National Institute for Health and Care Excellence

Final

Fertility problems: assessment and treatment

[U] Hormone treatment for male factor fertility problems

NICE guideline number NG257

Evidence reviews underpinning recommendations 1.17.5, 1.24.1, 1.24.2 and 1.24.3 and research recommendation in the NICE guideline

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K.1.2 What is the effectiveness of anti-oestrogens or gonadotrophins (alone or in combination) in men with impaired semen parameters, normal or high FSH, low or normal testosterone, and no hypogonadotropic hypogonadism or evidence of obstruction? 254

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Hormone treatment for male factor fertility problems

Review question

What is the effectiveness of hormone treatment in male factor fertility problems?

Introduction

Male factor fertility problems may arise due to testicular dysfunction and issues with the normal endocrine pathways involved in spermatogenesis, leading to azoospermia (an absence of sperm in the ejaculate) or impaired semen parameters. Correction of the endocrine abnormalities can improve spermatogenesis and therefore treatment with hormonal therapy may be an option.

The aim of this review is to determine whether hormone-related treatments used in male factor infertility have a beneficial effect on fertility.

Summary of the protocol

See Table 1 for a summary of the Population, Intervention, Comparison and Outcome (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

Population	**Inclusion:** People with health-related male factor fertility problems In this guideline, people with health-related fertility problems are those who have a known health-related impediment to fertility, or those who do not achieve a pregnancy: • after 12 months of regular unprotected sexual intercourse or • after 6 cycles of artificial insemination.
Intervention	Any hormone-related therapy for the treatment of male factor fertility problems, for example: • Gonadotrophin therapy • Anti-oestrogens (for example, clomifene and tamoxifen) • Aromatase inhibitors (for example, anastrozole) • Androgens (for example, testosterone and testosterone analogues) • Drugs for hyperprolactinaemia (for example, bromocriptine)
Comparison	• Head-to-head comparisons between different interventions within each category • Head-to-head comparisons between different interventions between each category • Placebo • No intervention
Outcome	Critical • Live birth • Clinical pregnancy rate (an ultrasound scan that has shown at least one fetal heart beat) Important

	• Generic health-related or disease-specific quality of life measured using a validated instrument in the person with male factor fertility problems, for example: ○ EQ-5D ○ Health Utilities Index Mark 3 (HUI3) questionnaire ○ FertiQoL • Increased testosterone production/ improved hormonal parameters • Improved semen parameters (for example, sperm concentration, motility, normal forms, total sperm count) • Miscarriage (loss of a baby before 24 weeks gestational age) • Rate of successful surgical sperm retrieval.

For further details see the review protocol in appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document (supplement 1).

In the initial version of the protocol, only live birth was listed as a critical outcome. However, during sifting, a number of studies were identified that fit the protocol criteria but were not relevant to the review question or useful for decision-making. This included studies which investigated relevant interventions and reported secondary outcomes such as hormone parameters, but did not specify whether the participants were actively trying to achieve pregnancy. It was agreed with the committee that evidence on semen or hormone parameters, or on quality of life (which were the outcomes these studies tended to investigate) without evidence regarding the impact on pregnancy or live birth for participants in these studies, was unlikely to affect decision-making. It was also noted that when studies did report pregnancy or live birth rates as an outcome, the majority of studies reported on pregnancy rates in preference to live birth rates. For this reason, the protocol was amended in order to reflect the evidence base and to ensure only studies which would aid decision-making were included: the outcome 'clinical pregnancy rate (an ultrasound scan that has shown at least one fetal heart beat)' became an additional critical outcome, and only studies which reported a critical outcome were included.

In the initial version of the protocol, improved semen parameters were not further defined or limited. However, the committee agreed there were a number of semen parameters reported by studies that were not of interest as they would be unlikely to influence decision-making. The committee agreed that the semen parameters of interest which were most likely to influence decision-making included motile sperm count/concentration (these terms tend to be used interchangeably in studies) and total sperm count/concentration. Therefore, data extraction and analyses were limited to these semen parameter outcomes.

Due to the amount of evidence and number of outcomes reported at different timepoints, meta-analyses grouped outcome data into short term (≤3 months), medium term (>3 to ≤12 months), and long term (>12 months) follow-up periods. These time periods were agreed based on the follow-up periods reported in the studies, and were consistent with other relevant systematic reviews. Data from the latest timepoint within each of these follow-up periods were extracted, and where possible, outcomes were meta-analysed according to these follow-up periods.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

Effectiveness evidence

Included studies

Twenty-eight randomised controlled trials (RCTs) were included for this review (Aafjes 1983, Adamopoulos 2003, Amirzargar 2012, Aribarg 1989, Babak 2018, Baccetti 2004, Cakan 2009, Cavallini 2013, Comhaire 1995, Crottaz 1992, Farrag 2015, Foresta 2005, Foresta 2009, Gregoriou 1993, Haje 2015, Kamischke 1998, Knuth 1987, Krause 1992, Maier 1988, Matorras 1997, Matsumiya 1998, Micic 1985, Paradisi 2006, Pusch 1989, Selice 2011, Sokol 1988, Srivannaboon 1992, Zhao 2019).

The included studies are summarised in Table 2.

Two studies compared anti-oestrogens with no treatment (Cakan 2009, Micic 1985), 4 compared anti-oestrogens with placebo (Haje 2015, Krause 1992, Sokol 1988, Srivannaboon 1992), 1 compared anti-oestrogens plus androgens with placebo (Adamopoulos 2003), 1 compared aromatase inhibitors with no treatment (Maier 1988), 1 compared aromatase inhibitors with placebo (Cavallini 2013), 8 compared gonadotrophin therapy with no treatment (Amirzargar 2012, Babak 2018, Baccetti 2004, Farrag 2015, Foresta 2005, Foresta 2009, Matorras 1997, Selice 2011), 5 compared gonadotrophin therapy with placebo (Crottaz 1992, Kamischke 1998, Knuth 1987, Paradisi 2006, Zhao 2019), 1 compared gonadotrophin therapy with anti-oestrogens (Matsumiya 1998), and 5 compared androgens with placebo (Aafjes 1983, Aribarg 1989, Comhaire 1995, Gregoriou 1993, Pusch 1989). There were no included studies which investigated the effectiveness of drugs for hyperprolactinaemia.

With regards to semen abnormalities, 22 studies included participants with impaired semen parameters only (Aafjes 1983, Adamopoulos 2003, Baccetti 2004, Cakan 2009, Comhaire 1995, Farrag 2015, Foresta 2005, Foresta 2009, Gregoriou 1993, Haje 2015, Kamischke 1998, Krause 1992, Maier 1988, Matorras 1997, Matsumiya 1998, Micic 1985, Paradisi 2006, Pusch 1989, Selice 2011, Sokol 1988, Srivannaboon 1992, Zhao 2019), 2 studies included participants with impaired semen parameters as well as those with azoospermia (Cavallini 2013, Crottaz 1992), and 4 studies did not report the severity of the participants' semen abnormality (Amirzargar 2012, Aribarg 1989, Babak 2018, Knuth 1987).

With regards to fertility diagnoses, 2 studies included participants with various causes for their semen abnormalities (unilateral or bilateral cryptorchidism or idiopathic a- or crypto-zoospermia: Cavallini 2013; cryptorchidism, varicocele, post-mumps orchitis, trauma, testicular torsion, or idiopathic oligozoospermia: Foresta 2009), 2 studies included participants with varicocele only (Amirzargar 2012, Babak 2018), 17 studies included participants with idiopathic semen abnormalities (oligozoospermia: Adamopoulos 2003, Farrag 2015, Foresta 2005, Knuth 1987, Krause 1992, Micic 1985, Pusch 1989, Zhao 2019; oligo- and/or astheno-zoospermia: Baccetti 2004, Srivannaboon 1992; oligoasthenoteratozoospermia: Cakan 2009; oligoasthenozoospermia: Crottaz 1992, Gregoriou 1993, Haje 2015, Matsumiya 1998, Paradisi 2006; abnormal semen parameters (not defined): Kamischke 1998), 1 study included participants with idiopathic testicular failure or idiopathic semen abnormalities (Aribarg 1989), and 6 studies included participants with semen abnormalities but did not report whether there was a known cause (oligozoospermia (cause not reported): Aafjes 1983, Selice 2011, Sokol 1988; oligoasthenozoospermia (cause not reported): Maier 1988; oligo- and/or astheno- and/or terato-zoospermia (cause not reported): Comhaire 1995, Matorras 1997).

With regards to age, 19 studies included participants with a mean age or age range <45 years (Amirzargar 2012, Aribarg 1989, Babak 2018, Baccetti 2004, Cakan 2009, Crottaz 1992, Farrag 2015, Foresta 2005, Foresta 2009, Gregoriou 1993, Haje 2015, Kamischke 1998, Knuth 1987, Krause 1992, Matorras 1997, Matsumiya 1998, Pusch 1989, Srivannaboon 1992, Zhao 2019), 3 studies included participants <45 and ≥45 years old (Adamopoulos 2003, Cavallini 2013, Sokol 1988), and 6 studies did not report the age of the

participants (Aafjes 1983, Comhaire 1995, Maier 1988, Micic 1985, Paradisi 2006, Selice 2011).

See the literature search strategy in appendix B and study selection flow chart in appendix C.

Excluded studies

Studies not included in this review are listed, and reasons for their exclusion are provided in appendix J.

Summary of included studies

Summaries of the studies that were included in this review are presented in Table 2.

Table 2: Summary of included studies

Study	Population	Intervention	Comparison	Outcomes	Other comments

Aafjes 1983
 	
Cross-over randomised controlled trial
 	
The Netherlands
	N=59 oligozoospermic men (number of participants included at baseline not reported)
	
	Mesterolone group (n=27):
	
	• Mean age (SD): NR
	• Severity of semen abnormalities:
	  ○ Non-azoospermic: 27/27 (100%)
	• Fertility diagnosis:
	  ○ Oligozoospermia (cause NR): 27/27 (100%)
	
	Placebo group (n=32):
	
	• Mean age (SD): NR
	• Severity of semen abnormalities:
	  ○ Non-azoospermic: 32/32 (100%)
	• Fertility diagnosis:
	  ○ Oligozoospermia (cause NR): 32/32 (100%)
		Mesterolone:
		• Mesterolone, 25mg per tablet 3 times a day (for a total of 75mg per day) for 6 months
			Placebo:
			• Placebo tablets 3 times a day for 6 months
				• Pregnancy rate	After 6 months of initial treatment, participants in each group were crossed over to receive the alternate medication. Only data from the first phase were extracted

Adamopoulous 2003 RCT Greece	N=212 men with idiopathic oligozoospermia • Mean age (range): NR (24-48 years) Tamoxifen + testosterone group (n=106): • Mean age (SD): NR	Tamoxifen + testosterone: • Tamoxifen citrate, 10mg twice a day for 6 months • Testosterone undecanoate, 40mg three times a day for 6 months	Placebo: • Placebo for 6 months	• Spontaneous pregnancy rate • Semen parameters: ○ Sperm motility rate (%)	82 normo-zoospermic men 26 to 38 years of age were also included to account for possible regression toward the mean effect, but data from these participants

Study	Population	Intervention	Comparison	Outcomes	Other comments
	• Severity of semen abnormalities: ○ Non-azoospermic: 106/106 (100%) • Fertility diagnosis: ○ Idiopathic oligozoospermia: 106/106 (100%) Placebo group (n=106): • Mean age (SD): NR • Semen abnormalities: ○ Non-azoospermic: 106/106 (100%) • Fertility diagnosis: ○ Idiopathic oligozoospermia: 106/106 (100%)				were not extracted
Amirzargar 2012 RCT Iran	N=113 infertile men with varicocele Human chorionic gonadotrophin (HCG) group (n=25): • Mean age (SD): 32.4 (5.3) years • Severity of semen abnormalities: NR • Fertility diagnosis: ○ Varicocele: 25/25 (100%) Human menopausal gonadotrophin (HMG) group (n=21): • Mean age (SD): 32.6 (6.2) years • Severity of semen abnormalities: NR • Fertility diagnosis: ○ Varicocele: 21/21 (100%) Recombinant human follicle-stimulating hormone (rhFSH) group (n=32): • Mean age (SD): 32.28 (6.6) years • Severity of semen abnormalities: NR • Fertility diagnosis:	HCG: • Intramuscular HCG (Choriomon), 5000 IU weekly for 3 months HMG: • Subcutaneous HMG (Merional), 75 IU 3 times a week for 3 months rhFSH: • Subcutaneous rhFSH (Gonal-F), 75 IU 3 times a week for 3 months	No treatment: • No medical treatment	• Pregnancy rates: ○ Spontaneous or assisted pregnancy rate ○ Spontaneous pregnancy rate • Semen parameters: ○ Number of participants with sperm concentration >20×10⁶/ml ○ Number of participants with sperm motility rate >50%	Participants in all groups had a varicocelectomy prior to medical treatment, which was done by a single surgeon with the inguinal procedure without microsurgery

Study	Population	Intervention	Comparison	Outcomes	Other comments
	○ Varicocele: 32/32 (100%) No treatment group (n=35): • Mean age (SD): 31.3 (5.09) years • Severity of semen abnormalities: NR • Fertility diagnosis: ○ Varicocele: 35/35 (100%)				
Aribarg 1989 RCT Country not reported	N=157 infertile couples (N=248 originally recruited but n=91 couples later found not to meet inclusion criteria). Mesterolone (75mg) group (n=54): • Mean age (SD): 31.4 (5.2) years • Severity of semen abnormalities: NR* • Fertility diagnosis: NR** Mesterolone (150mg) group (n=50): • Mean age (SD): 31.0 (4.9) years • Severity of semen abnormalities: NR* • Fertility diagnosis: NR** Placebo group (n=53): • Mean age (SD): 29.9 (5.1) years • Severity of semen abnormalities: NR* • Fertility diagnosis: NR** *All participants had sperm concentration <20 x10⁶/ml but it is not reported if/ how many participants were azoospermic (e.g. due to idiopathic testicular failure)	<u>Mesterolone (75mg):</u> • Mesterolone (17P-hydroxy-la-methyl-5a-androstan-3-one), 25mg taken 3 times a day for 6 months (corresponding to daily doses of 75mg) <u>Mesterolone (150mg):</u> • Mesterolone (17P-hydroxy-la-methyl-5a-androstan-3-one), 50mg taken 3 times a day for 6 months (corresponding to daily doses of 150mg)	<u>Placebo:</u> • Placebo, packaged identically for 6 months	• Pregnancy rate	Results for the 2 treatment groups (mesterolone 75mg, and mesterolone 1 50mg) were combined into 1 arm in order to compare androgens to placebo

Study	Population	Intervention	Comparison	Outcomes	Other comments
	** All participants had idiopathic testicular failure or semen abnormalities without aetiological reasons, but it is not reported how many participants have either of these diagnoses				
Babak 2018 RCT Iran	N=188 infertile people with varicocele and abnormal semen analysis Human chorionic gonadotrophin (HCG) group (n=91): • Mean age (SD): 29.91 (2.67) years • Severity of semen abnormalities: NR • Fertility diagnosis: ○ Varicocele: 91/91 (100%) No treatment (n=97): • Mean age (SD): 32.79 (3.12) years • Severity of semen abnormalities: NR • Fertility diagnosis: ○ Varicocele: 97/97 (100%)	HCG: • HCG, 5000 IU administered intramuscularly every week for 3 consecutive months	No treatment: • No medical treatment	• Pregnancy rate • Semen parameters: ○ Sperm concentration (x10⁶/ml) ○ Sperm motility rate (%)	Participants in both groups had an open inguinal varicocelectomy prior to medical treatment
Baccetti 2004 RCT Germany	N=44 men with idiopathic male factor infertility: • Mean age (range): NR (28-45 years) • Severity of semen abnormalities: ○ Non-azoospermic: 44/44 (100%) • Fertility diagnosis: ○ Idiopathic oligo- and/or astheno-zoospermia: 44/44 (100%) Participant characteristics not reported separately for each group	Follicle stimulating hormone (FSH): • FSH, 150 IU/day delivered subcutaneously for 12 weeks	No treatment: • No treatment given	• Assisted pregnancy rate	None
Cakan 2009 RCT Turkey	N=127* men with idiopathic oligoastheno-teratozoospermia	Tamoxifen citrate: • Tamoxifen citrate, 10mg taken orally twice a day for 25 days every	No treatment: • No treatment given	• Pregnancy rate • Hormone parameters: ○ Testosterone (ng/dl)	In the first study period, participants were randomised to tamoxifen or no treatment.

Study	Population	Intervention	Comparison	Outcomes	Other comments
	Tamoxifen citrate group (n=103): • Mean age (SD): 27.3 (4.9) years • Severity of semen abnormalities: ○ Non-azoospermic: 103/103 (100%) • Fertility diagnosis: ○ Idiopathic oligoasthenoteratozoospermia: 103/103 (100%) No treatment group (n=25): • Mean age (SD): 26.8 (5.0) years • Severity of semen abnormalities: ○ Non-azoospermic: 25/25 (100%) • Fertility diagnosis: ○ Idiopathic oligoasthenoteratozoospermia: 25/25 (100%) *Total number of participants reported throughout the study does not match the total of the numbers reported in each group	month for 3 months		○ Oestradiol (pg/ml) • Semen parameters: ○ Sperm motility rate (%)	In the second study period, participants with a normal testosterone/ oestradiol ratio continued to receive tamoxifen (data from these participants not extracted as not randomised), while participants with low T/E2 ratios were randomised either to continue with tamoxifen alone as well, or to tamoxifen with additional anastrozole. Only data from the first treatment period were extracted
Cavallini 2013 RCT Italy	N=45 people with non-obstructive azoospermia or cryptozoospermia (N=52 randomised but data for n=7 participants who did not complete study not reported) Letrozole group (n=22; n=26 initially randomised)*: • Mean age (range): 44 (37–52) years • Severity of semen abnormalities: ○ Azoospermia (non-obstructive): 6/22 (27%) ○ Non-azoospermia: 16/22 (73%)	<u>Letrozole:</u> • Letrozole, 2.5mg once a day for 6 months	<u>Placebo:</u> • Starch, 100mg once a day for 6 months	• Spontaneous pregnancy rate	None

Study	Population	Intervention	Comparison	Outcomes	Other comments
	• Fertility diagnosis: ○ Previous bilateral cryptorchidism: 3/22 (14%) ○ Previous unilateral cryptorchidism: 5/22 (23%) ○ Idiopathic a- or crypto-zoospermia: 14/22 (64%) Placebo group (n=24; n=26 initially randomised)**: • Mean age (SD): 45 (NR; range: 38–53) years • Severity of semen abnormalities: ○ Azoospermia (non-obstructive): 5/24 (21%) ○ Non-azoospermia: 19/24 (79%) • Fertility diagnosis: ○ Previous bilateral cryptorchidism: 4/24 (17%) ○ Previous unilateral cryptorchidism: 5/24 (21%) ○ Idiopathic a- or crypto-zoospermia: 15/24 (63%) *Data for only n=21 participants reported at baseline **Data for only n=22 participants reported at baseline				
Comhaire 1995 RCT Country not reported	N=64 infertile couples (N=75 initially randomised but n=11 participants who breached the protocol or who did not take the capsule for 3 months were excluded from analysis) Testosterone undecanoate group (n=30):	<u>Testosterone undecanoate:</u> • Testosterone undecanoate (Andriol), 40mg capsules 3 times a day (for a total of 120mg per day) for 3 months	<u>Placebo:</u> • Identically packaged placebo, 3 times a day for 3 months	• Assisted pregnancy rate	After 3 months of capsule intake, participants in both groups underwent repeat IVF treatment using the same clinical and laboratory techniques as during the first attempt

Study	Population	Intervention	Comparison	Outcomes	Other comments
	• Mean age (SD): NR. Female partner age (SD): 31 (3.4) years • Severity of semen abnormalities: ○ Non-azoospermia: 30/30 (100%) • Fertility diagnosis: ○ Oligo- and/or astheno- and/or terato-zoospermia (cause NR): 30/30 (100%) Placebo group (n=34): • Mean age (SD): NR. Female partner age (SD): 30.4 (3.2) years • Severity of semen abnormalities: ○ Non-azoospermia: 34/34 (100%) • Fertility diagnosis: ○ Oligo- and/or astheno- and/or terato-zoospermia (cause NR): 34/34 (100%)				
Crottaz 1992 RCT Switzerland	N=28 men with idiopathic normogonadotropic oligoasthenozoospermia (N=39 randomised but data for n=11 participants who did not complete study not reported) Gonadotrophin-releasing hormone (GnRH) group (n=14; number initially randomised not reported): • Mean age (SD): 31.7 (1.0) years • Severity of semen abnormalities: ○ Azoospermia: 1/14 (7%) ○ Non-azoospermia: 13/14 (93%) • Fertility diagnosis:	<u>GnRH:</u> • GnRH, 0.2mg self-administered using a nasal spray (0.1 mL per puff) every 2 hours from 8:00AM to 8:00PM for 3 months	<u>Placebo:</u> • Placebo, self-administered using a nasal spray (0.1 ml per puff) every 2 hours from 8:00AM to 8:00PM for 3 months	• Pregnancy rate • Semen parameters: ○ Total motile sperm count ($x10^6$) ○ Sperm concentration ($x10^6$/ml) ○ Total sperm count ($x10^6$/ml) • Miscarriage rate	After the first 3-month phase whereby participants were randomised to the treatments above, participants went 1 month without treatment, and then participants in both initial groups underwent a 3-month period of open GnRH treatment. Only data from the first treatment phase were extracted

