 5/22 (22.7%) Satisfaction with pain relief same in both groups		RCT	1b
Kim et al. 2000 ⁸⁸⁹	3 RCTs and 1 non RCT (women undergoing laparoscopic oocyte retrieval)	General anaesthesia versus locoregional anaesthesia	Pregnancy rate	No significant difference: OR 0.71 (CI 0.47 to 1.08) Excluding 1 non-RCT OR 0.84 (CI 0.28 to 2.50)		MA	1a

12.7 Follicle flushing in oocytes retrieval

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Kingsland et al. 1991 ⁸⁹⁴	34 women undergoing IVF	Follicular aspiration + flushing (n = 18) versus follicular aspiration only (n = 16)	Mean no. of oocytes retrieved Fertilisation rate Pregnancy rate/woman Ongoing pregnancy rate	No significant difference: Mean no. of oocytes retrieved 7 versus 8.5 Fertilisation rate 64% versus 60% Pregnancy rate/woman 3/18 (17%) versus 3/16 (19%) Ongoing pregnancy rate 3/18 (17%) versus 3/16 (19%) Significantly longer time needed	Method of randomisation and allocation concealment unclear Small sample size Maximum of up to 5 flushes/follicle	RCT	Ib
Tan et al. 1992 ⁸⁹⁵	100 women undergoing IVF	Follicular aspiration + flushing (n = 50) versus follicular aspiration only (n = 50)	Mean no. of oocytes retrieved Fertilisation rate Clinical pregnancy rate/woman	No significant difference: Mean no. of oocytes retrieved 9 versus 11 Fertilisation rate 60% versus 55.6% Clinical pregnancy rate/woman 13/50 (26%) versus 12/50 (24%) RR 0.92 (CI 0.47 to 1.82) Significantly longer time and higher doses of pethidine needed	Randomisation by drawing serially numbered sealed envelopes Maximum of up to 6 flushes/follicle	RCT	Ib

12.8 Techniques in sperm recovery

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Van Peperstraten et al. 2003 ⁸⁹⁹	I RCT (59 couples, men with CBAVD or failed vasovasostomy or epididymovasostomy)	MESA versus micropuncture with nerve stimulation	Pregnancy rate	Significant lower pregnancy with MESA: OR 0.19 (CI 0.04 to 0.83)	Small no of participants; method of randomisation unclear	SR	1a

12.8 Assisted hatching

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Edi-Osagie et al. 2003 ⁹⁴²	23 RCTs (2572 women; 8036 embryos)	Assisted hatching versus no assisted hatching	Live birth rate (6 RCTs) Clinical pregnancy rate (19 RCTs) Clinical pregnancy rate, repeat attempt at IVF/ICSI (4 RCTs)	No significant difference: Live birth rate OR 1.21 (CI 0.82 to 1.78) Significant difference: Clinical pregnancy rate: OR 1.63 (CI 1.27 to 2.09) Sensitivity analysis on randomisation: OR 1.34 (CI 0.79 to 2.26) Sensitivity analysis on balanced age at baseline: OR 1.81 (CI 1.23 to 2.66) Subgroup analysis in women with previous failed IVF: Significant difference: OR 2.33 (CI 1.63 to 3.34)	None of the 23 RCTs had clear method of randomisation; adequate allocation concealment; power calculation; or intention-to-treat analysis Significant heterogeneity	SR	1a