Study	Population	Intervention	Comparison	Outcomes	Other comments
	○ Idiopathic normogona-dotropic oligoasthenozoospermia: 14/14 (100%) Placebo group (n=14; number initially randomised not reported): • Mean age (SD): 32.9 (1.1) years • Severity of semen abnormalities: ○ Non-azoospermia: 14/14 (100%) • Fertility diagnosis: ○ Idiopathic normogona-dotropic oligoasthenozoospermia: 14/14 (100%)				
Farrag 2015 RCT Italy	N=82 male partners of couples with idiopathic male factor infertility undergoing ICSI treatment (N=92 randomised but data for n=10 participants who did not complete study not reported) Recombinant human follicle-stimulating hormone (rhFSH) group (n=36; n=46 initially randomised): • Mean age (SD): 36.9 (5.1) years • Severity of semen abnormalities: ○ Non-azoospermia: 36/36 (100%) • Fertility diagnosis: ○ Idiopathic oligozoospermia: 36/36 (100%) No treatment group (n=46): • Mean age (SD): 38.4 (5.2) years • Severity of semen abnormalities:	<u>rhFSH:</u> • rhFSH, 150 IU delivered subcutaneously 3 times a week for 3 months	<u>No treatment:</u> • No treatment given to male partners	• Assisted pregnancy rate • Miscarriage rate	Couples in both groups received the following interventions: • Ovarian stimulation • ICSI • Luteal phase support

Study	Population	Intervention	Comparison	Outcomes	Other comments
	○ Non-azoospermia: 46/46 (100%) • Fertility diagnosis: ○ Idiopathic oligozoospermia: 46/46 (100%)				
Foresta 2005 RCT Italy	N=112 men with idiopathic oligozoospermia (N=128 randomised but data for n=16 participants who did not complete study not reported) Recombinant human follicle-stimulating hormone (rhFSH) group (n=62; n=65 initially randomised): • Mean age (SD): 34.2 (4.8) years • Severity of semen abnormalities: ○ Non-azoospermia: 62/62 (100%) • Fertility diagnosis: ○ Idiopathic oligozoospermia: 62/62 (100%) No treatment group (n=50; n=63 initially randomised): • Mean age (SD): 34.0 (4.6) years • Severity of semen abnormalities: ○ Non-azoospermia: 50/50 (100%) • Fertility diagnosis: ○ Idiopathic oligozoospermia: 50/50 (100%)	<u>rhFSH:</u> • rhFSH, 100 IU administered through intramuscular injection on alternate days for 3 months	<u>No treatment:</u> • No treatment received	• Spontaneous pregnancy rate • Semen parameters: ○ Sperm concentration ($x10^6$/ml) ○ Total sperm count ($x10^6$)	n=40 fertile men were also included as controls but data from these participants were not extracted. After the first study period where participants were randomised to the above treatments, all participants who had not had spontaneous pregnancy underwent ARTs. Only data from the first period are extracted
Foresta 2009 RCT Italy	N=90 men with severe testiculopathy (N=87 completed the study): • Mean age (SD): 34.2 (4.5) years • Severity of semen abnormalities: ○ Non-azoospermia: 90/90 (100%) • Fertility diagnosis:	<u>GnRH-a, FSH + HCG:</u> • Gonadotrophin suppression through GnRH-a injection: leuprolide acetate, 3.75 mg delivered intra-muscularly every 30 days for 4 months	<u>No treatment:</u> • No treatment received	• Spontaneous pregnancy rate • Semen parameters: ○ Sperm concentration ($x10^6$/ml) ○ Total sperm	n=32 fertile men were also included as controls but data from these participants were not extracted.

Study	Population	Intervention	Comparison	Outcomes	Other comments
	○ Cryptorchidism: 20/90 (22%) ○ Varicocele: 18/90 (20%) ○ Post-mumps orchitis: 9/90 (10%) ○ Trauma: 6/90 (7%) ○ Testicular torsion: 3/90 (3%) ○ Idiopathic oligozoospermia*: 34/90 (38%) Participant characteristics not reported separately for each group. *Participants are reported as having idiopathic oligozoospermia, but all oligozoospermia was due to severe hypospermatogenesis	• 30 days from the first leuprolide administration, recombinant human FSH, 150 IU on alternate days for 3 months • HCG, 2000 IU twice a week for 3 months		count ($x10^6$) ○ Sperm motility rate (%)	After the first study period where participants were randomised to the above treatments, all participants who had not had spontaneous pregnancy underwent ARTs. Only data from the first period are extracted
Gregoriou 1993 RCT Greece	N=50 couples with infertility: • Mean age (SD): 28.4 (1.1) years • Severity of semen abnormalities: ○ Non-azoospermia: 50/50 (100%) • Fertility diagnosis: ○ Idiopathic oligoasthenospermia: 50/50 (100%) Participant characteristics were not reported separately for each group	<u>Testosterone undecanoate:</u> • Testosterone undecanoate (Restandol), 40mg capsules 3 times a day (for a total of 120mg per day) for 3 months	<u>Placebo:</u> • Identically packed placebo capsules 3 times a day for 3 months	• Pregnancy rate • Hormone parameters: ○ Dihydrotestosterone (ng/ml) ○ Total testosterone (ng/ml) ○ Oestradiol (pg/ml) • Semen parameters ○ Sperm concentration ($x10^6$/ml) ○ Sperm motility rate (%) • Miscarriage rate	None
Haje 2015 RCT Iraq	N=128 men with idiopathic oligoasthenozoospermia: • Mean age (SD): 37.54 (2.46) years • Severity of semen abnormalities:	<u>Tamoxifen:</u> • Tamoxifen, 20 mg/day for 3 to 6 months	<u>Placebo:</u> • No details reported	• Assisted pregnancy rate • Semen parameters: ○ Sperm concentration ($x10^6$/ml)	Participants in all groups received ICSI following treatment conclusion. Two additional group received either L-carnitine only

Study	Population	Intervention	Comparison	Outcomes	Other comments
	○ Non-azoospermia: 128/128 (100%) • Fertility diagnosis: ○ Idiopathic oligoasthenozoospermia: 128/128 (100%) Participant characteristics not reported separately for each group			○ Sperm motility rate (%)	(antioxidant, n=20) or L-carnitine and tamoxifen (n=34), but data were not extracted from these groups
Kamischke 1998 RCT Germany	N=65 couples with idiopathic male infertility (N=67 randomised but data for n=2 participants who did not complete study not reported) • Mean age (SD): 32.89 (0.56) years • Severity of semen abnormalities: ○ Non-azoospermia: 66/66 (100%) • Fertility diagnosis: ○ Idiopathic abnormal semen parameters: 66/66 (100%) Participant characteristics not reported separately for each group	<u>rhFSH:</u> • rhFSH, 150 IU with 30 mg saccharose, delivered by subcutaneous injection into abdominal wall daily for 12 weeks • Patients injected themselves after initial instruction by the examiners	<u>Placebo:</u> • Placebo containing saccharose alone, delivered by subcutaneous injection into abdominal wall daily for 12 weeks • Patients injected themselves after initial instruction by the examiners	• Pregnancy rates: ○ Spontaneous or assisted pregnancy rate ○ Spontaneous pregnancy rate • Hormone parameters: ○ Testosterone (nmol/l) ○ Oestradiol (pmol/l) • Semen parameters: ○ Sperm motility rate (%) ○ Sperm concentration ($x10^6$/ml)	None
Knuth 1987 RCT Germany	N=37 infertile men (N=39 randomised but data for n=2 participants who did not complete study not reported) Human chorionic gonadotrophin (HCG) + human menopausal gonadotrophin (HMG) group (n=17; number initially randomised not reported): • Mean age (SD): 31.1 (3.6) years • Severity of semen abnormalities: NR • Fertility diagnosis:	<u>HCG + HMG:</u> • HCG, 2500 IU delivered by intramuscular injection by the participant's GP on Mondays and Fridays for 13 weeks • HMG, 150 IU delivered by intramuscular injection by the participant's GP on Mondays, Wednesdays, and Fridays for 13 weeks	<u>Placebo:</u> • Sodium chloride was injected by the participant's GP on the same days as the HCG and HMG group for 13 weeks	• Pregnancy rate • Hormone parameters: ○ Testosterone (nmol/l) • Semen parameters: ○ Sperm concentration ($x10^6$/ml) ○ Sperm motility rate (%)	None

Study	Population	Intervention	Comparison	Outcomes	Other comments
	○ Idiopathic oligozoospermia: 17/17 (100%) Placebo group (n=20; number initially randomised not reported): • Mean age (SD): 33.2 (6.5) years • Severity of semen abnormalities: NR • Fertility diagnosis: ○ Idiopathic oligozoospermia: 20/20 (100%)				
Krause 1992 RCT Germany	N=76 men with idiopathic oligozoospermia Tamoxifen group (n=39): • Mean age (SD): 31 years (NR) • Severity of semen abnormalities: ○ Non-azoospermia: 39/39 (100%) • Fertility diagnosis: ○ Idiopathic oligozoospermia: 39/39 (100%) Placebo group (n=37): • Mean age (SD): 28.5 years (NR) • Severity of semen abnormalities: ○ Non-azoospermia: 37/37 (100%) • Fertility diagnosis: ○ Idiopathic oligozoospermia: 37/37 (100%)	<u>Tamoxifen:</u> • Tamoxifen 30mg/day for 3 months	<u>Placebo:</u> • Placebo for 3 months	• Spontaneous pregnancy rate • Hormone parameters: ○ Testosterone (ng/ml) • Semen parameters: ○ Sperm concentration (x10⁶/ml) ○ Sperm motility rate (%)	None
Maier 1988 RCT Austria	N=40 men with mild oligoasthenozoospermia: • Mean age (SD): NR • Severity of semen abnormalities: ○ Non-azoospermia: 40/40 (100%) • Fertility diagnosis:	<u>Tamoxifen:</u> • Tamoxifen, 10 mg 3 times a day for 3 months	<u>Tamoxifen + testolactone:</u> • Tamoxifen, 10mg 3 times a day for 3 months • Testolactone, 50mg 3 times a	• Pregnancy rate • Hormone parameters: ○ Oestradiol levels	None

Study	Population	Intervention	Comparison	Outcomes	Other comments
	○ Oligoasthenozoospermia (cause NR): 40/40 (100%) Participant characteristics not reported separately for each group		day for 3 months		
Matorras 1997 RCT Spain	N=148 subfertile men: • Fertility diagnosis: ○ Asthenoteratozoospermia (cause NR): 109/148 (74%) ○ Oligoasthenozoospermia (cause NR): 19/148 (13%) ○ Asthenozoospermia (cause NR): 9/148 (6%) ○ Teratozoospermia (cause NR): 3/148 (2%) ○ Oligoteratozoospermia (cause NR): 8/148 (5%) Follicle-stimulating hormone (FSH) group (n=68): • Mean age (SD): 34.06 (3.16) years • Severity of semen abnormalities: ○ Non-azoospermic: 68/68 (100%) • Fertility diagnosis: NR separately for each group Non-FSH group (n=80): • Mean age (SD): 34.63 (4.28) years • Severity of semen abnormalities: ○ Non-azoospermic: 80/80 (100%) • Fertility diagnosis: NR separately for each group	<u>FSH:</u> • FSH, 150 IU administered intramuscularly or subcutaneously 3 times a week, starting 3 months before the beginning of IUI cycles and maintained until the 5th IUI cycle	<u>Non-FSH:</u> • IUI without treatment of the male partner	• Pregnancy rates: ○ Pregnancy rate (per IUI cycle) ○ Pregnancy rate (per woman) ○ Assisted pregnancy rate (per IUI cycle) ○ Assisted pregnancy rate (per woman)	None
Matsumiya 1998	N=44 men with idiopathic normogonadotropic	<u>GnRH analogue:</u> • GnRH analogue (buserelin	<u>Clomiphene citrate:</u> • Clomiphene citrate,	• Pregnancy rates: ○ Spontaneous or	None

Study	Population	Intervention	Comparison	Outcomes	Other comments
RCT Japan	oligoasthenozoospermia Gonadotrophin releasing hormone (GnRH) analogue group (n=23): • Mean age (SD): 33.1 (4.5) years • Severity of semen abnormalities: ○ Non-azoospermic: 23/23 (100%) • Fertility diagnosis: ○ Idiopathic normogonado-tropic oligoasthenozoospermia: 23/23 (100%) Clomiphene citrate group (n=21): • Mean age (SD): 31.7 (4.1) years • Severity of semen abnormalities: ○ Non-azoospermic: 21/21 (100%) • Fertility diagnosis: ○ Idiopathic normogonado tropic oligoasthenozoospermia: 21/21 (100%)	acetate), 15µg (original concentration diluted to 10% with sterile saline, since 1 spray of Suprecur contained 150µg of GnRH analogue) once a day intranasally for ≥3 months	50 mg administrated orally every day for ≥3 months	assisted pregnancy rate ○ Spontaneous pregnancy rate • Semen parameters: ○ Sperm concentration (x10⁶/ml) ○ Sperm motility rate (%)	
Micic 1985 RCT Serbia (Yugoslavia at time of study)	N=101 men with idiopathic oligozoospermia: • Mean age (SD): NR • Severity of semen abnormalities: ○ Non-azoospermic: 101/101 (100%) • Fertility diagnosis: ○ Idiopathic oligozoospermia: 101/101 (100%) Participant characteristics not reported separately for each group	<u>Clomiphene citrate:</u> • Clomiphene citrate, 50 mg daily for 6 to 9 months	<u>No treatment:</u> • No treatment received	• Pregnancy rate • Semen parameters: ○ Sperm concentration (x10⁶/ml) ○ Sperm motility rate (%)	None
Paradisi 2006 RCT	N=30 men with idiopathic	<u>rhFSH:</u> • rhFSH, 300 IU (2 vials of 150 IU lyophilized	<u>Placebo:</u> • Matching placebo (2 vials	• Live birth rate	None

Study	Population	Intervention	Comparison	Outcomes	Other comments
Italy	oligoasthenozoospermia Recombinant human FSH (rhFSH) group (n=15) • Mean age (SD): NR • Severity of semen abnormalities: ○ Non-azoospermic: 15/15 (100%) • Fertility diagnosis: ○ Idiopathic oligoasthenozoospermia: 15/15 (100%) Placebo group (n=15) • Mean age (SD): NR • Severity of semen abnormalities: ○ Non-azoospermic: 15/15 (100%) • Fertility diagnosis: ○ Idiopathic oligoasthenozoospermia: 15/15 (100%)	FSH with 30mg saccharose) administered by subcutaneous injection every other day for at least 4 months	containing 30mg saccharose-only) administered by subcutaneous injection every other day for at least 4 months	• Spontaneous pregnancy rate • Hormone parameters: ○ Testosterone (µg/l) ○ Free testosterone (µg/l) • Semen parameters: ○ Sperm concentration ($x10^6$/ml) ○ Total sperm count ($x10^6$) ○ Sperm motility rate (%)	
Pusch 1989 RCT Austria	N=60 normogonadotropic oligozoospermic men: • Mean age (SD): NR. All men were aged <30 years • Severity of semen abnormalities: ○ Non-azoospermic: 60/60 (100%) • Fertility diagnosis: ○ Idiopathic normogonadotropic oligozoospermia: 60/60 (100%) Participant characteristics were not reported separately for each group	<u>Testosterone undecanoate:</u> • Testosterone undecanoate, 40mg capsules 3 times per day (for a total of 120mg per day) for 3 months	<u>Placebo:</u> • Identical placebo capsule. Further details not reported	• Pregnancy rate • Hormone parameters: ○ Free testosterone (pg/ml) ○ Total testosterone (ng/ml) ○ Oestradiol (pg/ml) • Semen parameters: ○ Sperm concentration ($x10^6$/ml) ○ Sperm motility rate (%) • Miscarriage rate	None
Selice 2011 RCT Italy	N=105 men with oligozoospermia	<u>rFSH:</u> • rFSH, 150 IU 3 times per week for 3 months	<u>No treatment:</u> • No treatment given for 3 months	• Spontaneous pregnancy rate • Hormone parameters: ○ Testosterone (nmol/l)	None

Study	Population	Intervention	Comparison	Outcomes	Other comments
	Recombinant follicle-stimulating hormone (rFSH) group (n=70): • Mean age (SD): NR • Severity of semen abnormalities: ○ Non-azoospermia: 70/70 (100%) • Fertility diagnosis: ○ Oligozoospermia (cause NR*): 70/70 (100%) No treatment group (n=35): • Mean age (SD): NR • Severity of semen abnormalities: ○ Non-azoospermia: 35/35 (100%) • Fertility diagnosis: ○ Oligozoospermia (cause NR*): 35/35 (100%) *All oligozoospermia was due to hypospermatogenesis, but cause not reported			○ Oestradiol (pmol/l) • Semen parameters: ○ Sperm concentration (x10⁶/ml) ○ Total sperm count (x10⁶) ○ Sperm motility rate (%) ○ Total motile sperm count (x10⁶)	
Sokol 1988 RCT USA	N=20 men with oligozoospermia (N=23 randomised but data for n=3 participants lost to follow-up not reported): • Mean age (range): NR (23-49 years) • Severity of semen abnormalities: ○ Non-azoospermia: 23/23 (100%) • Fertility diagnosis: ○ Oligozoospermia (cause NR): 23/23 (100%) Participant characteristics not reported separately for each group	<u>Clomiphene citrate:</u> • Clomiphene citrate, 25mg per day for 12 months	<u>Placebo:</u> • Placebo, 1 tablet per day for 12 months	• Spontaneous pregnancy rate • Hormone parameters: ○ Change in oestradiol from baseline (pg/ml) ○ Change in testosterone from baseline (ng/dl) • Semen parameters: ○ Change in sperm motility rate from baseline (%) ○ Change in total sperm count from	The difference between the outcomes sperm count and total sperm count is not reported

Study	Population	Intervention	Comparison	Outcomes	Other comments
				baseline ($x10^6$)	
Srivannaboon 1992 RCT 11 centres in: Australia; Belgium; Cuba; Hungary; India; Sweden; Switzerland; Thailand; Tunisia; UK	N=141 men with idiopathic oligozoospermia or asthenozoospermia (N=190 randomised before diagnosis and later found to be ineligible, only data for eligible participants reported) • Mean age (SD): 30.4 (4.2) years Clomiphene group (n=70) • Mean age (SD): 30.3 (4.4) years • Severity of semen abnormalities: ○ Non-azoospermia: 70/70 (100%) • Fertility diagnosis: ○ Idiopathic oligo- or astheno-zoospermia: 70/70 (100%) Placebo group (n=71) • Mean age (SD): 30.5 (4.1) years • Severity of semen abnormalities: ○ Non-azoospermia: 71/71 (100%) • Fertility diagnosis: ○ Idiopathic oligo- or astheno-zoospermia: 71/71 (100%)	<u>Clomiphene citrate:</u> • Clomiphene citrate, 25mg per day	<u>Placebo:</u> • Placebo for 6 months, no further details reported	• Spontaneous pregnancy rate	None
Zhao 2019 RCT China	N=316 infertile men with idiopathic oligozoospermia Human chorionic gonadotrophin (HCG) + human menopausal gonadotrophin (HMG) group (n=158): • Mean age (SE): ○ Lower-level group (inhibin B level	<u>HCG + HMG:</u> • HCG, 2000 IU through intramuscular injection twice a week for 3 months • HMG, 150 IU through intramuscular injection 3 times a week for 3 months	<u>Placebo:</u> • Intramuscular injections of physiological saline solution for 3 months	• Spontaneous pregnancy rate • Hormone parameters: ○ Testosterone (μg/l) • Semen parameters: ○ Sperm concentration ($x10^6$/ml)	None

Study	Population	Intervention	Comparison	Outcomes	Other comments
	<92 pg/ml): 31.96 (3.62) ○ Medium-level group (92 pg/ml < inhibin B level <316 pg/ml): 33.31 (4.16) ○ Higher-level group (inhibin B level >316 pg/ml): 32.45 (3.81) • Severity of semen abnormalities: ○ Non-azoospermia: 158/158 (100%) • Fertility diagnosis: ○ Idiopathic oligozoospermia: 158/158 (100%) Placebo group (n=158): • Mean age (SE): ○ Lower-level group (inhibin B level <92 pg/ml): 33.93 (4.15) ○ Medium-level group (92 pg/ml < inhibin B level <316 pg/ml): 32.34 (3.92) ○ Higher-level group (inhibin B level >316 pg/ml): 31.96 (2.96) • Severity of semen abnormalities: ○ Non-azoospermia: 158/158 (100%) • Fertility diagnosis: ○ Idiopathic oligozoospermia: 158/158 (100%)			○ Sperm motility rate (%) ○ Total motile sperm count (x10⁶)	

ART: assisted reproductive therapy; FSH: follicle stimulating hormone; GnRH: gonadotrophin-releasing hormone; GnRH-a: gonadotrophin-releasing hormone agonist; GP: general practitioner; HCG: human chorionic gonadotrophin; HMG: human menopausal gonadotrophin; ICSI: intracytoplasmic sperm injection; IUI: intrauterine insemination; IVF: in-vitro fertilisation; N: number; NR: not reported; RCT: randomised controlled trial; rFSH: recombinant follicle-stimulating hormone; rhFSH: recombinant human follicle-stimulating hormone; SD: standard deviation; SE: standard error

See the full evidence tables in appendix D and the forest plots in appendix E.

Summary of the evidence

Most of the evidence was on participants with semen abnormalities (non-azoospermia), with 22 studies exclusively including this population. Two studies included a mixed population, including both participants with impaired semen parameters as well as those with

azoospermia, and 4 studies did not report the severity of the participants' semen abnormality. As per the protocol, results were stratified according to these groups.

There was no available evidence on the effectiveness of drugs for hyperprolactinaemia for any of the stratified groups.

Studies with participants with semen abnormalities (non-azoospermia) only:

In addition to drugs for hyperprolactinaemia, there was no available evidence on the effectiveness of aromatase inhibitors for participants with impaired semen parameters.

Two studies including only non-azoospermic participants compared anti-oestrogens with no treatment and 4 compared anti-oestrogens with placebo. The evidence ranged from very low to moderate quality and was usually downgraded for risk of bias and/or imprecision. The evidence about the effectiveness of anti-oestrogens on pregnancy rates was unclear, with low quality evidence of a benefit only found in single studies in the medium term, and other evidence showing no important difference between anti-oestrogens and placebo or no treatment (very low to low quality). Regarding hormone parameters, anti-oestrogens tended to have a beneficial effect on testosterone levels (low to moderate quality), but there was evidence of an important harm in terms of effects on oestradiol levels when anti-oestrogens were compared with no treatment or placebo (low to moderate quality). There was consistent evidence of a benefit of using anti-oestrogens in terms of semen parameters when compared to no treatment (low quality), however the evidence comparing anti-oestrogens to placebo complicated this, with most evidence for this comparison tending to showing no important difference between treatments when it was compared with placebo (very low to low quality). These differences were not explained by looking at types of semen parameters together, such as sperm concentration. There was no evidence for these comparisons for the following outcomes: live birth, generic health-related or disease-specific quality of life, miscarriage, or rate of successful surgical sperm retrieval.

One study including only non-azoospermic participants compared anti-oestrogens and androgens to placebo. The evidence ranged from very low to moderate quality, and was usually downgraded for risk of bias and imprecision. The evidence found no clinically important difference between anti-oestrogens plus androgens and placebo with regards to spontaneous pregnancy rate or semen parameters in the short term (very low to low quality), but an important benefit of anti-oestrogens and androgens in the medium term for both of these outcomes (low to moderate quality). There was no evidence for this comparison for the following outcomes: live birth, generic health-related or disease-specific quality of life, hormone parameters, miscarriage, or rate of successful surgical sperm retrieval.

One study including only non-azoospermic participants compared aromatase inhibitors to no treatment. The evidence was all very low quality and was downgraded for risk of bias and imprecision. There was no clinically important difference between aromatase inhibitors and no treatment with regards to pregnancy rate in the short term, but the evidence for this outcome was very low quality with very serious imprecision, and pregnancy was not defined in the study. In terms of hormone parameters, there was very low quality evidence that aromatase inhibitors had an important benefit in terms of oestradiol levels in the short term, but there was serious imprecision in the effect estimate. There was no evidence for this comparison for the following outcomes: live birth, generic health-related or disease-specific quality of life, semen parameters, miscarriage, or rate of successful surgical sperm retrieval.

Six studies including only non-azoospermic participants compared gonadotrophin therapy with no treatment and 3 compared gonadotrophin therapy with placebo. The evidence ranged from very low to high quality and was usually downgraded for risk of bias and/or imprecision. Evidence from 1 study showed an important benefit of gonadotrophins in terms of live birth rate when compared to placebo (very low quality), but there was inconsistency in the evidence regarding pregnancy rates, whereby some studies showed a benefit of gonadotrophins while others showed no important difference between gonadotrophin therapy

and no treatment or placebo (very low to high quality). The highest quality evidence on pregnancy rates from 1 study demonstrated an important benefit of gonadotrophin therapy on spontaneous pregnancy rates in the short term (high quality). In terms of hormone levels, evidence consistently showed no important difference between gonadotrophins and no treatment or placebo for oestradiol levels (low to moderate quality), but evidence for testosterone from single studies showed both an important benefit and no important difference between outcomes (very low to high quality). For semen parameters outcomes, the evidence tended to be contradictory: for total sperm count and sperm concentration, the evidence showed an important benefit of gonadotrophin therapy compared to no treatment (very low to moderate quality), but there was also moderate to high quality evidence of no important difference compared to placebo; whereas for sperm motility, the evidence showed no important difference between gonadotrophin therapy and placebo (low to moderate quality), but the evidence was inconsistent when gonadotrophin therapy was compared to no treatment, showing both an important benefit of gonadotrophins and no important difference between interventions (low quality). This evidence was also mostly of low or very low quality, and where there was high or moderate quality evidence, this was usually from single studies and contradicted other high or moderate quality evidence. One study reported on miscarriage rates when comparing gonadotrophin therapy with no treatment and found no clinically important difference between interventions in the short term, but the evidence was very low quality with very serious imprecision. There was no evidence for these comparisons for the following outcomes: generic health-related or disease-specific quality of life, or rate of successful surgical sperm retrieval.

One study including only non-azoospermic participants compared gonadotrophin therapy to anti-oestrogens. The evidence was very low to low quality and was downgraded for risk of bias and imprecision. There was no clinically important difference between gonadotrophin therapy and anti-oestrogens with regards to pregnancy outcomes (very low quality), or semen parameters outcomes (low quality). There was no evidence for this comparison for the following outcomes: live birth, generic health-related or disease-specific quality of life, hormone parameters, miscarriage, or rate of successful surgical sperm retrieval.

Five studies including only non-azoospermic participants compared androgens with placebo. The evidence ranged from very low to high quality and was usually downgraded for risk of bias and/or imprecision. There was no clinically important difference between androgens and placebo for pregnancy rate outcomes (very low quality), semen parameter outcomes (very low to moderate quality) and miscarriage (very low quality). The evidence showed that androgens were effective for some hormone parameters but had no clinically important effect on others (very low to moderate quality). There was no evidence for this comparison for the following outcomes: live birth, generic health-related or disease-specific quality of life, or rate of successful surgical sperm retrieval.

Studies with a mixed population which included participants with impaired or reduced semen parameters (non-azoospermia) and azoospermia:

In addition to drugs for hyperprolactinaemia, there was no evidence on the effectiveness of anti-oestrogens or androgens for mixed populations including both people with impaired or reduced semen parameters as well as those with azoospermia.

One study including the mixed population compared aromatase inhibitors to placebo. The evidence was very low quality and was downgraded for risk of bias and imprecision. The evidence showed no clinically important difference between aromatase inhibitors and placebo in terms of spontaneous pregnancy rate in the medium term. There was no evidence for this comparison for the following outcomes: live birth, generic health-related or disease-specific quality of life, hormone parameters, semen parameters, miscarriage rates, or rate of successful surgical sperm retrieval.

One study including both people with impaired or reduced semen parameters as well as those with azoospermia compared gonadotrophin therapy with placebo. The evidence was very low to low quality and was downgraded for risk of bias, reporting bias and usually imprecision. There was very low quality evidence which showed no clinically important difference between gonadotrophin therapy and placebo in terms of pregnancy rate or miscarriage rate in the short term, and there tended to be no clinically important difference between interventions for semen parameters outcomes (very low quality). There was no evidence for this comparison for the following outcomes: live birth, generic health-related or disease-specific quality of life, hormone parameters, semen parameters, miscarriage rates, or rate of successful surgical sperm retrieval.

Studies where participants' severity of semen abnormality was not reported:

In addition to drugs for hyperprolactinaemia, there was no evidence on the effectiveness of anti-oestrogens or aromatase inhibitors for participants whose semen abnormality was not reported.

Three studies which did not report the severity of the participants' semen abnormality compared gonadotrophin therapy to placebo or no treatment. The evidence was moderate to very low quality and was downgraded for risk of bias and/ or imprecision. For pregnancy outcomes, the highest quality evidence showed an important benefit of gonadotrophin therapy (low to moderate quality), although there was also very low quality evidence of no important difference between interventions. The evidence showed no clinically important difference between gonadotrophin therapy and placebo for hormone parameters (low quality), and the evidence tended to show no clinically important difference between gonadotrophin therapy and placebo in terms of semen parameters (very low to high quality). There was no evidence for this comparison for the following outcomes: live birth, generic health-related or disease-specific quality of life, miscarriage rates, or rate of successful surgical sperm retrieval.

One study which did not report the type of the participants' semen abnormalities compared androgens to placebo. The evidence was very low quality and was downgraded for risk of bias and imprecision. There was no clinically important difference between androgens and placebo for pregnancy rates in the short term when pregnancy was not defined (very low quality). There was no evidence for this comparison for the following outcomes: live birth, generic health-related or disease-specific quality of life, hormone parameters, semen parameters, miscarriage rates, or rate of successful surgical sperm retrieval.

See appendix F for full GRADE tables.

Economic evidence

A total of 3,156 studies were identified in the health economic literature search for this review question. After duplicates were removed, 1,644 studies were screened on title and abstract. Three of these studies were included for full text review but all were excluded at this stage.

Included studies

A systematic review of the economic literature was conducted but no economic studies were identified which were applicable to this review question.

Also see the literature search strategy in appendix B and the economic study selection flow chart in appendix G.

Excluded studies

Economic studies not included in this review are listed, and reasons for their exclusion are provided in appendix J.

Economic model

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation.

Unit costs

Table 3: Unit costs

Resource	Unit costs	Source
Gonadotrophin therapy		
Cetrorelix	£27.13	British National Formulary (BNF) – date accessed 7.2.25; cost per injection
Granirelix	£27.13	British National Formulary (BNF) – date accessed 7.2.25; cost per injection
Choriogonadotropin alfa	£37.66	British National Formulary (BNF) – date accessed 7.2.25; cost per injection
Follitropin delta	£118.31	British National Formulary (BNF) – date accessed 7.2.25; cost per injection
Menotrophin	£18.02	British National Formulary (BNF) – date accessed 7.2.25; cost per injection
Lutropin alfa	£31.38	British National Formulary (BNF) – date accessed 7.2.25; cost per injection
Urofollitropin	£27.90	British National Formulary (BNF) – date accessed 7.2.25; cost per injection (75 unit)
Follitropin alfa	£144.70	British National Formulary (BNF) – date accessed 7.2.25; cost per injection (625 unit per 1 ml)
Anti-oestrogens		
Clomifene	£0.34	British National Formulary (BNF) – date accessed 7.2.25; cost per day (30, 50mg tablets £10.15)
Tamoxifen	£0.07	British National Formulary (BNF) – date accessed 7.2.25; cost per day (30, 20mg tablets £2.17)
Letrozole	£0.10	British National Formulary (BNF) – date accessed 7.2.25; cost per day (28, 2.5mg tablets £2.82)
Aromatase inhibitors		
Anastrozole	£0.05	British National Formulary (BNF) – date accessed 7.2.25; cost per day (28, 1mg tablets £1.29)
Drugs for hyperprolactinaemia		
Bromocriptine	£2.00	British National Formulary (BNF) – date accessed 7.2.25; cost per day (30, 2.5mg tablets £60.20)

Costs for androgens were not publicly available.

The committee's discussion and interpretation of the evidence

The outcomes that matter most

The committee agreed that live birth was the critical outcome because it is the most important outcome for people with fertility problems, and other outcomes that directly measured the effects of any intervention, such as improved hormone parameters, were usually only important if they resulted in live birth. They agreed that live birth rate was most important because, unlike pregnancy rates, it takes into account both pregnancy and the effects of miscarriage or other antenatal loss. The committee agreed not to restrict the definition of this outcome to full term live birth because this was not likely to be reported in studies. However, after reviewing the studies, it became clear that very few papers reported on live birth, and pregnancy rates were reported much more often than live birth rates. The committee therefore agreed it was appropriate to make pregnancy rates a critical outcome as well, to reflect the evidence available and to ensure evidence on improved fertility was prioritised over other measures of effectiveness.

The committee agreed a number of other outcomes were important. Generic health-related or disease-specific quality of life was chosen as a measure of well-being which may capture long-term health-related outcomes associated with the effectiveness of interventions, which is important as it can have a direct impact on the quality of life of people affected by fertility problems. The committee agreed that hormone and semen parameters were important because they are a direct measure of the differential effects associated with hormone treatments in people with male-factor fertility problems. Miscarriage was agreed to be an important outcome because it can be devastating for people trying to have a baby and can indicate when an intervention is effective for achieving pregnancy but does not lead to a live birth. Rate of successful surgical sperm retrieval was also agreed to be an important outcome by the committee because it is a measure of whether hormone treatments are effective in improving the viability of assisted reproductive techniques to achieve pregnancy when there is a male factor fertility problem.

The quality of the evidence

The quality of the evidence was assessed using GRADE methodology and was very low to high quality. Where evidence was downgraded, this was mainly due to risk of bias assessed using version 2 of the Cochrane risk of bias tool, and imprecision in the effect estimate. Where outcomes were downgraded for risk of bias, this was mainly due to deviations from the intended interventions, missing outcome data, measurement of the outcome (especially with regards to pregnancy rates outcomes) and/or selection of the reported result. In some cases, there was also bias arising from the randomisation process. For some outcomes, there was additionally inconsistency between studies reporting the outcome due to heterogeneity, and/or suspected publication bias due to the majority of studies contributing to the outcome being industry funded.

There was no evidence available for drugs for hyperprolactinaemia, and no evidence for some of the secondary outcomes (generic health-related or disease-specific quality of life and rate of successful surgical sperm retrieval). Only 1 study reported the critical outcome live birth rate.

Benefits and harms

The committee agreed that the evidence presented for this review was often conflicting. They had concerns about the quality and conduct of some of the studies and, where information about the baseline hormonal status of the study participants was reported, only participants with normal hormone levels were included. Therefore, although there was some evidence of benefit seen with some of the hormonal treatments, it was difficult for them to draw clear conclusions about the effectiveness of most of the interventions considered.

The committee first discussed the fact that, for participants with abnormal semen parameters at baseline, an increased motile sperm concentration and increased total sperm count were most likely to positively affect fertility. However, the committee agreed it was important to consider whether any improvements in semen parameters translated to improved pregnancy rates, as this is the most direct measure of any differential effectiveness of hormone treatments on fertility.

Gonadotrophins

All of the studies reporting on the effectiveness of gonadotrophins either excluded people with hypogonadotropic hypogonadism, excluded people with abnormal hormone parameters at baseline, or did not report on these characteristics of the included participants. People with hypogonadotropic hypogonadism, in which a lack of the pituitary hormones FSH and LH leads to reduced production of testosterone, usually benefit from gonadotrophin therapy, although improving testosterone levels does not necessarily improve semen quality. The committee noted that some of included studies excluded people with this condition on the basis that gonadotrophin therapy has already been proven effective in this population. They agreed, based on their knowledge and experience, that gonadotrophin therapy should routinely be offered to people with hypogonadotropic hypogonadism. This recommendation was made despite the lack of evidence for this population from the studies included in this review, because this treatment can stimulate spermatogenesis and it is current standard good clinical practice to treat hypogonadotropic hypogonadism with gonadotrophins.

The committee next discussed the evidence for the use of gonadotrophins in non-azoospermic participants. This showed an important benefit of gonadotrophins in terms of live birth rate when compared to placebo. However, this was low quality evidence and live birth rates were only reported by 1 pilot study which had very small numbers, was industry funded and did not lead to a subsequent full study suggesting that the evidence was not strong enough to justify further investigation. The committee were therefore hesitant to make a strong recommendation on the basis of this live birth evidence alone. The committee reviewed the evidence on pregnancy rates and noted some inconsistency whereby some studies showed a benefit while others showed no important difference between gonadotrophin therapy and no treatment or placebo. There was some high quality evidence from 1 study which demonstrated an important benefit of gonadotrophin therapy on spontaneous pregnancy rates in the short term, but the committee noted that the study actually reported lower pregnancy rates than might be expected in a 3 month period after a round of ICSI, and the difference between treatment groups was unusually large considering there was no important difference between the groups with regards to semen parameters. The committee had further reservations about the applicability of the evidence to the UK population and concerns about the randomisation. They therefore were hesitant to assign significance to this 1 study and its outcomes alone. There was other evidence which showed an important benefit of gonadotrophins on pregnancy rates, but this was low to very low quality, and was contradicted by evidence from further studies which showed no difference between gonadotrophin therapy and no treatment or placebo. The committee agreed that if gonadotrophin therapy had a significant benefit in terms of pregnancy rates, the evidence should also show gonadotrophin therapy to be more effective than anti-oestrogens (for which the evidence base was very uncertain, as discussed below), but instead the evidence showed no important difference between gonadotrophin therapy and anti-oestrogens for any pregnancy rates outcomes, or for semen parameters outcomes.

The next evidence the committee discussed was on gonadotrophin therapy from studies including both azoospermic and non-azoospermic people, which also showed no important difference between gonadotrophin therapy and placebo for pregnancy rates. The committee discussed the moderate quality evidence from 1 study which did not report the type of the participants' semen abnormalities and which showed that gonadotrophin therapy had an important benefit for pregnancy rates when compared to no treatment. The committee agreed the long-term follow-up period of this study was positive but that the study also had a

very narrow scope, as all participants had a varicocelectomy prior to receiving medical treatment. Varicocelectomy could have had a significant impact on the participants' fertility depending on the grade or severity of their varicocele, and as this was not controlled for in the study, this could explain the important difference in pregnancy rate outcomes between groups. The committee also agreed the data from this study were not generalisable and could not be extrapolated even to all people with male-factor fertility problems due to a varicocele, as it makes the assumption that everyone with a varicocele will have theirs removed, which the committee agreed based on their knowledge and experience is not always the case. There was also contradictory evidence regarding pregnancy rates for this population as further evidence showed no important difference between gonadotrophin therapy and placebo or no treatment.

The committee discussed the remaining evidence for gonadotrophin therapy when it was compared to no treatment or placebo with regards to hormone levels and semen parameters and agreed the evidence tended to be inconclusive and mostly of low or very low quality, with evidence from single studies usually contradicting others. The evidence from studies including both azoospermic and non-azoospermic people comparing gonadotrophin therapy with placebo was contradictory and very low quality for the semen parameters outcomes. Studies which did not report the severity of the participants' semen abnormalities, consistently showed no important difference between gonadotrophin therapy and no treatment or placebo in terms of both hormone and semen parameters.

The committee agreed that, with such an inconclusive evidence base, it was not possible to recommend gonadotrophin therapy to all people with male-factor fertility problems because it was difficult to justify offering the intervention to such a large population when the evidence regarding its benefits were so uncertain (see the section on cost effectiveness and resource use below for more information).

Anti-oestrogens

The evidence about the effectiveness of anti-oestrogens on pregnancy rates was unclear, and although there was some evidence of a benefit from using anti-oestrogens in terms of semen parameters when compared to no treatment, this contradicted evidence showing no important difference between treatments when it was compared with placebo. There was also evidence of an important harm in terms of effects on oestradiol levels when anti-oestrogens were compared with no treatment or placebo. Without more conclusive evidence showing an effect on pregnancy or any evidence on live birth rates, anti-oestrogens could not be recommended for all people with male-factor fertility problems. There was some moderate quality evidence of an important benefit in terms of spontaneous pregnancy rate when anti-oestrogens were used in combination with androgens compared to placebo, but the committee were concerned about the legitimacy of the data: this evidence came from 1 study with a small cohort and the large effect size was considered to be unusual when compared to the other available data about the effectiveness of anti-oestrogens and androgens alone. The committee agreed this might be due to differences between groups at baseline, because information about duration of the fertility problems and female partners' ages at baseline was not reported and not controlled for in the analysis. Overall, the committee agreed that they could not make a recommendation for combination therapy with anti-oestrogens and androgens on the basis of the available evidence, especially considering the potential harms of androgens on overall fertility as discussed below.