12.10 Use of ultrasound in embryo transfer

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Prapa et al., 1995 ⁹⁴⁹	132 women undergoing embryo transfer: Transabdominal ultrasound (n = 61) Clinical feel (n = 71)	Transabdominal ultrasound versus blind embryo transfer	Pregnancy rate	Significant difference: Transabdominal ultrasound: 36.1% (22/61) Blind embryo transfer: 22.6% (16/71)		QRCT	Ib
Kan et al. 1999 ⁹⁵⁰	187 women undergoing embryo transfer: Ultrasound (n = 93) Clinical touch (n = 94)	Ultrasound versus clinical touch	Pregnancy rate	No significant difference: Ultrasound: 37/98 (37.8%) Blind: 28/97 (28.9%)		QRCT	Ib
Hurley et al., 1991 ⁹⁵¹	340 women undergoing embryo transfer	Ultrasound versus blind embryo transfer	Pregnancy rate	No significant difference: Ultrasound: 19/94 (20.2%) Blind: 43/246 (17.5%)		QRCT	2a
Sallam et al., 2002 ⁹⁵²	640 women undergoing embryo transfer: Ultrasound (n = 320) Clinical feel (n = 320)	Ultrasound versus clinical touch transfer	Clinical pregnancy rate	Significant difference: OR 1.57 95% CI 1.08 –2.27 Results improved by assessment of uterocervical angle by ultrasound and moulding embryo transfer catheter accordingly	Alternate allocation Measurement of uterocervical angle before embryo transfer	QRCT	Ib
Matorras et al., 2002 ⁹⁴⁷	515 women undergoing embryo transfer: Transabdominal ultrasound (n = 255) Clinical touch (n = 260)	Transabdominal ultrasound versus clinical touch transfer	Clinical pregnancy	Significant difference: Transabdominal ultrasound: 67/255 (26.3%) Clinical touch: 47/260 (18.1%)		RCT	Ib
Tang et al., 2001 ⁹⁴⁶	800 women undergoing embryo transfer: Ultrasound (n = 400) Clinical touch (n = 400)	Ultrasound versus clinical touch	Clinical pregnancy	No significant difference: Ultrasound: 104/400 (26%) Clinical touch: 90/400 (22.5%)		RCT	Ib
Coroleu et al. 2000 ⁹⁴⁵	362 women undergoing embryo transfer: US (n = 182) Clinical touch (n = 180)	Ultrasound versus clinical touch	Pregnancy rate	Significant difference: Ultrasound: 91/182 (50%) Clinical touch: 61/180 (33.9%)		RCT	Ib
Garcia-Velasco et al. 2002 ⁹⁴⁸	374 women undergoing embryo transfer US (n = 187) Blind transfers (n = 187)	Ultrasound versus blind transfers	Pregnancy rate	No significant difference: Ultrasound: 112/187 (59.9%) Blind transfers: 103/187 (55.1%)		RCT	Ib

12.10 Day two to three versus day five to six embryo transfers

Study	Population	Intervention	Outcomes	Results	Study type	EL
Auwers 2002 ⁹⁵⁴	136 women undergoing IVF/ICSI	Day 2 embryo transfer (n = 63) versus day 5/6 embryo transfer (n = 66)	Clinical pregnancy rate/oocyte retrieval Clinical pregnancy rate/embryo transfer Live birth/oocyte retrieval Live birth/embryo transfer	No significant difference: Clinical pregnancy rate/oocyte retrieval: Day 2/3:20/63 (31.7%) Day 5/6:29/66 (44%) Significant difference: Clinical pregnancy rate/embryo transfer: Day 2/3: 20/57 (35%) Day 5/6: 29/48 (60%) No significant difference: Live birth/oocyte retrieval: Day 2/3: 17/63 (27%) Day 5/6:24/66 (36%) Significant difference: Live birth/embryo transfer: Day 2/3: 17/57 (30%) Day 5/6: 24/48 (50%)	RCT	Ib
Reizeni 2002 ⁹⁵⁵	98 attempts of ICSI fresh cycles	Day 3 embryo transfer (n = 48 attempts) versus day 5 embryo transfer (n = 50 attempts)	Clinical pregnancy rate Live birth rate	No significant difference: Clinical pregnancy rate: Day 2/3: 27/48 (56%) Day 5/6: 29/50 (58%) Live birth rate: Day 2/3: 24/48 (50%) Day 5/6: 24/50 (48%)	RCT	Ib
Utsunomiya 2002 ⁹⁵⁶	235 women undergoing 273 IVF/ICSI cycles	Day 3 ET (n = 121; 152 cycles) versus Day 5 ET (n = 114; 121 cycles)	Clinical pregnancy rate/cycle Clinical pregnancy rate/embryo transfer	No significant difference: Clinical pregnancy rate/cycle: Day 2/3: 40/152 (26.3%) Day 5/6: 30/121 (24.8%) Clinical pregnancy rate/embryo transfer: Day 2/3: 40/151 (26.5%) Day 5/6: 30/117 (25.9%)	QR	Ib

12.10 Day two to three versus day five to six embryo transfers (continued)

Study	Population	Intervention	Outcomes	Results	Study type	EL
Frattarelli 2003 ⁹⁵⁷	57 women undergoing IVF	Day 3 ET (n = 23) versus Day 5 ET (n = 26)	Clinical pregnancy rate Live birth rate	Significant difference: Clinical pregnancy rate: Day 2/3: 10/28 (35.7%) Day 5/6: 18/29 (62%) Live birth rate: Day 2/3: 8/23 (34.8%) Day 5/6: 15/26 (57.7%)	RCT	1b
Blake et al. 2003 ⁹⁵³	9 RCTs and 1 quasi-RCT		Live birth (1 quasi RCT) Pregnancy rate (4 RCTs)	No significant difference: Live birth: combined OR 1.59 (CI 0.80 to 3.15) Pregnancy rate: combined OR 0.86 (CI 0.57 to 1.29)	SR	1a