Aromatase inhibitors

The evidence regarding aromatase inhibitors was very limited: only 1 study including both azoospermic and non-azoospermic participants investigated the effectiveness of aromatase inhibitors compared to placebo. This study only reported on the outcome pregnancy rates and found no important difference between aromatase inhibitors and placebo. The committee agreed the low quality and scarceness of the evidence meant it was not possible to make recommendations on this intervention.

Androgens

The committee discussed the evidence on androgens and agreed it would be expected that androgens would improve some hormone parameters, but it was important that this also translated into improved pregnancy and live birth rates. The evidence showed that androgens alone did not have any effect on pregnancy rates (either for non-azoospermic people or when the severity of the participants' semen abnormalities were not reported), semen parameters, or miscarriage rates. The committee discussed the evidence alongside their knowledge that the use of androgens can commonly be associated with the important harm of worsened fertility, and their experience that it is standard practice to ensure people are not using androgens when trying to achieve pregnancy. They therefore agreed that androgens should not be offered to people with male-factor fertility problems and made a new recommendation to state this.

Drugs for hyperprolactinaemia

As there was no evidence on drugs for hyperprolactinaemia the committee could not make recommendations on their use.

Linking the benefits and harms of interventions to the recommendations

The committee agreed, as discussed above, that they could not make any recommendations on the use of aromatase inhibitors or drugs for hyperprolactinaemia, and that androgens should not be offered to people with male-factor fertility problems. They discussed whether anti-oestrogens and gonadotrophins should be offered to people with male-factor fertility problems and no hypogonadotropic hypogonadism, but agreed the evidence was not robust enough to make a recommendation for their routine use, especially considering the diversity of this population. For example, there are some instances in current practice in which hormone treatment might be offered to people with semen abnormalities who do not have hypogonadotropic hypogonadism but do have normal or high levels of FSH and low testosterone, but the evidence tended to exclude people with hormone abnormalities, so it was also not possible to make a recommendation for this population. Additionally, some people with semen abnormalities and normal hormone parameters have testicular dysfunction instead of an obstruction (as is normally indicated by these factors). Therefore, while most people with normal FSH and testosterone levels but abnormal semen parameters will have a blockage that won't be fixed by hormone treatments, there is a subgroup of people who have testicular dysfunction (mimicking an obstruction) for whom hormone treatments might be useful. As it was not possible to separate out subgroups based on hormone levels using the studies included in this review, the committee agreed that further research was needed on the effectiveness of hormonal treatment specifically for people with semen abnormalities who do not have hypogonadotropic hypogonadism or evidence of obstruction but do have normal or high levels of FSH and low or normal testosterone (see research recommendation in appendix K). However, without existing robust evidence on this population, treatment with anti-oestrogens or gonadotrophins should only be given to this group in the context of a clinical trial, and not routinely offered. The committee referred to the European Association of Urology's (EAU) guideline on Sexual and Reproductive Health, which found that no conclusions could be drawn regarding the use of hormone therapy for people with idiopathic infertility due to the weak evidence, and therefore that its use could not be routinely advocated, and the committee noted that this was in accordance with the recommendations they had made based on their review of the evidence.

The committee discussed that semen and hormone profile analyses are often used together when someone presents with a male fertility problem, however clinical practice varies. They also agreed that male hormone profile evaluation is an easy and relatively cheap test to do and it can be helpful in assessing male fertility problems. The committee wanted to unify and standardise clinical practice, therefore, based on the committee's consensus, they agreed that, when someone has 2 or more abnormal semen analyses, health professionals should consider measuring serum testosterone and gonadotrophin levels.

Cost effectiveness and resource use

This review question was initially prioritised for economic analysis but, after the clinical evidence was presented, the committee concluded that it was no longer warranted and instead they made a qualitative assessment of the cost-effectiveness of interventions covered by this review.

All of the included studies identified in the clinical review reporting on the effectiveness of gonadotrophins excluded people with hypogonadotropic hypogonadism. However, the committee acknowledged that people with hypogonadotropic hypogonadism usually benefit from gonadotrophin therapy and therefore agreed that gonadotrophin therapy should be routinely offered to people with hypogonadotropic hypogonadism. The committee discussed that this recommendation is reflective of standard good clinical practice – also noting that gonadotrophin therapy can stimulate spermatogenesis for people with hypogonadotropic hypogonadism and therefore increase the chance of a live birth, thus eliminating the need for further treatment. The committee therefore concluded that this consensus recommendation would not result in a significant resource impact and is highly likely to be cost-effective when compared to no treatment.

For all other health-related male factor fertility problems, the committee considered that the evidence base for gonadotrophins and anti-oestrogens was very inconclusive with no clear evidence of beneficial treatment effect established. The committee noted the high cost of gonadotrophin therapy and concluded that these treatments could not be considered a cost-effective use of NHS resources. Furthermore, the committee did not think the clinical evidence suggested that aromatase inhibitors, androgens or drugs for hyperprolactinaemia would be effective or cost-effective and therefore no recommendations were made for the use of these interventions in the NHS for people with male factor infertility.

Recommendation to consider measuring serum testosterone and gonadotrophin levels for those with 2 or more abnormal semen analyses is not expected to have a significant resource impact.

Recommendations supported by this evidence review

This evidence review supports recommendations 1.17.5, 1.24.1, 1.24.2 and 1.24.3 and the research recommendation on the effectiveness of hormone treatment in male factor fertility problems.

References – included studies

Effectiveness

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Appendices

Appendix A Review protocols

Review protocol for review question: What is the effectiveness of hormone treatment in male factor fertility problems?

Table 4: Review protocol

ID	Field	Content
0.	PROSPERO registration number	CRD42023392273
1.	Review title	Effectiveness of hormone treatment in male factor fertility problems
2.	Review question	What is the effectiveness of hormone treatment in male factor fertility problems?
3.	Objective	To determine the effectiveness of hormone treatment in male factor fertility problems
4.	Searches	The following databases will be searched: • Clinical searches • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE ALL • Epistemonikos Economic searches • MEDLINE ALL • Embase • International Network of Agencies for Health Technology Assessment (INAHTA) • HTA Economic evaluations and quality of life filters will be applied.

ID	Field	Content
		Searches will be restricted by: • English language • Human studies The full search strategies for MEDLINE database will be published in the final review. For each search, the principal database search strategy is quality assured by a second information scientist using an adaptation of the PRESS 2015 Guideline Evidence-Based Checklist.
5.	Condition or domain being studied	Male factor fertility problems
6.	Population	**Inclusion:** People with health-related male factor fertility problems In this guideline, people with health-related fertility problems are those who have a known health-related impediment to fertility, or those who do not achieve a pregnancy: • after 12 months of regular unprotected sexual intercourse or • after 6 cycles of artificial insemination.
7.	Intervention	Any hormone-related therapy for the treatment of male factor fertility problems, for example: • Gonadotrophin therapy • Anti-oestrogens (for example, clomifene and tamoxifen) • Aromatase inhibitors (for example, anastrozole) • Androgens (for example, testosterone and testosterone analogues) • Drugs for hyper-prolactinaemia (for example, bromocriptine)
8.	Comparator	• Head-to-head comparisons between different interventions within each category • Head-to-head comparisons between different interventions between each category • Placebo • No intervention

ID	Field	Content

9.	Types of study to be included	• Include published full-text papers:
		  ○ Systematic reviews of RCTs
		  ○ Parallel RCTs (individual or cluster)
		• If insufficient RCTs*:
		  ○ Quasi-randomised controlled trials
		  ○ Randomised studies that use a crossover design (data from the first phase only)
		  ○ Prospective and retrospective cohort studies**
		*These studies will be considered for inclusion if insufficient RCT evidence is available for guideline decision making. Sufficiency will be judged taking into account factors including number/quality/sample size of RCTs, outcomes reported and availability of data from subgroups of interest.
		**Prospective and retrospective studies will be downgraded for risk of bias if they do not adequately adjust for the following covariates, but will not be excluded for this reason:
		• Age
		• Different male factor fertility problems
		• Duration of infertility
		• Female factor diagnoses

10.	Other exclusion criteria	Interventions: • Kinin-enhancing drugs Other exclusion criteria: • Language limitations: studies published not in English-language • Conference abstracts will not be included because these do not typically have sufficient information to allow full critical appraisal.
11.	Context	This guidance will fully update the following NICE guideline: Fertility problems: assessment and treatment (last updated 2017; CG156)
12.	Primary outcomes (critical outcomes)	• Live birth
13.	Secondary outcomes (important outcomes)	• Generic health-related or disease-specific quality of life measured using a validated instrument in the person with male factor fertility problems, for example:

ID	Field	Content
		○ EQ-5D ○ Health Utilities Index Mark 3 (HUI3) questionnaire ○ FertiQoL • Increased testosterone production/ improved hormonal parameters • Improved semen parameters (for example, sperm concentration, motility, normal forms, total sperm count) • Miscarriage (loss of a baby before 24 weeks gestational age) • Clinical pregnancy rate (an ultrasound scan that has shown at least one fetal heart beat) • Rate of successful surgical sperm retrieval
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI and de-duplicated. Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol. Full versions of the selected studies will be obtained for assessment. Studies that fail to meet the inclusion criteria once the full version has been checked will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the reason for its exclusion. A standardised form will be used to extract data from studies. The following data will be extracted: study details (reference, country where study was carried out, type and dates), participant characteristics, inclusion and exclusion criteria, details of the interventions if relevant, setting and follow-up, relevant outcome data and source of funding. One reviewer will extract relevant data into a standardised form, and this will be quality assessed by a senior reviewer.
15.	Risk of bias (quality) assessment	Quality assessment of individual studies will be performed using the following checklists: • ROBIS tool for systematic reviews • Cochrane RoB tool v.2 for RCTs and quasi-RCTs • Cochrane RoB tool v.2 for cluster-randomised trials • Cochrane RoB tool v.2 for crossover trials • Cochrane ROBINS-I tool for non-randomised (clinical) controlled trials and cohort studies The quality assessment will be performed by one reviewer and this will be quality assessed by a senior reviewer.
16.	Strategy for data synthesis	Depending on the availability of the evidence, the findings will be summarised narratively or quantitatively. Where possible, meta-analyses will be conducted using Cochrane Review Manager software. A fixed effect meta-analysis will be conducted and data will be presented as risk ratios or odds ratios for dichotomous outcomes, and mean differences or standardised mean differences for continuous outcomes. Heterogeneity in the effect estimates of the individual studies will be assessed using the I2 statistic. Alongside visual inspection of the point estimates and

ID	Field	Content
		confidence intervals, I2 values of greater than 50% and 80% will be considered as significant and very significant heterogeneity, respectively. Heterogeneity will be explored as appropriate using sensitivity analyses and pre-specified subgroup analyses. If heterogeneity cannot be explained through subgroup analysis then a random effects model will be used for meta-analysis, or the data will not be pooled. The confidence in the findings across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group: http://www.gradeworkinggroup.org/ Importance and imprecision of findings will be assessed against minimally important differences (MIDs). The following MIDs will be used: • Live birth: statistical significance • Validated scales/continuous outcomes: published MIDs where available • All other outcomes & where published MIDs are not available: 0.8 and 1.25 for all relative dichotomous outcomes; +/- 0.5x control group SD for continuous outcomes

17.	Analysis of sub-groups	Evidence will be stratified by:
		• Level of severity of infertility
		  ○ People with azoospermia
		  ○ People without azoospermia
		
		Evidence will be sub-grouped by the following only in the event that there is significant heterogeneity in outcomes:
		• Male factor fertility diagnosis
		  ○ unexplained
		  ○ congenital or acquired urogenital abnormalities
		  ○ gonadotoxic exposure (e.g., radiotherapy or chemotherapy)
		  ○ malignancies
		  ○ urogenital tract infections
		  ○ increased scrotal temperature (e.g., as a consequence of varicocele)
		  ○ endocrine disturbances
		  ○ genetic abnormalities
		  ○ immunological factors
		• Age

ID	Field	Content			
		○ <45 years ○ ≥45 years Where evidence is stratified or subgrouped the committee will consider on a case by case basis if separate recommendations should be made for distinct groups. Separate recommendations may be made where there is evidence of a differential effect of interventions in distinct groups. If there is a lack of evidence in one group, the committee will consider, based on their experience, whether it is reasonable to extrapolate and assume the interventions will have similar effects in that group compared with others.			
18.	Type and method of review	☒	Intervention		
		☐	Diagnostic		
		☐	Prognostic		
		☐	Qualitative		
		☐	Epidemiologic		
		☐	Service Delivery		
		☐	Other (please specify)		
19.	Language	English			
20.	Country	England			
21.	Anticipated or actual start date	14/11/2022			
22.	Anticipated completion date	06/11/2024			
23.	Stage of review at time of this submission	Review stage		Started	Completed
		Preliminary searches		☑	☑
		Piloting of the study selection process		☑	☑
		Formal screening of search results against eligibility criteria		☑	☑

ID	Field	Content		
		Data extraction	☑	☑
		Risk of bias (quality) assessment	☑	☑
		Data analysis	☑	☑
24.	Named contact	5a. Named contact Guideline Development Team A 5b. Named contact e-mail FertilityProblems@nice.org.uk 5c. Organisational affiliation of the review Guideline Development Team A, Centre for Guidelines, National Institute for Health and Care Excellence (NICE)		
25.	Review team members	• Senior Technical Analyst • Technical Analyst		
26.	Funding sources/sponsor	This systematic review is being completed by the Guideline Development Team A, Centre for Guidelines, which receives funding from the National Institute for Health and Care Excellence (NICE)		
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.		
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10263		

ID	Field	Content	
29.	Other registration details	None	
30.	URL for published protocol	https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=392273	
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: notifying registered stakeholders of publication publicising the guideline through NICE's newsletter and alerts issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
32.	Keywords	Male factor fertility problems, infertility, hormone treatment, hormones	
33.	Details of existing review of same topic by same authors	None	
34.	Current review status	☒	Ongoing
		☒	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35..	Additional information	None	
36.	Details of final publication	www.nice.org.uk	

HTA: Health Technology Assessment; MID: minimally important difference; NICE: National Institute for Health and Care Excellence; RCT: randomised controlled trial; RoB: risk of bias; SD: standard deviation

Appendix B Literature search strategies

Literature search strategies for review question: What is the effectiveness of hormone treatment in male factor fertility problems?

Database: Ovid MEDLINE(R) ALL <1946 to January 03, 2025>

Date of last search: 06/01/2025

1	exp infertility, male/
2	(male/ or men/ or exp "Sexual and Gender Minorities"/) and (Infertility/ or fertility/)
3	((male? or men or man or transgender* or trans gender* or transwom?n or transfemale* or transfeminine or transperson* or transpeople or transsex* or intersex* or inter sex* or nonbinary or non binary or TGNB or genderqueer* or two spirit or sex reassign* or "assigned male at birth" or AMAB or agender) adj4 (infertil* or subfertil* or fertil* or hypofertil* or subfecund* or fecund* or infecund* or steril*)).tw.
4	((trans or transgender*) adj1 (wom?n or female* or feminin* or person* or people or sex* or patient* or identit* or nonbinary or "non binary") adj4 (infertil* or subfertil* or fertil* or hypofertil* or subfecund* or fecund* or infecund* or steril*)).tw.
5	(gender adj1 (expansive* or queer* or nonconform* or "non conform*" or dysphori* or fluid* or divers* or neutral or reassign* or affirm* or variance* or Incongruent or minorit* or transition*) adj4 (infertil* or subfertil* or fertil* or hypofertil* or subfecund* or fecund* or infecund* or steril*)).tw.
6	((abnormal or block* or defect* or deficien* or fail* or immobil* or impair* or insufficien* or low* or reduc* or suboptimal*) adj2 sperm*).tw.
7	((abnormal or defect* or deficien* or impair* or insufficien* or low* or reduc* or suboptimal*) adj2 semen*).tw.
8	(aspermi* or asperma* or asthenospermi* or asthenoteratozoospermi* or asthenozoospermi* or azoosperm* or cryptozoospermi* or cryptospermi* or globozoospermi* or hypospermatogen* or oligoasthenoteratozoospermi* or oligospermi* or oligozoospermi* or teratospermi* or teratozoospermi*).tw.
9	(germinal cell aplasia or (("sertoli cell only" or "del castillo") adj2 syndrome)).tw.
10	retrograde ejaculation/ or retrograde ejaculat*.tw.
11	hypogonadism/ or kallmann syndrome/ or klinefelter syndrome/
12	(hypogonad* or hypogenitalis* or Kallman* or (gonad* adj (failure* or insufficien* or deficien*))).tw.
13	(Klinefelter* or ("47" adj XXY)).tw.
14	((xxyy or xxy or xxxy or xxxxy) adj2 (syndrome* or trisom* or constitution or male* or men or man)).tw.
15	((early or late) adj1 "maturation arrest").tw.
16	or/1-15
17	(hormon* adj2 therap*).tw.
18	hormone replacement therapy/
19	gonadotropins/ or exp chorionic gonadotropin/ or exp gonadotropins, pituitary/ or Gonadotropin-Releasing Hormone/
20	(gonadotrop* or GnRH or gn-rh or gonadorelin or hCG or choriogonadotropin* or choriogonadotrophin* or choriogonin or buserelin or suprecur or cystorelin or factrel or dirigestran or gonadoliberin or pregonadotropin or gonan or folistiman or ambinon or anthrogon or kryptocur or luliberin or bigonist or profact or receptal or suprefact or tiloryth or goserelin or zoladex or leuprolide or enantone or leuprorelin or lupron or nafarelin or synarel or triptorelin or decapeptyl or trelstar or cetrorelix or cetrotide or ganirelix or fyremadel or ovitrelle or follitropin or bemfola or gonal-f or ovaleap or pergoveris or rekovelle or lutropin or luveris or meriofert or fostimon or biogonadil or chorulon or gonabion or novarel or pregnyl or FSH or rFSH or uFSH or asgph or lutotropin or thyrotropin or tsh or trh or icsh or lh or ulh or rlh or lhfsh or lhfshrh or lhrh or lfrh or luteoziman or luteozyman or hmg or humegon or menogon or menopur or menotrophin* or menotropin* or normegon or pergonal or urofollitropin or bravelle or fertinex or follitrin or metrodin or fertinorm or thyrotropin or thyrotrophin or thyrogen).tw.
21	((interstitial cell-stimulating or luteini?ing or follicle stimulating or folliculostimulating or gonad* stimulat* or pituitary or glycoprotein or thyroid) adj2 hormone*).tw.
22	exp Estrogen Receptor Modulators/
23	((?estrogen or ?estradiol) adj2 (modulator* or inhibitor* or antagonist* or blocker* or suppress*)).tw.
24	(SERM or antiestrogen* or anti estrogen* or antioestrogen* or anti oestrogen* or tamoxifen or fulvestrant or faslodex or toremifene or fareston or nolvadex or novaldex or soltamox or tomaxithen or zitazonium or clomifene or clomid or androxal or clomiphene or chloramiphene or clomide or clomifen or clostilbegit or clostilbegyt or enclomid or enclomifene or enclomiphen* or serophene or transclomiphene or zuclomifene or dyneric or gravosan or klostilbegit or serophene or uclomiphene or evista or keoxifene or isomer).tw.
25	exp Androgens/ or Testosterone/

26	((synthetic adj2 hormone*) or androgen* or anaprotin or andractim or androstanolone or dihydroepitestosterone or dihydrotestosterone or gelovit or stanolone or nandrolone or estrenolone or norandrostenolone or nortestosterone or anavar or oxandrin or oxandrolone or oxymetholone or anadrol or anapolon or hydroxymetholone or oxymethalone or stanazolol or stanozolol or androstanazol or methylstanazol or stromba or winstrol or androgel or androderm or andropatch or androtop or histerone or sterotate or sustanon or testim or testoderm or testolin or testopel or testosterone or testavan or testim or testogel or tostran).tw.
27	((male fertil* or male infert*) adj2 (agent* or hormone*)).tw.
28	Bromocriptine/ or Cabergoline/
29	((dopamine adj2 agonist*) or DA or bromocriptin* or bromocryptin* or bromoergocryptine or parlodel or arolac or carbamide or cuvalit or dopergin* or lisuride or lysuride or revanil or quinagolide or norprolac or cabergoline or cabaser* or cabergoline or dostinex).tw.
30	exp Aromatase Inhibitors/
31	((aromatase adj1 (inhibit* or antagonist*)) or aminoglutethimide or anastrazole or arimidex or cytadren or exemestane or fadrozole or aromasin or femara or letrozole or orimeten or testolactone or zeneca).tw.
32	or/17-31
33	16 and 32
34	letter/
35	editorial/
36	news/
37	exp historical article/
38	Anecdotes as Topic/
39	comment/
40	case reports/
41	(letter or comment*).ti.
42	or/34-41
43	randomized controlled trial/ or random*.ti,ab.
44	42 not 43
45	animals/ not humans/
46	exp Animals, Laboratory/
47	exp Animal Experimentation/
48	exp Models, Animal/
49	exp Rodentia/
50	(rat or rats or mouse or mice or rodent*).ti.
51	or/44-50
52	33 not 51
53	limit 52 to english language
54	randomized controlled trial.pt.
55	controlled clinical trial.pt.
56	pragmatic clinical trial.pt.
57	randomi#ed.ab.
58	placebo.ab.
59	randomly.ab.
60	Clinical Trials as topic.sh.
61	trial.ti.
62	or/54-61
63	Meta-Analysis/
64	Meta-Analysis as Topic/
65	(meta analy* or metanaly* or metaanaly*).ti,ab.
66	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
67	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
68	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
69	(search* adj4 literature).ab.
70	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
71	cochrane.jw.

72	or/63-71
73	53 and (62 or 72)
74	Observational Studies as Topic/
75	Observational Study/
76	Epidemiologic Studies/
77	exp Case-Control Studies/
78	exp Cohort Studies/
79	Cross-Sectional Studies/
80	Controlled Before-After Studies/
81	Historically Controlled Study/
82	Interrupted Time Series Analysis/
83	Comparative Study.pt.
84	case control$.tw.
85	case series.tw.
86	(cohort adj (study or studies)).tw.
87	cohort analy$.tw.
88	(follow up adj (study or studies)).tw.
89	(observational adj (study or studies)).tw.
90	longitudinal.tw.
91	prospective.tw.
92	retrospective.tw.
93	cross sectional.tw.
94	or/74-93
95	53 and 94
96	95 not 73

Database: Embase <1974 to 2025 January 03>

Date of last search: 06/01/2025

1	exp male infertility/ or semen abnormality/
2	(male/ or "sexual and gender minority"/ or "transgender and gender nonbinary"/) and (infertility/ or subfertility/)
3	((male? or men or man or transgender* or trans gender* or transwom?n or transfemale* or transfeminine or transperson* or transpeople or transsex* or intersex* or inter sex* or nonbinary or non binary or TGNB or genderqueer* or two spirit or sex reassign* or "assigned male at birth" or AMAB or agender) adj4 (infertil* or subfertil* or fertil* or hypofertil* or subfecund* or fecund* or infecund* or steril*)).tw.
4	((trans or transgender*) adj1 (wom?n or female* or feminin* or person* or people or sex* or patient* or identit* or nonbinary or "non binary") adj4 (infertil* or subfertil* or fertil* or hypofertil* or subfecund* or fecund* or infecund* or steril*)).tw.
5	(gender adj1 (expansive* or queer* or nonconform* or "non conform*" or dysphori* or fluid* or divers* or neutral or reassign* or affirm* or variance* or Incongruent or minorit* or transition*) adj4 (infertil* or subfertil* or fertil* or hypofertil* or subfecund* or fecund* or infecund* or steril*)).tw.
6	((abnormal or block* or defect* or deficien* or fail* or immobil* or impair* or insufficien* or low* or reduc* or suboptimal*) adj2 sperm*).tw.
7	((abnormal or defect* or deficien* or impair* or insufficien* or low* or reduc* or suboptimal*) adj2 semen*).tw.
8	(aspermi* or asperma* or asthenospermi* or asthenoteratozoospermi* or asthenozoospermi* or azoosperm* or cryptozoospermi* or cryptospermi* or globozoospermi* or hypospermatogen* or oligoasthenoteratozoospermi* or oligospermi* or oligozoospermi* or teratospermi* or teratozoospermi*).tw.
9	(germinal cell aplasia or (("sertoli cell only" or "del castillo") adj2 syndrome)).tw.
10	retrograde ejaculat*.tw.
11	hypogonadism/ or hypergonadotropic hypogonadism/ or hypogonadotropic hypogonadism/ or Kallmann syndrome/
12	(hypogonad* or hypogenitalis* or Kallman* or (gonad* adj (failure* or insufficien* or deficien*))).tw.
13	Klinefelter syndrome/
14	(Klinefelter* or ("47" adj XXY)).tw.

15	((xxyy or xxy or xxxy or xxxxy) adj2 (syndrome* or trisom* or constitution or male* or men or man)).tw.
16	((early or late) adj1 maturation arrest).tw.
17	or/1-16
18	(hormon* adj1 therap*).tw.
19	hormonal therapy/
20	exp fertility promoting agent/ or chorionic gonadotropin derivative/ or exp luteinizing hormone derivative/ or exp follitropin derivative/
21	(gonadotrop* or GnRH or gn-rh or gonadorelin or hCG or choriogonadotropin* or choriogonadotrophin* or choriogonin or buserelin or suprecur or cystorelin or factrel or dirigestran or gonadoliberin or pregonadotropin or gonan or folistiman or ambinon or anthrogon or kryptocur or luliberin or bigonist or profact or receptal or suprefact or tiloryth or goserelin or zoladex or leuprolide or enantone or leuprorelin or lupron or nafarelin or synarel or triptorelin or decapeptyl or trelstar or cetrorelix or cetrotide or ganirelix or fyremadel or ovitrelle or follitropin or bemfola or gonal-f or ovaleap or pergoveris or rekovelle or lutropin or luveris or meriofert or fostimon or biogonadil or chorulon or gonabion or novarel or pregnyl or FSH or rFSH or uFSH or asgph or lutotropin or thyrotropin or tsh or trh or icsh or lh or ulh or rlh or lhfsh or lhfshrh or lhrh or lfrh or luteoziman or luteozyman or hmg or humegon or menogon or menopur or menotrophin* or menotropin* or normegon or pergonal or urofollitropin or bravelle or fertinex or follitrin or metrodin or fertinorm or thyrotropin or thyrotrophin or thyrogen).tw.
22	((interstitial cell-stimulating or luteini?ing or follicle stimulating or folliculostimulating or gonad* stimulat* or pituitary or glycoprotein or thyroid) adj2 hormone*).tw.
23	exp antiestrogen/
24	((?estrogen or ?estradiol) adj2 (modulator* or inhibitor* or antagonist* or blocker* or suppress*)).tw.
25	(SERM or antiestrogen* or anti estrogen* or antioestrogen* or anti oestrogen* or tamoxifen or fulvestrant or faslodex or toremifene or fareston or nolvadex or novaldex or soltamox or tomaxithen or zitazonium or clomifene or clomid or androxal or clomiphene or chloramiphene or clomide or clomifen or clostilbegit or clostilbegyt or enclomid or enclomifene or enclomiphen* or serophene or transclomiphene or zuclomifene or dyneric or gravosan or klostilbegit or serophene or uclomiphene or evista or keoxifene or isomer).tw.
26	exp Androgens/ or Testosterone/
27	((synthetic adj2 hormone*) or androgen* or anaprotin or andractim or androstanolone or dihydroepitestosterone or dihydrotestosterone or gelovit or stanolone or nandrolone or estrenolone or norandrostenolone or nortestosterone or anavar or oxandrin or oxandrolone or oxymetholone or anadrol or anapolon or hydroxymetholone or oxymethalone or stanazolol or stanozolol or androstanazol or methylstanazol or stromba or winstrol or androgel or androderm or andropatch or androtop or histerone or sterotate or sustanon or testim or testoderm or testolin or testopel or testosterone or testavan or testim or testogel or tostran).tw.
28	((male fertil* or male infert*) adj2 (agent* or hormone*)).tw.
29	bromocriptine/ or cabergoline/ or lisuride/ or quinagolide/
30	((dopamine adj2 agonist*) or DA or bromocriptin* or bromocryptin* or bromoergocryptine or parlodel or arolac or carbamide or cuvalit or dopergin* or lisuride or lysuride or revanil or quinagolide or norprolac or cabergoline or cabaser* or cabergoline or dostinex).tw.
31	exp aromatase inhibitor/
32	((aromatase adj1 (inhibit* or antagonist*)) or aminoglutethimide or anastrazole or arimidex or cytadren or exemestane or fadrozole or aromasin or femara or letrozole or orimeten or testolactone or zeneca).tw.
33	or/18-32
34	17 and 33
35	letter.pt. or letter/
36	note.pt.
37	editorial.pt.
38	case report/ or case study/
39	(letter or comment*).ti.
40	or/35-39
41	randomized controlled trial/ or random*.ti,ab.
42	40 not 41
43	animal/ not human/
44	nonhuman/
45	exp Animal Experiment/
46	exp Experimental Animal/
47	animal model/
48	exp Rodent/
49	(rat or rats or mouse or mice).ti.

50	or/42-49
51	34 not 50
52	limit 51 to english language
53	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.
54	52 not 53
55	random*.ti,ab.
56	factorial*.ti,ab.
57	(crossover* or cross over*).ti,ab.
58	((doubl* or singl*) adj blind*).ti,ab.
59	(assign* or allocat* or volunteer* or placebo*).ti,ab.
60	crossover procedure/
61	single blind procedure/
62	randomized controlled trial/
63	double blind procedure/
64	or/55-63
65	systematic review/
66	meta-analysis/
67	(meta analy* or metanaly* or metaanaly*).ti,ab.
68	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
69	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
70	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
71	(search* adj4 literature).ab.
72	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
73	((pool* or combined) adj2 (data or trials or studies or results)).ab.
74	cochrane.jw.
75	or/65-74
76	54 and (64 or 75)
77	Clinical study/
78	Case control study/
79	Family study/
80	Longitudinal study/
81	Retrospective study/
82	comparative study/
83	Prospective study/
84	Randomized controlled trials/
85	83 not 84
86	Cohort analysis/
87	cohort analy$.tw.
88	(Cohort adj (study or studies)).tw.
89	(Case control$ adj (study or studies)).tw.
90	(follow up adj (study or studies)).tw.
91	(observational adj (study or studies)).tw.
92	(epidemiologic$ adj (study or studies)).tw.
93	(cross sectional adj (study or studies)).tw.
94	case series.tw.
95	prospective.tw.
96	retrospective.tw.
97	or/77-82,85-96
98	54 and 97
99	98 not 76

Database: Cochrane Database of Systematic Reviews, Issue 1 of 12, January 2025

Date of last search: 06/01/2025

#1	MeSH descriptor: [Male] explode all trees
#2	MeSH descriptor: [Men] this term only
#3	MeSH descriptor: [Sexual and Gender Minorities] explode all trees
#4	{or #1-#3}
#5	MeSH descriptor: [Infertility] this term only
#6	MeSH descriptor: [Fertility] this term only
#7	{or #5-#6}
#8	#4 and #7
#9	MeSH descriptor: [Infertility, Male] explode all trees
#10	((male* or men or man or transgender* or trans next gender* or transwomen or transwoman or transfemale* or transfeminine or transperson* or transpeople or transsex* or intersex* or inter next sex* or nonbinary or "non binary" or TGNB or genderqueer* or "two spirit" or sex next reassign* or "assigned male at birth" or AMAB or agender) near/4 (infertil* or subfertil* or fertil* or hypofertil* or subfecund* or fecund* or infecund* or steril*)):ti,ab
#11	((trans or transgender*) near/1 (woman or women or female* or feminin* or person* or people or sex* or patient* or identit* or nonbinary or "non binary") near/4 (infertil* or subfertil* or fertil* or hypofertil* or subfecund* or fecund* or infecund* or steril*)):ti,ab
#12	(gender near/1 (expansive* or queer* or nonconform* or non next conform* or dysphori* or fluid* or divers* or neutral or reassign* or affirm* or variance* or Incongruent or minorit* or transition*) near/4 (infertil* or subfertil* or fertil* or hypofertil* or subfecund* or fecund* or infecund* or steril*)):ti,ab
#13	((abnormal or block* or defect* or deficien* or fail* or immobil* or impair* or insufficien* or low* or reduc* or suboptimal*) near/2 sperm*):ti,ab
#14	((abnormal or defect* or deficien* or impair* or insufficien* or low* or reduc* or suboptimal*) near/2 semen*):ti,ab
#15	(aspermi* or asperma* or asthenospermi* or asthenoteratozoospermi* or asthenozoospermi* or azoosperm* or cryptozoospermi* or cryptospermi* or globozoospermi* or hypospermatogen* or oligoasthenoteratozoospermi* or oligospermi* or oligozoospermi* or teratospermi* or teratozoospermi*):ti,ab
#16	("germinal cell aplasia" or (("sertoli cell only" or "del castillo") near/2 syndrome)):ti,ab
#17	MeSH descriptor: [Retrograde Ejaculation] this term only
#18	retrograde next ejaculat*:ti,ab
#19	MeSH descriptor: [Hypogonadism] this term only
#20	MeSH descriptor: [Kallmann Syndrome] this term only
#21	MeSH descriptor: [Klinefelter Syndrome] this term only
#22	(hypogonad* or hypogenitalis* or Kallman* or (gonad* next (failure* or insufficien* or deficien*))):ti,ab
#23	(Klinefelter* or ("47" next XXY)):ti,ab
#24	((xxyy or xxy or xxxy or xxxxy) near/2 (syndrome* or trisom* or constitution or male* or men or man or person* or people)):ti,ab
#25	("early maturation arrest" or "late maturation arrest"):ti,ab
#26	{or #8-#25}
#27	(hormon* near/2 therap*):ti,ab
#28	MeSH descriptor: [Hormone Replacement Therapy] this term only
#29	MeSH descriptor: [Gonadotropins] this term only
#30	MeSH descriptor: [Chorionic Gonadotropin] explode all trees
#31	MeSH descriptor: [Gonadotropins, Pituitary] explode all trees
#32	MeSH descriptor: [Gonadotropin-Releasing Hormone] this term only
#33	(gonadotrop* or GnRH or "gn-rh" or gonadorelin or hCG or choriogonadotropin* or choriogonadotrophin* or choriogonin or buserelin or suprecur or cystorelin or factrel or dirigestran or gonadoliberin or pregonadotropin or gonan or folistiman or ambinon or anthrogon or kryptocur or luliberin or bigonist or profact or receptal or suprefact or tiloryth or goserelin or zoladex or leuprolide or enantone or leuprorelin or lupron or nafarelin or synarel or triptorelin or decapeptyl or trelstar or cetrorelix or cetrotide or ganirelix or fyremadel or ovitrelle or follitropin or bemfola or "gonal-f" or ovaleap or pergoveris or rekovelle or lutropin or luveris or meriofert or fostimon or biogonadil or chorulon or gonabion or novarel or pregnyl or FSH or rFSH or uFSH or asgph or lutotropin or thyrotropin or tsh or trh or icsh or lh or ulh or rlh or lhfsh or lhfshrh or lhrh or lfrh or luteoziman or luteozyman or hmg or humegon or menogon or menopur or menotrophin* or menotropin* or normegon or pergonal or urofollitropin or bravelle or fertinex or follitrin or metrodin or fertinorm or thyrotropin or thyrotrophin or thyrogen):ti,ab

#34	(("interstitial cell stimulating" or luteinising or luteinizing or "follicle stimulating" or folliculostimulating or gonad* next stimulat* or pituitary or glycoprotein or thyroid) near/2 hormone*):ti,ab
#35	MeSH descriptor: [Estrogen Receptor Modulators] explode all trees
#36	((estrogen or oestrogen or estradiol or oestradiol) near/2 (modulator* or inhibitor* or antagonist* or blocker* or suppress*)):ti,ab
#37	(SERM or antiestrogen* or anti next estrogen* or antioestrogen* or anti next oestrogen* or tamoxifen or fulvestrant or faslodex or toremifene or fareston or nolvadex or novaldex or soltamox or tomaxithen or zitazonium or clomifene or clomid or androxal or clomiphene or chloramiphene or clomide or clomifen or clostilbegit or clostilbegyt or enclomid or enclomifene or enclomiphen* or serophene or transclomiphene or zuclomifene or dyneric or gravosan or klostilbegit or serophene or uclomiphene or evista or keoxifene or isomer):ti,ab
#38	MeSH descriptor: [Androgens] explode all trees
#39	MeSH descriptor: [Testosterone] this term only
#40	((synthetic near/2 hormone*) or androgen* or anaprotin or andractim or androstanolone or dihydroepitestosterone or dihydrotestosterone or gelovit or stanolone or nandrolone or estrenolone or norandrostenolone or nortestosterone or anavar or oxandrin or oxandrolone or oxymetholone or anadrol or anapolon or hydroxymetholone or oxymethalone or stanazolol or stanozolol or androstanazol or methylstanazol or stromba or winstrol or androgel or androderm or andropatch or androtop or histerone or sterotate or sustanon or testim or testoderm or testolin or testopel or testosterone or testavan or testim or testogel or tostran):ti,ab
#41	((male next fertil* or male next infert*) near/2 (agent* or hormone*)):ti,ab
#42	MeSH descriptor: [Bromocriptine] this term only
#43	MeSH descriptor: [Cabergoline] this term only
#44	((dopamine near/2 agonist*) or DA or bromocriptin* or bromocryptin* or bromoergocryptine or parlodel or arolac or carbamide or cuvalit or dopergin* or lisuride or lysuride or revanil or quinagolide or norprolac or cabergoline or cabaser* or cabergoline or dostinex):ti,ab
#45	MeSH descriptor: [Aromatase Inhibitors] explode all trees
#46	((aromatase near/1 (inhibit* or antagonist*)) or aminoglutethimide or anastrazole or arimidex or cytadren or exemestane or fadrozole or aromasin or femara or letrozole or orimeten or testolactone or zeneca):ti,ab
#47	{or #27-#46}
#48	#26 and #47
#49	conference:pt or (clinicaltrials or trialsearch):so
#50	#48 not #49 in Cochrane Reviews

Database: Cochrane Central Register of Controlled Trials, Issue 12 of 12, December 2024

Date of last search: 06/01/2025

#1	MeSH descriptor: [Male] explode all trees
#2	MeSH descriptor: [Men] this term only
#3	MeSH descriptor: [Sexual and Gender Minorities] explode all trees
#4	{or #1-#3}
#5	MeSH descriptor: [Infertility] this term only
#6	MeSH descriptor: [Fertility] this term only
#7	{or #5-#6}
#8	#4 and #7
#9	MeSH descriptor: [Infertility, Male] explode all trees
#10	((male* or men or man or transgender* or trans next gender* or transwomen or transwoman or transfemale* or transfeminine or transperson* or transpeople or transsex* or intersex* or inter next sex* or nonbinary or "non binary" or TGNB or genderqueer* or "two spirit" or sex next reassign* or "assigned male at birth" or AMAB or agender) near/4 (infertil* or subfertil* or fertil* or hypofertil* or subfecund* or fecund* or infecund* or steril*)):ti,ab
#11	((trans or transgender*) near/1 (woman or women or female* or feminin* or person* or people or sex* or patient* or identit* or nonbinary or "non binary") near/4 (infertil* or subfertil* or fertil* or hypofertil* or subfecund* or fecund* or infecund* or steril*)):ti,ab