12.10 Catheters used in embryo transfer

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Wisanto et al. 1989 ⁹⁵⁸	400 IVF-embryo transfers	Soft single lumen (TDT® catheter, Prodimed, Neuilly en Thelles) (n = 99) versus soft double Frydman (n = 96) versus soft double Wallace (n = 99) versus ultrasound-guided TDT (n = 98)	Pregnancy rates	Significant difference: TDT 9/98 (9.2%) Frydman 31/96 (32.3%) Wallace 19/99 (19.2%)		RCT	Ib
Meriano et al. ⁹⁵⁹	66 embryo transfers	Firm single lumen Tomcat (n = 32) versus TDT (n = 34)	Pregnancy rates	Significant difference: Tomcat 16/34 (47%) TDT 5/32 (14.7%)		RCT	Ib
Boone et al. 2001 ⁹⁶²	105 couples undergoing 117 IVF cycles	Soft double lumen (Cook) (n = 52) versus soft double (Wallace) (n = 53)	Pregnancy rates	No significant difference: 85/220 (39%) 89/209 (43%)		RCT	Ib
Ghazzawi et al., 1999 ⁹⁶³	320 IVF patients	Wallace (n = 160) versus Erlanger (soft double + introducer) (n = 160)	Pregnancy rates	No significant difference: Wallace: 31/160 (19%) Erlanger: 48/160 (30%)		RCT	Ib
Al Shawaf 1993 ⁹⁶⁴	178 IVF- embryo transfers 63 FER	Frydman versus Wallace	Pregnancy rates	No significant differences: Frydman 30.7% Wallace 30.3%		RCT	Ib
Weering et al. 2002 ⁹⁶⁰	1296 women IVF & ICSI	K soft (n = 639) versus TDT (n = 657)	Pregnancy rate	Significant difference: K soft 27.1% TDT 20.5%	Intention to treat analysis	RCT	Ib
McDonald et al. 2002 ⁹⁶¹	650 cycles IVF	Cook catheter (CC) (n = 324) Tomcat catheter (TCC) (n = 326)	Pregnancy/cycle	No significant differences: CC 96/324 (29.6%) TCC 67/326 (20.5%) OR 1.63 (CI 1.14 to 2.3)		RCT	Ib

12.10 Bed rest after embryo transfer

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Botta et al. 1997 ⁹⁷⁰	182 infertile women undergoing IVF	24-hour bed rest (n = 97) 20-minutes bed rest (n = 95)	Pregnancy/embryo transfer Miscarriage	No significant differences: Pregnancy/embryo transfer: 24-hour bed rest: 24.1% 20-minutes bed rest: 23.6% Miscarriage: 24-hour bed rest: 19% 20-minute bed rest: 18.1%	RCT	Ib	

12.11 Progesterone for luteal support

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Daya 1988 ⁹⁷²	5 RCTs (1142 participants)	Progesterone support following IVF-embryo transfer or GIFT versus no treatment	Pregnancy rate	No significant difference: OR 1.25 (CI 0.93 to 1.66)	Demographic details of women in study limited All women received ovarian stimulation with CC + hMG, and hCG for ovulation induction	MA	1a
Soliman et al. 1994 ⁸⁶⁶	18 RCTs	hCG versus no treatment Progesterone versus no treatment hCG versus progesterone ± GnRHa use	Pregnancy rate/cycle Spontaneous abortion rate OHSS	Significant difference: Pregnancy rate/cycle: hCG versus no treatment: OR 1.9 (CI 1.3 to 3.1) Progesterone versus no treatment: OR 1.2 (CI 1.0 to 1.7) hCG versus progesterone OR 2.0 (CI 1.1 to 3.9) No significant difference: Spontaneous abortion rate: Luteal support versus none: OR 0.8 (CI 0.4 to 1.7) OHSS: hCG: 11/220 (5%) Progesterone or no treatment: 0/193 (0%)		MA	1a
Pritts et al. 2002 ⁹⁷³	30 RCTs	hCG versus none Progesterone versus none Intramuscular/oral progesterone versus vaginal progesterone hCG versus progesterone E ₂ + P versus progesterone Different doses of hCG/progesterone	Clinical pregnancy rate Ongoing pregnancy rate Delivery rate Implantation rate Miscarriage rate	Significant difference: Intramuscular hCG versus no treatment: Clinical pregnancy rate: RR 2.72 (CI 1.56 to 4.90) Intramuscular progesterone versus placebo (long GnRHa protocol): Clinical pregnancy rate: RR 2.38 (CI 1.3 6 to 4.27) Ongoing pregnancy rate: RR 3.8 (CI 1.42 to 11.38) Delivery rate: RR (5.50 (CI 1.25 to 35.53) Vaginal versus oral progesterone: Implantation rate: RR 1.5 (CI 1.10 to 2.05)		MA	1a