#12	(gender near/1 (expansive* or queer* or nonconform* or non next conform* or dysphori* or fluid* or divers* or neutral or reassign* or affirm* or variance* or Incongruent or minorit* or transition*) near/4 (infertil* or subfertil* or fertil* or hypofertil* or subfecund* or fecund* or infecund* or steril*)):ti,ab
#13	((abnormal or block* or defect* or deficien* or fail* or immobil* or impair* or insufficien* or low* or reduc* or suboptimal*) near/2 sperm*):ti,ab
#14	((abnormal or defect* or deficien* or impair* or insufficien* or low* or reduc* or suboptimal*) near/2 semen*):ti,ab
#15	(aspermi* or asperma* or asthenospermi* or asthenoteratozoospermi* or asthenozoospermi* or azoosperm* or cryptozoospermi* or cryptospermi* or globozoospermi* or hypospermatogen* or oligoasthenoteratozoospermi* or oligospermi* or oligozoospermi* or teratospermi* or teratozoospermi*):ti,ab
#16	("germinal cell aplasia" or (("sertoli cell only" or "del castillo") near/2 syndrome)):ti,ab
#17	MeSH descriptor: [Retrograde Ejaculation] this term only
#18	retrograde next ejaculat*:ti,ab
#19	MeSH descriptor: [Hypogonadism] this term only
#20	MeSH descriptor: [Kallmann Syndrome] this term only
#21	MeSH descriptor: [Klinefelter Syndrome] this term only
#22	(hypogonad* or hypogenitalis* or Kallman* or (gonad* next (failure* or insufficien* or deficien*))):ti,ab
#23	(Klinefelter* or ("47" next XXY)):ti,ab
#24	((xxyy or xxy or xxxy or xxxxy) near/2 (syndrome* or trisom* or constitution or male* or men or man or person* or people)):ti,ab
#25	("early maturation arrest" or "late maturation arrest"):ti,ab
#26	{or #8-#25}
#27	(hormon* near/2 therap*):ti,ab
#28	MeSH descriptor: [Hormone Replacement Therapy] this term only
#29	MeSH descriptor: [Gonadotropins] this term only
#30	MeSH descriptor: [Chorionic Gonadotropin] explode all trees
#31	MeSH descriptor: [Gonadotropins, Pituitary] explode all trees
#32	MeSH descriptor: [Gonadotropin-Releasing Hormone] this term only
#33	(gonadotrop* or GnRH or "gn-rh" or gonadorelin or hCG or choriogonadotropin* or choriogonadotrophin* or choriogonin or buserelin or suprecur or cystorelin or factrel or dirigestran or gonadoliberin or pregonadotropin or gonan or folistiman or ambinon or anthrogon or kryptocur or luliberin or bigonist or profact or receptal or suprefact or tiloryth or goserelin or zoladex or leuprolide or enantone or leuprorelin or lupron or nafarelin or synarel or triptorelin or decapeptyl or trelstar or cetrorelix or cetrotide or ganirelix or fyremadel or ovitrelle or follitropin or bemfola or "gonal-f" or ovaleap or pergoveris or rekovelle or lutropin or luveris or meriofert or fostimon or biogonadil or chorulon or gonabion or novarel or pregnyl or FSH or rFSH or uFSH or asgph or lutotropin or thyrotropin or tsh or trh or icsh or lh or ulh or rlh or lhfsh or lhfshrh or lhrh or lfrh or luteoziman or luteozyman or hmg or humegon or menogon or menopur or menotrophin* or menotropin* or normegon or pergonal or urofollitropin or bravelle or fertinex or follitrin or metrodin or fertinorm or thyrotropin or thyrotrophin or thyrogen):ti,ab
#34	(("interstitial cell stimulating" or luteinising or luteinizing or "follicle stimulating" or folliculostimulating or gonad* next stimulat* or pituitary or glycoprotein or thyroid) near/2 hormone*):ti,ab
#35	MeSH descriptor: [Estrogen Receptor Modulators] explode all trees
#36	((estrogen or oestrogen or estradiol or oestradiol) near/2 (modulator* or inhibitor* or antagonist* or blocker* or suppress*)):ti,ab
#37	(SERM or antiestrogen* or anti next estrogen* or antioestrogen* or anti next oestrogen* or tamoxifen or fulvestrant or faslodex or toremifene or fareston or nolvadex or novaldex or soltamox or tomaxithen or zitazonium or clomifene or clomid or androxal or clomiphene or chloramiphene or clomide or clomifen or clostilbegit or clostilbegyt or enclomid or enclomifene or enclomiphen* or serophene or transclomiphene or zuclomifene or dyneric or gravosan or klostilbegit or serophene or uclomiphene or evista or keoxifene or isomer):ti,ab
#38	MeSH descriptor: [Androgens] explode all trees
#39	MeSH descriptor: [Testosterone] this term only
#40	((synthetic near/2 hormone*) or androgen* or anaprotin or andractim or androstanolone or dihydroepitestosterone or dihydrotestosterone or gelovit or stanolone or nandrolone or estrenolone or norandrostenolone or nortestosterone or anavar or oxandrin or oxandrolone or oxymetholone or anadrol or anapolon or hydroxymetholone or oxymethalone or stanazolol or stanozolol or androstanazol or methylstanazol or stromba or winstrol or androgel or androderm or andropatch or androtop or histerone or sterotate or sustanon or testim or testoderm or testolin or testopel or testosterone or testavan or testim or testogel or tostran):ti,ab
#41	((male next fertil* or male next infert*) near/2 (agent* or hormone*)):ti,ab
#42	MeSH descriptor: [Bromocriptine] this term only

#43	MeSH descriptor: [Cabergoline] this term only
#44	((dopamine near/2 agonist*) or DA or bromocriptin* or bromocryptin* or bromoergocryptine or parlodel or arolac or carbamide or cuvalit or dopergin* or lisuride or lysuride or revanil or quinagolide or norprolac or cabergoline or cabaser* or cabergoline or dostinex):ti,ab
#45	MeSH descriptor: [Aromatase Inhibitors] explode all trees
#46	((aromatase near/1 (inhibit* or antagonist*)) or aminoglutethimide or anastrazole or arimidex or cytadren or exemestane or fadrozole or aromasin or femara or letrozole or orimeten or testolactone or zeneca):ti,ab
#47	{or #27-#46}
#48	#26 and #47
#49	conference:pt or (clinicaltrials or trialsearch):so
#50	#48 not #49 in Trials

Database: Epistemonikos

Date of last search: 06/01/2025

Search 1:

1	(((male* OR men OR man OR transgender* OR "trans gender" OR "trans genders" OR "trans gendered" OR transwoman OR transwomen OR transfemale* OR transfeminine OR transperson* OR transpeople OR transex* OR intersex* OR "inter sex" OR "inter sexual" OR nonbinary OR "non binary" OR TGNB OR genderqueer* OR "two spirit" OR "sex reassign" OR "sex reassigned" OR "sex reassignment" OR "sex reassignments" OR "assigned male at birth" or AMAB or agender) OR ((trans OR transgender*) AND (woman OR women OR female* OR feminin* OR person* OR people OR sex* OR patient* OR identit* OR nonbinary OR "non binary")) OR (gender AND (expansive* or queer* or nonconform* or "non conform" OR "non conforming" OR "non conformity" OR dysphori* OR fluid* OR divers* OR neutral OR reassign* OR affirm* OR variance* OR Incongruent OR minorit* OR transition*))) AND (infertil* OR subfertil* OR fertil* OR subfecund* OR "sub fecundity" OR infecund* OR steril*))
2	((oestrogen OR estrogen OR oestradiol OR estradiol) AND (modulator* OR inhibitor* OR antagonist* OR blocker* OR suppress*)) OR (aromatase AND (inhibit* OR antagonist*)) OR (dopamine AND agonist*) OR (synthetic AND hormone*) OR (hormon* AND therap*) OR (("male fertillty" OR "male infertility") AND (agent* OR hormone*)) OR (gonadotrop* OR "luteinizing hormone" OR "luteinising hormone" OR LH OR follicle-stimulating OR "follicle stimulating" OR FSH OR hcg OR "interstitial cell" OR anti-oestrogens OR anti-oestrogen OR anti-estrogens OR anti-estrogen OR "anti oestrogens" OR "anti oestrogen" OR "anti estrogens" OR "anti estrogen" OR clomifene OR tamoxifen OR anastrozole OR testolactone OR letrozole OR exemestane OR androgens OR testosterone OR bromocriptine OR cabergoline OR quinagolide)
3	1 AND 2
4	Limit results to systematic reviews

Search 2:

1	(aspermi* OR asperma* OR asthenospermi* OR asthenoteratozoospermi* OR asthenozoospermi* OR azoosperm* OR cryptozoospermi* OR cryptospermi* OR globozoospermi* OR hypospermatogen* OR oligoasthenoteratozoospermi* OR oligospermi* OR oligozoospermi* OR teratospermi* OR teratozoospermi* OR "germinal cell aplasia" OR hypogonad* OR hypogenitalis* OR Kallman* OR "retrograde ejaculation" OR Klinefelter* OR "retrograde ejaculation" OR Klinefelter* OR "early maturation arrest" OR "late maturation arrest") OR (("sertoli cell only" OR "del castillo") AND syndrome) OR (gonad* AND (failure* OR insufficien* OR deficien*)) OR ((abnormal OR block* OR defect* OR deficien* OR fail* OR immobil* OR impair* OR insufficien* OR low* OR reduc* OR suboptimal*) AND (sperm* OR semen)) OR ("47" AND XXY) OR ((xxyy OR xxy OR xxxy OR xxxxy) AND (syndrome* OR trisom* OR constitution OR male* OR men OR man OR person* OR people))
2	((oestrogen OR estrogen OR oestradiol OR estradiol) AND (modulator* OR inhibitor* OR antagonist* OR blocker* OR suppress*)) OR (aromatase AND (inhibit* OR antagonist*)) OR (dopamine AND agonist*) OR (synthetic AND hormone*) OR (hormon* AND therap*) OR (("male fertillty" OR "male infertility") AND (agent* OR hormone*)) OR (gonadotrop* OR "luteinizing hormone" OR "luteinising hormone" OR LH OR follicle-stimulating OR "follicle stimulating" OR FSH OR hcg OR "interstitial cell" OR anti-oestrogens OR anti-oestrogen OR anti-estrogens OR anti-estrogen OR "anti oestrogens" OR "anti oestrogen" OR "anti estrogens" OR "anti estrogen" OR clomifene OR tamoxifen OR anastrozole OR testolactone OR letrozole OR exemestane OR androgens OR testosterone OR bromocriptine OR cabergoline OR quinagolide)
3	1 AND 2
4	Limit results to systematic reviews

Health Economic Literature search strategies for review question: What is the effectiveness of hormone treatment in male factor fertility problems?

Database: Ovid MEDLINE(R) ALL <1946 to January 06, 2025>

Date of last search: 08/01/2025

1	exp infertility, male/
2	(male/ or men/ or exp "Sexual and Gender Minorities"/) and (Infertility/ or fertility/)
3	((male? or men or man or transgender* or trans gender* or transwom?n or transfemale* or transfeminine or transperson* or transpeople or transsex* or intersex* or inter sex* or nonbinary or non binary or TGNB or genderqueer* or two spirit or sex reassign* or "assigned male at birth" or AMAB or agender) adj4 (infertil* or subfertil* or fertil* or hypofertil* or subfecund* or fecund* or infecund* or steril*)).tw.
4	((trans or transgender*) adj1 (wom?n or female* or feminin* or person* or people or sex* or patient* or identit* or nonbinary or "non binary") adj4 (infertil* or subfertil* or fertil* or hypofertil* or subfecund* or fecund* or infecund* or steril*)).tw.
5	(gender adj1 (expansive* or queer* or nonconform* or "non conform*" or dysphori* or fluid* or divers* or neutral or reassign* or affirm* or variance* or Incongruent or minorit* or transition*) adj4 (infertil* or subfertil* or fertil* or hypofertil* or subfecund* or fecund* or infecund* or steril*)).tw.
6	((abnormal or block* or defect* or deficien* or fail* or immobil* or impair* or insufficien* or low* or reduc* or suboptimal*) adj2 sperm*).tw.
7	((abnormal or defect* or deficien* or impair* or insufficien* or low* or reduc* or suboptimal*) adj2 semen*).tw.
8	(aspermi* or asperma* or asthenospermi* or asthenoteratozoospermi* or asthenozoospermi* or azoosperm* or cryptozoospermi* or cryptospermi* or globozoospermi* or hypospermatogen* or oligoasthenoteratozoospermi* or oligospermi* or oligozoospermi* or teratospermi* or teratozoospermi*).tw.
9	(germinal cell aplasia or (("sertoli cell only" or "del castillo") adj2 syndrome)).tw.
10	retrograde ejaculation/ or retrograde ejaculat*.tw.
11	hypogonadism/ or kallmann syndrome/ or klinefelter syndrome/
12	(hypogonad* or hypogenitalis* or Kallman* or (gonad* adj (failure* or insufficien* or deficien*))).tw.
13	(Klinefelter* or ("47" adj XXY)).tw.
14	((xxyy or xxy or xxxy or xxxxy) adj2 (syndrome* or trisom* or constitution or male* or men or man)).tw.
15	((early or late) adj1 "maturation arrest").tw.
16	or/1-15
17	(hormon* adj2 therap*).tw.
18	hormone replacement therapy/
19	gonadotropins/ or exp chorionic gonadotropin/ or exp gonadotropins, pituitary/ or Gonadotropin-Releasing Hormone/
20	(gonadotrop* or GnRH or gn-rh or gonadorelin or hCG or choriogonadotropin* or choriogonadotrophin* or choriogonin or buserelin or suprecur or cystorelin or factrel or dirigestran or gonadoliberin or pregonadotropin or gonan or folistiman or ambinon or anthrogon or kryptocur or luliberin or bigonist or profact or receptal or suprefact or tiloryth or goserelin or zoladex or leuprolide or enantone or leuprorelin or lupron or nafarelin or synarel or triptorelin or decapeptyl or trelstar or cetrorelix or cetrotide or ganirelix or fyremadel or ovitrelle or follitropin or bemfola or gonal-f or ovaleap or pergoveris or rekovelle or lutropin or luveris or meriofert or fostimon or biogonadil or chorulon or gonabion or novarel or pregnyl or FSH or rFSH or uFSH or asgph or lutotropin or thyrotropin or tsh or trh or icsh or lh or ulh or rlh or lhfsh or lhfshrh or lhrh or lfrh or luteoziman or luteozyman or hmg or humegon or menogon or menopur or menotrophin* or menotropin* or normegon or pergonal or urofollitropin or bravelle or fertinex or follitrin or metrodin or fertinorm or thyrotropin or thyrotrophin or thyrogen).tw.
21	((interstitial cell-stimulating or luteini?ing or follicle stimulating or folliculostimulating or gonad* stimulat* or pituitary or glycoprotein or thyroid) adj2 hormone*).tw.
22	exp Estrogen Receptor Modulators/
23	((?estrogen or ?estradiol) adj2 (modulator* or inhibitor* or antagonist* or blocker* or suppress*)).tw.
24	(SERM or antiestrogen* or anti estrogen* or antioestrogen* or anti oestrogen* or tamoxifen or fulvestrant or faslodex or toremifene or fareston or nolvadex or novaldex or soltamox or tomaxithen or zitazonium or clomifene or clomid or androxal or clomiphene or chloramiphene or clomide or clomifen or clostilbegit or clostilbegyt or enclomid or enclomifene or enclomiphen* or serophene or transclomiphene or zuclomifene or dyneric or gravosan or klostilbegit or serophene or uclomiphene or evista or keoxifene or isomer).tw.
25	exp Androgens/ or Testosterone/

26	((synthetic adj2 hormone*) or androgen* or anaprotin or andractim or androstanolone or dihydroepitestosterone or dihydrotestosterone or gelovit or stanolone or nandrolone or estrenolone or norandrostenolone or nortestosterone or anavar or oxandrin or oxandrolone or oxymetholone or anadrol or anapolon or hydroxymetholone or oxymethalone or stanazolol or stanozolol or androstanazol or methylstanazol or stromba or winstrol or androgel or androderm or andropatch or androtop or histerone or sterotate or sustanon or testim or testoderm or testolin or testopel or testosterone or testavan or testim or testogel or tostran).tw.
27	((male fertil* or male infert*) adj2 (agent* or hormone*)).tw.
28	Bromocriptine/ or Cabergoline/
29	((dopamine adj2 agonist*) or DA or bromocriptin* or bromocryptin* or bromoergocryptine or parlodel or arolac or carbamide or cuvalit or dopergin* or lisuride or lysuride or revanil or quinagolide or norprolac or cabergoline or cabaser* or cabergoline or dostinex).tw.
30	exp Aromatase Inhibitors/
31	((aromatase adj1 (inhibit* or antagonist*)) or aminoglutethimide or anastrazole or arimidex or cytadren or exemestane or fadrozole or aromasin or femara or letrozole or orimeten or testolactone or zeneca).tw.
32	or/17-31
33	16 and 32
34	letter/
35	editorial/
36	news/
37	exp historical article/
38	Anecdotes as Topic/
39	comment/
40	case reports/
41	(letter or comment*).ti.
42	or/34-41
43	randomized controlled trial/ or random*.ti,ab.
44	42 not 43
45	animals/ not humans/
46	exp Animals, Laboratory/
47	exp Animal Experimentation/
48	exp Models, Animal/
49	exp Rodentia/
50	(rat or rats or mouse or mice or rodent*).ti.
51	or/44-50
52	33 not 51
53	limit 52 to english language
54	Economics/
55	Value of life/
56	exp "Costs and Cost Analysis"/
57	exp Economics, Hospital/
58	exp Economics, Medical/
59	exp Resource Allocation/
60	Economics, Nursing/
61	Economics, Pharmaceutical/
62	exp "Fees and Charges"/
63	exp Budgets/
64	budget*.ti,ab.
65	cost*.ti,ab.
66	(economic* or pharmaco?economic*).ti,ab.
67	(price* or pricing*).ti,ab.
68	(financ* or fee or fees or expenditure* or saving*).ti,ab.
69	(value adj2 (money or monetary)).ti,ab.
70	resourc* allocat*.ti,ab.
71	(fund or funds or funding* or funded).ti,ab.
72	(ration or rations or rationing* or rationed).ti,ab.

73	ec.fs.
74	or/54-73
75	quality-adjusted life years/
76	sickness impact profile/
77	(quality adj2 (wellbeing or well being)).ti,ab.
78	sickness impact profile.ti,ab.
79	disability adjusted life.ti,ab.
80	(qal* or qtime* or qwb* or daly*).ti,ab.
81	(euroqol* or eq5d* or eq 5*).ti,ab.
82	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
83	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
84	(hui or hui1 or hui2 or hui3).ti,ab.
85	(health* year* equivalent* or hye or hyes).ti,ab.
86	discrete choice*.ti,ab.
87	rosser.ti,ab.
88	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
89	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
90	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
91	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
92	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
93	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
94	or/75-93
95	53 and (74 or 94)

Database: Embase <1974 to 2025 January 07>

Date of last search: 08/01/2025

1	exp male infertility/ or semen abnormality/
2	(male/ or "sexual and gender minority"/ or "transgender and gender nonbinary"/) and (infertility/ or subfertility/)
3	((male? or men or man or transgender* or trans gender* or transwom?n or transfemale* or transfeminine or transperson* or transpeople or transsex* or intersex* or inter sex* or nonbinary or non binary or TGNB or genderqueer* or two spirit or sex reassign* or "assigned male at birth" or AMAB or agender) adj4 (infertil* or subfertil* or fertil* or hypofertil* or subfecund* or fecund* or infecund* or steril*)).tw.
4	((trans or transgender*) adj1 (wom?n or female* or feminin* or person* or people or sex* or patient* or identit* or nonbinary or "non binary") adj4 (infertil* or subfertil* or fertil* or hypofertil* or subfecund* or fecund* or infecund* or steril*)).tw.
5	(gender adj1 (expansive* or queer* or nonconform* or "non conform*" or dysphori* or fluid* or divers* or neutral or reassign* or affirm* or variance* or Incongruent or minorit* or transition*) adj4 (infertil* or subfertil* or fertil* or hypofertil* or subfecund* or fecund* or infecund* or steril*)).tw.
6	((abnormal or block* or defect* or deficien* or fail* or immobil* or impair* or insufficien* or low* or reduc* or suboptimal*) adj2 sperm*).tw.
7	((abnormal or defect* or deficien* or impair* or insufficien* or low* or reduc* or suboptimal*) adj2 semen*).tw.
8	(aspermi* or asperma* or asthenospermi* or asthenoteratozoospermi* or asthenozoospermi* or azoosperm* or cryptozoospermi* or cryptospermi* or globozoospermi* or hypospermatogen* or oligoasthenoteratozoospermi* or oligospermi* or oligozoospermi* or teratospermi* or teratozoospermi*).tw.
9	(germinal cell aplasia or (("sertoli cell only" or "del castillo") adj2 syndrome)).tw.
10	retrograde ejaculat*.tw.
11	hypogonadism/ or hypergonadotropic hypogonadism/ or hypogonadotropic hypogonadism/ or Kallmann syndrome/
12	(hypogonad* or hypogenitalis* or Kallman* or (gonad* adj (failure* or insufficien* or deficien*))).tw.
13	Klinefelter syndrome/
14	(Klinefelter* or ("47" adj XXY)).tw.
15	((xxyy or xxy or xxxy or xxxxy) adj2 (syndrome* or trisom* or constitution or male* or men or man)).tw.
16	((early or late) adj1 maturation arrest).tw.

17	or/1-16
18	(hormon* adj1 therap*).tw.
19	hormonal therapy/
20	exp fertility promoting agent/ or chorionic gonadotropin derivative/ or exp luteinizing hormone derivative/ or exp follitropin derivative/
21	(gonadotrop* or GnRH or gn-rh or gonadorelin or hCG or choriogonadotropin* or choriogonadotrophin* or choriogonin or buserelin or suprecur or cystorelin or factrel or dirigestran or gonadoliberin or pregonadotropin or gonan or folistiman or ambinon or anthrogon or kryptocur or luliberin or bigonist or profact or receptal or suprefact or tiloryth or goserelin or zoladex or leuprolide or enantone or leuprorelin or lupron or nafarelin or synarel or triptorelin or decapeptyl or trelstar or cetrorelix or cetrotide or ganirelix or fyremadel or ovitrelle or follitropin or bemfola or gonal-f or ovaleap or pergoveris or rekovelle or lutropin or luveris or meriofert or fostimon or biogonadil or chorulon or gonabion or novarel or pregnyl or FSH or rFSH or uFSH or asgph or lutotropin or thyrotropin or tsh or trh or icsh or lh or ulh or rlh or lhfsh or lhfshrh or lhrh or lfrh or luteoziman or luteozyman or hmg or humegon or menogon or menopur or menotrophin* or menotropin* or normegon or pergonal or urofollitropin or bravelle or fertinex or follitrin or metrodin or fertinorm or thyrotropin or thyrotrophin or thyrogen).tw.
22	((interstitial cell-stimulating or luteini?ing or follicle stimulating or folliculostimulating or gonad* stimulat* or pituitary or glycoprotein or thyroid) adj2 hormone*).tw.
23	exp antiestrogen/
24	((?estrogen or ?estradiol) adj2 (modulator* or inhibitor* or antagonist* or blocker* or suppress*)).tw.
25	(SERM or antiestrogen* or anti estrogen* or antioestrogen* or anti oestrogen* or tamoxifen or fulvestrant or faslodex or toremifene or fareston or nolvadex or novaldex or soltamox or tomaxithen or zitazonium or clomifene or clomid or androxal or clomiphene or chloramiphene or clomide or clomifen or clostilbegit or clostilbegyt or enclomid or enclomifene or enclomiphen* or serophene or transclomiphene or zuclomifene or dyneric or gravosan or klostilbegit or serophene or uclomiphene or evista or keoxifene or isomer).tw.
26	exp Androgens/ or Testosterone/
27	((synthetic adj2 hormone*) or androgen* or anaprotin or andractim or androstanolone or dihydroepitestosterone or dihydrotestosterone or gelovit or stanolone or nandrolone or estrenolone or norandrostenolone or nortestosterone or anavar or oxandrin or oxandrolone or oxymetholone or anadrol or anapolon or hydroxymetholone or oxymethalone or stanazolol or stanozolol or androstanazol or methylstanazol or stromba or winstrol or androgel or androderm or andropatch or androtop or histerone or sterotate or sustanon or testim or testoderm or testolin or testopel or testosterone or testavan or testim or testogel or tostran).tw.
28	((male fertil* or male infert*) adj2 (agent* or hormone*)).tw.
29	bromocriptine/ or cabergoline/ or lisuride/ or quinagolide/
30	((dopamine adj2 agonist*) or DA or bromocriptin* or bromocryptin* or bromoergocryptine or parlodel or arolac or carbamide or cuvalit or dopergin* or lisuride or lysuride or revanil or quinagolide or norprolac or cabergoline or cabaser* or cabergoline or dostinex).tw.
31	exp aromatase inhibitor/
32	((aromatase adj1 (inhibit* or antagonist*)) or aminoglutethimide or anastrazole or arimidex or cytadren or exemestane or fadrozole or aromasin or femara or letrozole or orimeten or testolactone or zeneca).tw.
33	or/18-32
34	17 and 33
35	letter.pt. or letter/
36	note.pt.
37	editorial.pt.
38	case report/ or case study/
39	(letter or comment*).ti.
40	or/35-39
41	randomized controlled trial/ or random*.ti,ab.
42	40 not 41
43	animal/ not human/
44	nonhuman/
45	exp Animal Experiment/
46	exp Experimental Animal/
47	animal model/
48	exp Rodent/
49	(rat or rats or mouse or mice).ti.
50	or/42-49
51	34 not 50

52	limit 51 to english language
53	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.
54	52 not 53
55	health economics/
56	exp economic evaluation/
57	exp health care cost/
58	exp fee/
59	budget/
60	funding/
61	resource allocation/
62	budget*.ti,ab.
63	cost*.ti,ab.
64	(economic* or pharmaco?economic*).ti,ab.
65	(price* or pricing*).ti,ab.
66	(financ* or fee or fees or expenditure* or saving*).ti,ab.
67	(value adj2 (money or monetary)).ti,ab.
68	resourc* allocat*.ti,ab.
69	(fund or funds or funding* or funded).ti,ab.
70	(ration or rations or rationing* or rationed).ti,ab.
71	or/55-70
72	quality adjusted life year/
73	"quality of life index"/
74	short form 12/ or short form 20/ or short form 36/ or short form 8/
75	sickness impact profile/
76	(quality adj2 (wellbeing or well being)).ti,ab.
77	sickness impact profile.ti,ab.
78	disability adjusted life.ti,ab.
79	(qal* or qtime* or qwb* or daly*).ti,ab.
80	(euroqol* or eq5d* or eq 5*).ti,ab.
81	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
82	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
83	(hui or hui1 or hui2 or hui3).ti,ab.
84	(health* year* equivalent* or hye or hyes).ti,ab.
85	discrete choice*.ti,ab.
86	rosser.ti,ab.
87	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
88	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
89	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
90	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
91	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
92	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
93	or/72-92
94	54 and (71 or 93)

Database: INAHTA

Date of last search: 08/01/2025

1	"male"[mh]
2	"men"[mh]
3	"Sexual and Gender Minorities"[mhe]
4	#3 OR #2 OR #1

5	"Infertility"[mh]
6	"Fertility"[mh]
7	#6 OR #5
8	#7 AND #4
9	"Infertility, Male"[mhe]
10	((male* or men or man or transgender* or "trans gender" or "trans genders" or "trans gendered" or transwoman or transwomen or transfemale* or transfeminine or transperson* or transpeople or transex* or intersex* or "inter sex" or "inter sexual" or nonbinary or "non binary" or TGNB or genderqueer* or "two spirit" or "sex reassign" or "sex reassigned" or "sex reassignment" or "sex reassignments" or "assigned male at birth" or AMAB or agender) and (infertil* or subfertil* or fertil* or hypofertil* or subfecund* or fecund* or infecund* or steril*))
11	((trans or transgender*) and (woman or women or female* or feminin* or person* or people or sex* or patient* or identit* or nonbinary or "non binary") and (infertil* or subfertil* or fertil* or hypofertil* or subfecund* or fecund* or infecund* or steril*))
12	(gender and (expansive* or queer* or nonconform* or "non conform" or "non conforming" or "non conformity" or dysphori* or fluid* or divers* or neutral or reassign* or affirm* or variance* or Incongruent or minorit* or transition*) and (infertil* or subfertil* or fertil* or hypofertil* or subfecund* or fecund* or infecund* or steril*))
13	((abnormal or block* or defect* or deficien* or fail* or immobil* or impair* or insufficien* or low* or reduc* or suboptimal*) and sperm*)
14	((abnormal or defect* or deficien* or impair* or insufficien* or low* or reduc* or suboptimal*) and semen*)
15	(aspermi* or asperma* or asthenospermi* or asthenoteratozoospermi* or asthenozoospermi* or azoosperm* or cryptozoospermi* or cryptospermi* or globozoospermi* or hypospermatogen* or oligoasthenoteratozoospermi* or oligospermi* or oligozoospermi* or teratospermi* or teratozoospermi*)
16	("sertoli cell only" or "del castillo")
17	"germinal cell aplasia"
18	"retrograde ejaculation"
19	"Hypogonadism"[mh]
20	"Kallmann Syndrome"[mh]
21	"Klinefelter syndrome"[mh]
22	(gonad* and (failure* or insufficien* or deficien*))
23	(hypogonad* or hypogenitalis* or Kallman*)
24	("47" and XXY)
25	(Klinefelter*)
26	((xxyy or xxy or xxxy or xxxxy) and (syndrome* or trisom* or constitution or male* or men or man or person* or people))
27	("early maturation arrest" or "late maturation arrest")
28	#27 OR #26 OR #25 OR #24 OR #23 OR #22 OR #21 OR #20 OR #19 OR #18 OR #17 OR #16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8
29	Limit to English Language

Database: HTA via CRD

Date of last search: 08/01/2025

1	MESH DESCRIPTOR Male EXPLODE ALL TREES
2	MESH DESCRIPTOR Men
3	MESH DESCRIPTOR Sexual and Gender Minorities EXPLODE ALL TREES
4	#1 or #2 or #3
5	MESH DESCRIPTOR Infertility
6	MESH DESCRIPTOR Fertility
7	#5 or #6
8	#4 and #7
9	MESH DESCRIPTOR Infertility, Male EXPLODE ALL TREES
10	((male* or men or man or transgender* or trans next gender* or transwomen or transwoman or transfemale* or transfeminine or transperson* or transpeople or transsex* or intersex* or inter next sex* or nonbinary or "non binary" or TGNB or genderqueer* or "two spirit" or sex next reassign* or "assigned male at birth" or AMAB or agender) near4 (infertil* or subfertil* or fertil* or hypofertil* or subfecund* or fecund* or infecund* or steril*))

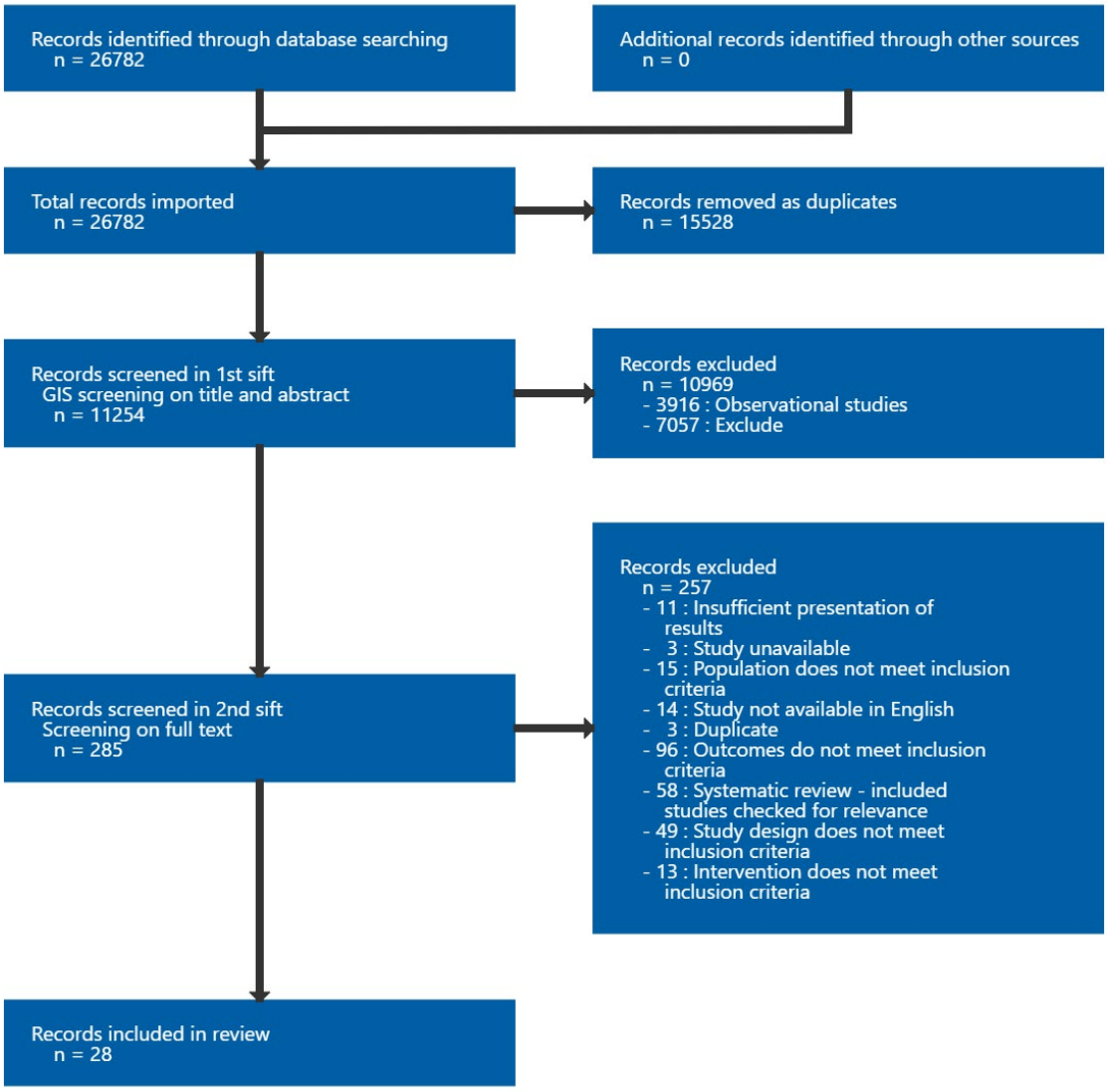
11	((trans or transgender*) near1 (woman or women or female* or feminin* or person* or people or sex* or patient* or identit* or nonbinary or "non binary") near4 (infertil* or subfertil* or fertil* or hypofertil* or subfecund* or fecund* or infecund* or steril*))
12	(gender near1 (expansive* or queer* or nonconform* or non next conform* or dysphori* or fluid* or divers* or neutral or reassign* or affirm* or variance* or Incongruent or minorit* or transition*) near4 (infertil* or subfertil* or fertil* or hypofertil* or subfecund* or fecund* or infecund* or steril*))
13	((abnormal or block* or defect* or deficien* or fail* or immobil* or impair* or insufficien* or low* or reduc* or suboptimal*) near2 sperm*)
14	((abnormal or defect* or deficien* or impair* or insufficien* or low* or reduc* or suboptimal*) near2 semen*)
15	(aspermi* or asperma* or asthenospermi* or asthenoteratozoospermi* or asthenozoospermi* or azoosperm* or cryptozoospermi* or cryptospermi* or globozoospermi* or hypospermatogen* or oligoasthenoteratozoospermi* or oligospermi* or oligozoospermi* or teratospermi* or teratozoospermi*)
16	("germinal cell aplasia" or (("sertoli cell only" or "del castillo") near2 syndrome))
17	retrograde next ejaculat*
18	MESH DESCRIPTOR Hypogonadism
19	MESH DESCRIPTOR Kallmann Syndrome
20	MESH DESCRIPTOR Klinefelter Syndrome
21	(hypogonad* or hypogenitalis* or Kallman* or (gonad* next (failure* or insufficien* or deficien*)))
22	(Klinefelter* or ("47" next XXY))
23	((xxyy or xxy or xxxy or xxxxy) near2 (syndrome* or trisom* or constitution or male* or men or man or person* or people))
24	("early maturation arrest" or "late maturation arrest")
25	#8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24
26	(hormon* near2 therap*)
27	MESH DESCRIPTOR Hormone Replacement Therapy
28	MESH DESCRIPTOR Gonadotropins
29	MESH DESCRIPTOR Chorionic Gonadotropin EXPLODE ALL TREES
30	MESH DESCRIPTOR Gonadotropins, Pituitary EXPLODE ALL TREES
31	MESH DESCRIPTOR Gonadotropin-Releasing Hormone
32	(gonadotrop* or GnRH or "gn-rh" or gonadorelin or hCG or choriogonadotropin* or choriogonadotrophin* or choriogonin or buserelin or suprecur or cystorelin or factrel or dirigestran or gonadoliberin or pregonadotropin or gonan or folistiman or ambinon or anthrogon or kryptocur or luliberin or bigonist or profact or receptal or suprefact or tiloryth or goserelin or zoladex or leuprolide or enantone or leuprorelin or lupron or nafarelin or synarel or triptorelin or decapeptyl or trelstar or cetrorelix or cetrotide or ganirelix or fyremadel or ovitrelle or follitropin or bemfola or "gonal-f" or ovaleap or pergoveris or rekovelle or lutropin or luveris or meriofert or fostimon or biogonadil or chorulon or gonabion or novarel or pregnyl or FSH or rFSH or uFSH or asgph or lutotropin or thyrotropin or tsh or trh or icsh or lh or ulh or rlh or lhfsh or lhfshrh or lhrh or lfrh or luteoziman or luteozyman or hmg or humegon or menogon or menopur or menotrophin* or menotropin* or normegon or pergonal or urofollitropin or bravelle or fertinex or follitrin or metrodin or fertinorm or thyrotropin or thyrotrophin or thyrogen)
33	(("interstitial cell stimulating" or luteinising or luteinizing or "follicle stimulating" or folliculostimulating or gonad* next stimulat* or pituitary or glycoprotein or thyroid) near2 hormone*)
34	MESH DESCRIPTOR Estrogen Receptor Modulators EXPLODE ALL TREES
35	((estrogen or oestrogen or estradiol or oestradiol) near2 (modulator* or inhibitor* or antagonist* or blocker* or suppress*))
36	(SERM or antiestrogen* or anti next estrogen* or antioestrogen* or anti next oestrogen* or tamoxifen or fulvestrant or faslodex or toremifene or fareston or nolvadex or novaldex or soltamox or tomaxithen or zitazonium or clomifene or clomid or androxal or clomiphene or chloramiphene or clomide or clomifen or clostilbegit or clostilbegyt or enclomid or enclomifene or enclomiphen* or serophene or transclomiphene or zuclomifene or dyneric or gravosan or klostilbegit or serophene or uclomiphene or evista or keoxifene or isomer)
37	MESH DESCRIPTOR Androgens EXPLODE ALL TREES
38	MESH DESCRIPTOR Testosterone
39	((synthetic near2 hormone*) or androgen* or anaprotin or andractim or androstanolone or dihydroepitestosterone or dihydrotestosterone or gelovit or stanolone or nandrolone or estrenolone or norandrostenolone or nortestosterone or anavar or oxandrin or oxandrolone or oxymetholone or anadrol or anapolon or hydroxymetholone or oxymethalone or stanazolol or stanozolol or androstanazol or methylstanazol or stromba or winstrol or androgel or androderm or andropatch or androtop or histerone or sterotate or sustanon or testim or testoderm or testolin or testopel or testosterone or testavan or testim or testogel or tostran)
40	((male next fertil* or male next infert*) near2 (agent* or hormone*))

41	MESH DESCRIPTOR Bromocriptine
42	MESH DESCRIPTOR Cabergoline
43	((dopamine near2 agonist*) or DA or bromocriptin* or bromocryptin* or bromoergocryptine or parlodel or arolac or carbamide or cuvalit or dopergin* or lisuride or lysuride or revanil or quinagolide or norprolac or cabergoline or cabaser* or cabergoline or dostinex)
44	MESH DESCRIPTOR Aromatase Inhibitors EXPLODE ALL TREES
45	((aromatase near1 (inhibit* or antagonist*)) or aminoglutethimide or anastrazole or arimidex or cytadren or exemestane or fadrozole or aromasin or femara or letrozole or orimeten or testolactone or zeneca)
46	#26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45
47	#25 and #46
48	(#25 and #46) IN HTA

Appendix C Effectiveness evidence study selection

Study selection for review question: What is the effectiveness of hormone treatment in male factor fertility problems?

Figure 1: Study selection flow chart



Appendix D Evidence tables

Evidence tables for review question: What is the effectiveness of hormone treatment in male factor fertility problems?