12.11 Progesterone for luteal support (continued)

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Pritts et al. 2002 ⁹⁷³				<p>Intramuscular hCG versus oral progesterone (short GnRHa protocol): Clinical pregnancy rate: RR 8.36 (CI 1.44 to 173.74) Ongoing pregnancy rate: RR 7.43 (CI 1.22 to 156.64)</p> <p>Intramuscular versus vaginal progesterone (long GnRHa protocol): Clinical pregnancy rate: RR 1.33 (CI 1.02 to 1.75) Delivery rate: RR 2.06 (CI 1.48 to 2.88)</p> <p>E₂ + progesterone versus progesterone only (long GnRHa protocol): RR 1.49 (CI 1.02 to 2.19)</p> <p>No significant differences in Clinical pregnancy, ongoing pregnancy, delivery and miscarriage rates for the following:</p> <p>Vaginal progesterone versus no treatment</p> <p>Different doses of progesterone</p> <p>Intramuscular versus oral progesterone</p> <p>Intramuscular hCG versus oral progesterone (long GnRHa protocol)</p> <p>Intramuscular hCG versus IM progesterone (long GnRHa protocol)</p> <p>E₂ + progesterone versus progesterone only (long GnRHa protocol)</p> <p>hCG + progesterone versus vaginal progesterone (long and short GnRHa protocol)</p> <p>Intramuscular progesterone + E₂ versus hCG</p>			

13.1 In vitro fertilisation and intracytoplasmic sperm injection: male infertility

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Van Rumste et al. 2003 ⁹⁷⁶	10 RCTs (437 couples) ICSI versus IVF (8 RCTs) ICSI versus SUZI (1 RCT) ICSI versus additional IVF (1 RCT)	ICSI versus IVF versus Additional IVF versus SUZI	Fertilisation rate/oocyte injected Pregnancy rate/embryo transfer Pregnancy rate/couple Miscarriage/pregnancy Fertilisation rate/oocyte retrieved	ICSI versus IVF: <i>Normal semen</i> No significant difference: Fertilisation rate/oocyte retrieved OR 0.88 (CI 0.76 to 1.03) Significant difference: Fertilisation rate/oocyte injected OR 1.42 (CI 1.17 to 1.72) Pregnancy rate/embryo transfer; pregnancy rate/couple: no significant differences Miscarriage/pregnancy OR 0.34 (CI 0.12 to 1.00) <i>Borderline semen</i> Significant difference: Fertilisation rate/oocyte retrieved OR 3.79 (CI 2.97 to 4.85) Fertilisation rate/oocyte injected OR 3.90 (CI 2.96 to 5.15) Pregnancy rate/embryo transfer; pregnancy rate/couple: no significant differences ICSI versus SUZI: <i>Poor semen</i> Significant difference: Fertilisation rate/oocyte injected: ICSI: (33%) SUZI: (16%) OR 2.59 (CI 1.11 to 6.04) ICSI versus additional IVF: Significant difference: Fertilisation rate/oocyte injected: ICSI: 63% IVF: 0% OR 13.77 (CI 7.96 to 23.82)	Randomisation based on oocytes in 8 trials Causes of infertility: male factor, tubal and unexplained infertility	SR	1a

13.1 In vitro fertilisation and intracytoplasmic sperm injection

Study	Population	Intervention	Outcomes	Results	Study type	EL
Van Rumste et al. 2003 ⁹⁹⁵	1 RCT	IVF versus ICSI in couples with non-male subfertility	Pregnancy rate	No significant difference: OR 1.44 (CI 0.95 to 2.21)	SR	1a

14.5 Insemination and intracervical insemination: fresh and frozen donor sperm

Study	Population	Intervention	Outcomes	Results	Comments	Study type	EL
O'Brien et al. 2003 ¹⁰⁴⁸	12 RCTs (697 participants, 2215 cycles)	frozen semen IUI versus ICI With/without stimulation	Pregnancy rate/cycle Pregnancy rate/woman Miscarriage rate Ectopic pregnancy rate Multiple pregnancy rate Adverse effects	<i>Frozen semen</i> In clomifene citrate or natural cycles: Significant differences: Pregnancy rate/cycle OR 2.63 (CI 1.85 to 3.73) Pregnancy rate/woman OR 3.86 (CI 1.81 to 8.25) In gonadotrophin cycles: Pregnancy rate/cycle OR 2.17 (CI 1.35 to 3.49) Pregnancy rate/cycle OR 2.72 (CI 1.37 to 5.40) <i>Fresh semen</i> No significant differences: Pregnancy rate/cycle OR 0.90 (CI 0.36 to 2.24) Multiple pregnancy rate OR 1.34 (CI 0.43 to 4.22) Adverse effects: no data	Overall quality of trials poor	SR	1a

14.7 Timing of donor insemination

Study	Population	Intervention	Outcomes	Results	Study type	EL
Flierman et al. 1999 ¹⁰⁵⁷	4 RCTs	Urinary LH versus basal body temperature for timing of donor insemination	Pregnancy rate/cycle	No significant difference: OR 0.98 (CI 0.64 to 1.48)	MA	1a

15.2 Screening of oocyte donors

Study	Population	Outcomes	Results	Study type	EL
Wallerstein et al. 1998 ¹⁰⁷⁹	73 oocyte donors	Prevalence of genetic conditions	Cystic fibrosis: 7% Abnormal karyotypes: 3.5% Skeletal dysplasia: 1.4%	SV	3

16 Cryostorage of gametes

Study	Population	Outcomes	Results	Study type	EL
Ginsburg et al. 2001 ¹¹¹⁸	70 women (111 cycles) undergoing IVF/ICSI/GIFT 82 IVF cycles 39 ICSI cycles 5 GIFT cycles Couples in whom the woman had cancer = 51 (71 cycles) Couples in whom the man had cancer = 19 (40 cycles)	Delivery rate/cycle	Women: Local cancer treatment: 14/56 (40%) Systemic cancer treatment: 2/15 (13.3%) Men: Local cancer treatment: 0/5 (0%) Systemic cancer treatment (pre-chemotherapy banked sperm): 2/11 (18.2%) Systemic cancer treatment (fresh sperm): 9/24 (18.2%) Couples in whom the woman had cancer: 17/71 (24%) Couples in whom the man had cancer: 11/40 (37.5%)	OB	3

17.1 Health of children born as a result of assisted reproduction

Study	Population	Outcomes	Results	Comments	Study type	EL
Tanbo et al. 2003 ¹¹³³	30 studies (13 cohort; 17 case studies)	Birth defects	Non-significant difference: RR 1.13 (CI 1.00 to 1.29)	Conclusions uncertain in these outcomes: chromosomal abnormalities, neurological and growth disturbances due to small number of accepted studies	SR	2b-3
Ludwig 2002 ¹¹²⁸	ICSI infants (n = 3372) Population-based control (n = 30,940)	Major malformation rate	Significant difference: ICSI infants: 291/3372 (8.6%) Population-based control: 2140/30940 (6.9%)	Major malformations defined by the EUROCAT: International Clearinghouse of Birth Defects Monitoring Systems, 1999)	OB	3
Klip et al. 2001 ¹¹³⁷	IVF children (n = 9484) Naturally conceived children (n = 7532) (mothers diagnosed with subfertility)	Cancer incidence	No significant difference: 16 cancers observed in both groups versus 15.5 expected: SIR 1.0 (CI 0.6 to 1.7) IVF versus naturally conceived children: RR 0.8 (CI 0.3 to 2.3)	6 years of follow-up	OB	3
Golombok et al. 1995 ¹¹⁴¹	184 families with a child conceived by IVF and donor insemination (n = 86) and a child conceived naturally or adopted (n = 98) Children aged 4–8 years	Separation Anxiety Test Family Relations Test Pictorial Scale of Perceived Competence and Social Acceptance	No significant differences	Exclusion criteria: children with congenital abnormality, brain damage and result of multiple birth	OB	3
Montgomery et al. 1999 ¹¹⁴²	743 IVF children aged > 4 years compared with normative sample used for establishing the Achenbach behavioural questionnaires	Thought problems Internalising problems Externalising problems Attention problems Social problems	No significant differences		SV	3