Aafjes, 1983

Bibliographic Reference	Aafjes, J H; van der Vijver, J C; Brugman, F W; Schenck, P E; Double-blind cross over treatment with mesterolone and placebo of subfertile oligozoospermic men value of testicular biopsy.; Andrologia; 1983; vol. 15specno; 531-5

Study details

Country/ies where study was carried out	The Netherlands
Study type	Cross-over randomised controlled trial
Study dates	Not reported
Inclusion criteria	Men with idiopathic oligozoospermia attending an infertility clinic with: • Unwanted primary infertility for ≥1 year • A partner who was supposed fertile on gynaecological examination with regular ovulation and ≥1 tube patent • Sperm count between 1 and 40 x 10^6/ml on ≥2 occasions • No varicocele present on palpation in the upright position • No history of cryptorchidism, hernia inguinalis surgery, venereal or other genital infection • No antibodies against spermatozoa in serum • Serum testosterone concentration above 14 nmol/l • A skull x-ray showing no sellar abnormalities
Exclusion criteria	Known possible causes for oligozoospermia
Patient characteristics	N=59 oligozoospermic men (number of participants included at baseline not reported) Mesterolone group (n=27):

	• Mean age (SD): not reported
	• Severity of semen abnormalities:
	  ○ Non-azoospermic: 27/27 (100%)
	• Fertility diagnosis:
	  ○ Idiopathic oligozoospermia: 27/27 (100%)
	• Hypogonadotropic hypogonadism: 0/27 (0%)*
	
	Placebo group (n=32):
	
	• Mean age (SD): not reported
	• Severity of semen abnormalities:
	  ○ Non-azoospermic: 32/32 (100%)
	• Fertility diagnosis:
	  ○ Idiopathic oligozoospermia: 32/32 (100%)
	• Hypogonadotropic hypogonadism: 0/32 (0%)*
	
	*People with known possible causes for oligozoospermia, such as hypogonadism, were excluded

Intervention(s)/control	Mesterolone: • Mesterolone, 25mg per tablet 3 times a day (for a total of 75mg per day) for 6 months Placebo: • Placebo tablets 3 times a day for 6 months After 6 months of initial treatment, participants in each group were crossed over to receive the alternate medication. Only data from the first phase were extracted
Duration of follow-up	6 months
Sources of funding	Not reported
Sample size	N=59 (number of participants included at baseline not reported): • Mesterolone group: n=27

	• Placebo group: n=32
Other information	Cross-over study; only data from the first phase were extracted. Results for sperm parameters outcomes were not reported separately for each phase and therefore could not be extracted

Study arms
Mesterolone (N = 27)

Placebo (N = 32)

Outcomes
Pregnancy rates

Outcome	Mesterolone, N = 27	Placebo, N = 32
Pregnancy rates at 3 months Reported in study as number of participants who impregnated/ fertilized their partner. Study does not report how these data were collected or how pregnancy was defined No of events	n = 4	n = 2

Critical appraisal with Cochrane RoB v2.0

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(No information reported on randomisation or participant characteristics at baseline. Allocation was assigned by the manufacturer and concealed from study investigators)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High *(Double-blind trial using placebo. No information reported on analysis used)*

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High *(Only the number of participants who could be evaluated at follow-up was reported; no information about number of participants or their characteristics at baseline, or on missing outcome data is reported.)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(No information reported on how data were collected for the outcome pregnancy rates or how pregnancy was defined - it is unclear whether pregnancy rate is defined in the study as an ultrasound scan that has shown at least one fetal heart beat. Double-blind study, so it is unlikely that assessment of the outcome could have been influenced by knowledge of the intervention received)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(No prespecified protocol was available. No information about how pregnancy was defined or measured. No evidence of selective reporting, though semen parameters outcomes could not be extracted due to insufficient presentation of results)*
Overall bias and Directness	Risk of bias judgement	High *(High risk of bias due to lack of information on deviations from the intended intervention and missing outcome data. Some concerns regarding a lack of information on the randomisation process, selection of the reported result, and measurement of the outcome)*
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	None

Adamopoulos, 2003

Bibliographic Reference	Adamopoulos, D.A.; Pappa, A.; Billa, E.; Nicopoulou, S.; Koukkou, E.; Michopoulos, J.; Effectiveness of combined tamoxifen citrate and testosterone undecanoate treatment in men with idiopathic oligozoospermia; Fertility and Sterility; 2003; vol. 80 (no. 4); 914-920

Study details

Country/ies where study was carried out	Greece
Study type	Randomised controlled trial (RCT)
Study dates	Not reported
Inclusion criteria	Men with idiopathic oligozoospermia and no apparent subfertility in the female partner
Exclusion criteria	Known or demonstrable causes of oligozoospermia (varicocele, infections, autoimmunity, stress, chromosomal abnormalities, environmental factors, or epididymopathy)

Patient characteristics	N=212 men with idiopathic oligozoospermia (N=175 completed trial):
	• Mean age (range): not reported (24-48 years)
	
	Tamoxifen + testosterone group (n=106; n=88 completed trial):
	• Mean age (SD): not reported
	• Severity of semen abnormalities:
	  ○ Non-azoospermic: 106/106 (100%)
	• Fertility diagnosis:
	  ○ Idiopathic oligozoospermia: 106/106 (100%)
	• Hypogonadotropic hypogonadism: 0/106 (0%)*
	
	Placebo group (n=106; n=87 completed trial):
	• Mean age (SD): not reported
	• Severity of semen abnormalities:
	  ○ Non-azoospermic: 106/106 (100%)
	• Fertility diagnosis:
	  ○ Idiopathic oligozoospermia: 106/106 (100%)

	• Hypogonadotropic hypogonadism: 0/106 (0%)* 82 normozoospermic men 26 to 38 years of age were also included to account for possible regression toward the mean effect, but results from these participants were not extracted * People with known or demonstrable possible causes for oligozoospermia, were excluded
Intervention(s)/control	Tamoxifen + testosterone: • Tamoxifen citrate, 10mg twice a day for 6 months • Testosterone undecanoate, 40mg three times a day for 6 months Placebo: • Placebo for 6 months, further details not reported
Duration of follow-up	3 months (halfway through treatment) and 6 months (end of treatment)
Sources of funding	Not industry funded
Sample size	N=212 (N=175 completed trial): • Tamoxifen + testosterone group: n=106 (n=88 completed trial) • Placebo group: n=106 (n=87 completed trial)
Other information	Medians and IQRs were reported but not extracted for the following outcomes, because they are not primary outcomes and the review is data heavy: functional sperm fraction at 9 months follow-up; total sperm count; sperm concentration. Data for the outcome seminal volume were only reported for the treatment group and could not be extracted. Pregnancy rate data at 6 months were not included in data extraction due to later data within the medium-term period (>3 months to ≤12 months) being reported (at 9 months)

	It is reported that 18 active treatment recipients and 19 placebo recipients dropped out, but it is not reported at what point they dropped out, so it is unclear how many participants have data at 3 months for semen parameters outcomes. Consequently, these results have been extracted using the numbers of participants who completed the trial. Results were reported in a graph and converted to numerical figures using a web plot digitizer as numerical figures not reported in text

Study arms
Tamoxifen + testosterone (N = 106)

Placebo (N = 106)

Outcomes
Pregnancy rates

Outcome	Tamoxifen + testosterone, N = 88	Placebo, N = 87
Spontaneous pregnancy rate at 3 months Reported as cumulative number of spontaneous pregnancies after treatment. Study does not report how these data were collected or how pregnancy was defined. Results converted from graph to numerical figures No of events	n = 4	n = 9
Spontaneous pregnancy rate at 9 months Reported as cumulative number of spontaneous pregnancies after treatment. Study does not report how these data were collected or how pregnancy was defined No of events	n = 36	n = 11

Semen parameters

Outcome	Tamoxifen + testosterone, N = 88	Placebo, N = 87
Sperm motility rate (%) at 3 months Reported as percentage of sperm with progressive motility Mean (SD) *Higher values are better*	38.5 (15.4)	32.9 (19.9)

Outcome	Tamoxifen + testosterone, N = 88	Placebo, N = 87
Sperm motility rate (%) at 6 months Reported as percentage of sperm with progressive motility Mean (SD) *Higher values are better*	41.6 (13.1)	30.7 (15.3)

Critical appraisal with Cochrane RoB v2.0

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Participants were randomised using numbered cards in closed envelopes. Information on age of participants not reported separately per group, but other baseline information does not indicate a problem with the randomisation process)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(Blinded study using placebo. No information on blinding of people delivering the intervention or deviations from the intended intervention. Authors report that 22 participants dropped out because they had a "change of priorities", but further information is not given)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(It is reported that 18 active treatment recipients and 19 placebo recipients dropped out, but it is not reported at what point they dropped out, so it is unclear how many participants have data at 3 months for semen parameters outcomes. Results were available for semen parameters outcomes at 6 months and for pregnancy rate for 88 participants (83%) in the active treatment group and 87 participants (82%) in the placebo group, and available for sperm morphology using strict criteria for 33 participants (31%) in the active treatment group and 29 participants (27%) in the placebo group. It is not clear why amount of data for this outcome is so low. Authors note that participants dropped out because their sexual problems were not solved, the participants had a change of priorities, or there were family problems. The numbers of participants who dropped out for these reasons are equal across treatment groups.)*

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Semen parameters were evaluated using World Health Organization criteria (sperm morphology evaluated using strict Kruger criteria), by an examiner who was blinded to treatment received. Some concerns for the outcomes pregnancy rate because it is not reported how these data were collected or how pregnancy was defined - it is unclear whether pregnancy rate is defined in the study as an ultrasound scan that has shown at least one fetal heart beat. It is unlikely that assessment of the outcome pregnancy rates could have been influenced by knowledge of the intervention received)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(No prespecified protocol was available. No information about how pregnancy was defined or measured. No evidence of selective reporting, though reporting methods through the use of graphs do not provide numerical figures and are unclear for the outcome pregnancy rate at 3 months)*
Overall bias and Directness	Risk of bias judgement	Some concerns *(Some concerns regarding missing outcome data and a lack of information on deviations from the intended intervention, selection of the reported result, and measurement of the outcome pregnancy rates)*
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	High risk of bias for the outcome sperm morphology using strict criteria, due to large amount of missing data with no explanation.

Amirzargar, 2012

Bibliographic Reference	Amirzargar, M.A.; Yavangi, M.; Basiri, A.; Moghaddam, S.M.H.; Babbolhavaeji, H.; Amirzargar, N.; Amirzargar, H.; Moadabshoar, L.; Comparison of recombinant human follicle stimulating hormone (rhFSH), human chorionic gonadotropin (HCG) and human menopausal gonadotropin (HMG) on semen parameters after varicocelectomy: A randomized clinical trial; Iranian Journal of Reproductive Medicine; 2012; vol. 10 (no. 5); 441-452

Study details

Country/ies where study was carried out	Iran
Study type	Randomised controlled trial (RCT)
Study dates	December 2008 to 2009
Inclusion criteria	People with the following: • Male factor infertility due to varicocele diagnosed by an expert urologist • Infertility clinically defined as failure to conceive after 12 months of unprotected intercourse during which pregnancy had not been achieved • Spontaneous onset of maturation and normal sexual development
Exclusion criteria	• Presence of infertility due to any factor other than varicocele, especially female infertility as diagnosed by an expert gynecologist • Clinically significant systemic disease • Underlying testis abnormalities • Abnormal reproductive hormone levels

Patient characteristics	N=113 infertile men with varicocele
	
	Human chorionic gonadotrophin (HCG) group (n=25):
	
	• Mean age (SD): 32.4 (5.3) years
	• Severity of semen abnormalities: not reported
	• Fertility diagnosis:
	  ○ Varicocele: 25/25 (100%)
	• Hypogonadotropic hypogonadism: 0/25 (0%)*
	
	Human menopausal gonadotrophin (HMG) group (n=21):
	
	• Mean age (SD): 32.6 (6.2) years
	• Severity of semen abnormalities: not reported
	• Fertility diagnosis:
	  ○ Varicocele: 21/21 (100%)

	• Hypogonadotropic hypogonadism: 0/21 (0%)*
	
	Recombinant human follicle-stimulating hormone (rhFSH) group (n=32):
	
	• Mean age (SD): 32.28 (6.6) years
	• Severity of semen abnormalities: not reported
	• Fertility diagnosis:
	  ○ Varicocele: 32/32 (100%)
	• Hypogonadotropic hypogonadism: 0/32 (0%)*
	
	No treatment group (n=35):
	
	• Mean age (SD): 31.3 (5.09) years
	• Severity of semen abnormalities: not reported
	• Fertility diagnosis:
	  ○ Varicocele: 35/35 (100%)
	• Hypogonadotropic hypogonadism: 0/35 (0%)*
	
	* People with infertility due to any factor other than varicocele were excluded

Intervention(s)/control	HCG: • Intramuscular HCG (Choriomon), 5000 IU weekly for 3 months HMG: • Subcutaneous HMG (Merional), 75 IU 3 times a week for 3 months

	rhFSH: • Subcutaneous rhFSH (Gonal-F), 75 IU 3 times a week for 3 months No treatment: • No medical treatment Participants in all groups had a varicocelectomy prior to medical treatment, which was done by a single surgeon with the inguinal procedure without microsurgery
Duration of follow-up	5 months (8 to 10 weeks after completion of each period of treatment) for semen parameters; 8 months (a further three months after the last control examination) for pregnancy rates
Sources of funding	Not industry funded
Sample size	N=113: • HCG group: n=25 • HMG group: n=21 • rhFSH group: n=32 • No treatment group: n=35
Other information	Results for the 3 treatment groups (HCG, HMG, and rhFSH) were combined into 1 arm in order to compare gonadotrophin therapy to no treatment

Study arms
Human chorionic gonadotrophin (HCG) (N = 25)

Human menopausal gonadotrophin (HMG) (N = 21)

Recombinant human follicle-stimulating hormone (rhFSH) (N = 32)

No treatment (N = 35)

Outcomes
Pregnancy rates

Outcome	HCG, HMG, or rhFSH, N = 78	No treatment, N = 35
Spontaneous or assisted pregnancy rate at 8 months Reported as number of pregnancies in female partners. All pregnancies in the treatment groups were spontaneous, and all in the no treatment group were achieved through IVF or ICSI. Study does not report how these data were collected or how pregnancy was defined. Results for 3 treatment groups combined into 1 arm: HCG: 8/25; HMG: 12/21; rhFSH: 20/32 No of events	n = 40	n = 15
Spontaneous pregnancy rate at 8 months Reported as number of spontaneous pregnancies in female partners. Study does not report how these data were collected or how pregnancy was defined. Results for 3 treatment groups combined into 1 arm: HCG: 8/25; HMG: 12/21; rhFSH: 20/32 No of events	n = 40	N=0

Semen parameters

Outcome	HCG, HMG, or rhFSH, N = 78	No treatment, N = 35
Number of participants with sperm concentration >20×10⁶/ml at 5 months Results for 3 treatment groups combined into 1 arm: HCG: 11/25; HMG: 10/21; rhFSH: 17/32 No of events *Higher values are better*	n = 38	n = 20

Outcome	HCG, HMG, or rhFSH, N = 78	No treatment, N = 35
Number of participants with sperm motility rate >50% at 5 months Results for 3 treatment groups combined into 1 arm: HCG: 11/25; HMG: 10/21; rhFSH: 19/32 No of events *Higher values are better*	n = 40	n = 18

Critical appraisal with Cochrane RoB v2.0

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(Participants were randomised using "the central method" but no further information about randomisation or allocation concealment is reported (p442). Patients were divided into four groups considering the similarity of compound variables to minimize the effects of confounding factors, and numbers in groups at follow-up do not reflect a problem with the randomisation process)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Information about blinding of participants and people delivering the interventions not reported, but due to nature of interventions, participants would have been able to tell if they were receiving an active treatment or not. People delivering the interventions would likely have been able to tell which treatment each participant was receiving due to the delivery of interventions (subcutaneous, intramuscular, or no treatment). However, no deviations from intended interventions reported)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Data were available for nearly all randomised participants. Figure 1 shows that 2 participants (3%) were excluded from the study prior to randomisation, however it is narratively reported that these participants discontinued treatment for various reasons)*

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Semen parameters were evaluated using World Health Organization criteria using the SQALLC-P sperm analysis system. Some concerns for the outcome pregnancy rate, because it is not reported how these data were collected or how pregnancy was defined - it is unclear whether pregnancy rate is defined in the study as an ultrasound scan that has shown at least one fetal heart beat. It is unlikely that assessment of the outcome pregnancy rates could have been influenced by knowledge of the intervention received)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(No prespecified protocol was available. High risk of bias for the pregnancy rates outcomes because it is unclear from the text whether number of spontaneous pregnancies are reported for the no treatment group, and whether number of assisted pregnancies are reported for the treatment groups. This strengthens the argument that the results for spontaneous pregnancy rate are implausible because there is a very large risk ratio for a primary outcome in a small study. Additionally, it is reported that further pregnancies occurred spontaneously or with the aid of ART after the 6 month observation period after treatment, but these data are not reported. No information about how the reported pregnancy rate was defined or measured)*
Overall bias and Directness	Risk of bias judgement	Low *(Very minor concerns regarding lack of prespecified protocol)*
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	High risk of bias for the pregnancy rates outcomes due to selection of the reported result and lack of information on measurement of the outcome

Aribarg, 1989

Bibliographic Reference	Aribarg, A.; Comhaire, F.; Mateo-de-Acosta, O.; Padron, R.S.; Mas, J.; Andolsek-Jeras, L.; Ograjensek, Z.; Coutinho, E.; Ratnam, S.S.; Wong, P.C.; Resch, B.; Szollosi, J.; Hazelden, C.; Hargreave, T.B.; Farley, T.M.M.; Rowe, P.J.; Mesterolone and idiopathic male infertility: A double-blind study; International Journal of Andrology; 1989; vol. 12 (no. 4); 254-264

Study details

Country/ies where study was carried out	Not reported
Study type	Randomised controlled trial (RCT)
Study dates	Not reported
Inclusion criteria	Infertile couples with infertility ≥12 months, in whom: • The male partner had primary idiopathic testicular failure (i .e. no aetiological factors and sperm concentration <20 x10^6/ml in the best of two semen analyses), OR any sperm abnormality not accompanied by any aetiological factors • The female partner had no demonstrable cause of infertility (i.e. normal menstrual pattern, regular ovulation, normal prolactin levels, bilateral patent tubes determined by laparoscopy or hysterosalpinography, and no pelvic adhesions or evidence of endometriosis), OR was under successful treatment for a minor endocrine problem (e.g. anovulation with regular cycles, oligomenorrhoea, hyperprolactinaemia, or hypothyroidism)
Exclusion criteria	Not reported

Patient characteristics	N=157 infertile couples (N=248 originally recruited but n=91 couples later found not to meet inclusion criteria).
	
	Mesterolone (75mg) group (n=54):
	
	• Mean age (SD): 31.4 (5.2) years
	• Severity of semen abnormalities:
	  ○ Non-azoospermic: 54/54 (100%)*
	• Fertility diagnosis: not reported*
	• Hypogonadotropic hypogonadism: 0/54***
	
	Mesterolone (150mg) group (n=50):
	
	• Mean age (SD): 31.0 (4.9) years
	• Severity of semen abnormalities:
	  ○ Non-azoospermic: 50/50 (100%)*
	• Fertility diagnosis: not reported*

	• Hypogonadotropic hypogonadism: 0/50 (0%)*** Placebo group (n=53): • Mean age (SD): 29.9 (5.1) years • Severity of semen abnormalities: ○ Non-azoospermic: 53/53 (100%)* • Fertility diagnosis: not reported* • Hypogonadotropic hypogonadism: 0/53 (0%)*** * All participants had idiopathic oligozoospermia or idiopathic low sperm motility ** All participants had idiopathic testicular failure or semen abnormalities without aetiological reasons, but it is not reported how many participants have either of these diagnoses *** People with aetiological factors associated with their testicular failure or their sperm abnormalities were excluded
Intervention(s)/control	Mesterolone (75mg): • Mesterolone (17P-hydroxy-la-methyl-5a-androstan-3-one), 25mg taken 3 times a day for 6 months (corresponding to daily doses of 75mg) Mesterolone (150mg): • Mesterolone (17P-hydroxy-la-methyl-5a-androstan-3-one), 50mg taken 3 times a day for 6 months (corresponding to daily doses of 150mg) Placebo: • Placebo, packaged identically for 6 months

Duration of follow-up	12 months
Sources of funding	Not reported
Sample size	N=157 (N=248 originally recruited): • Mesterolone (75mg) group: n=54 • Mesterolone (150mg) group: n=50 • Placebo group: n=53
Other information	Results for the 2 treatment groups (mesterolone 75mg, and mesterolone 150mg) were combined into 1 arm in order to compare androgens to placebo. Data for the following semen parameters outcomes could not be extracted because of insufficient presentation of results (only changes in levels from baseline are reported and no measure of deviation or additional statistics reported): sperm motility, sperm viability, sperm morphology, and sperm concentration. Study also reported the number of viable pregnancies, but this was reported for all participants included in the study, including those later found not eligible for inclusion. Data from participants who were eligible for inclusion were not reported separately and therefore could not be extracted.

Study arms
Mesterolone (75mg) (N = 54)

Mesterolone (150mg) (N = 50)

Placebo (N = 53)

Outcomes
Pregnancy rates

Outcome	Mesterolone (at 75mg or 150mg), N = 82	Placebo, N = 43
Pregnancy rates at 3 months Reported in study as occurrence of pregnancy. Study does not report how these data were collected or how pregnancy was defined	n = 15	n = 5

Outcome	Mesterolone (at 75mg or 150mg), N = 82	Placebo, N = 43
No of events		

Critical appraisal with Cochrane RoB v2.0

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Randomisation was done using consecutive subject numbering which corresponded to the medication received. Knowledge of numbering and therefore treatment allocation were known only by a data co-ordinating centre. Baseline participant characteristics do not suggest a problem with randomisation)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Double-blind study using placebo. Intention to treat analysis was used)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(32/157 participants (20%) dropped out or were lost to follow-up (17 were lost to follow-up and 15 discontinued the study). Authors report participants who discontinued did so for personal or medical reasons, and the majority of these were due to dissatisfaction with the therapy offered or non-adherence to the treatment schedule. It's reported that 3 participants discontinued due to adverse events (severe abdominal pain and discomfort, frequent headaches and dizziness, or severe exanthema), but it is not reported whether these participants were part of the group who were eligible for the study according to the inclusion criteria. Overall there was not a significant difference between the number of participants who were lost to follow-up or who discontinued between each group.)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(No information reported on how data were collected for the outcome pregnancy rates or how pregnancy was defined - it is unclear whether*

Section	Question	Answer
		pregnancy rate is defined in the study as an ultrasound scan that has shown at least one fetal heart beat. Double-blind study, so it is unlikely that assessment of the outcome could have been influenced by knowledge of the intervention received)
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(No prespecified protocol was available. No information about how pregnancy was defined or measured. No evidence of selective reporting, though semen parameters outcomes could not be extracted due to insufficient presentation of results)*
Overall bias and Directness	Risk of bias judgement	Some concerns *(Some concerns due to missing outcome data and lack of information on measurement of the outcome and selection of the reported result)*
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	None

Babak, 2018

Bibliographic Reference	Babak, J.; Behruz, F.; Mohammadreza, Y.; Morteza, F.-K.; The Effect of Human Chorionic Gonadotropin Therapy on Semen Parameters and Pregnancy Rate after Varicocelectomy; Current Urology; 2018; vol. 11 (no. 2); 92-96

Study details

Country/ies where study was carried out	Iran
Study type	Randomised controlled trial (RCT)
Study dates	July 2012 to August 2014
Inclusion criteria	Infertile people with varicocele and an abnormal semen analysis. Infertility was defined as: failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse

Exclusion criteria	• Infertility for any other reason other than varicocele (for example history of cryptorchidism, endocrinopathy, testicular failure or ejaculatory dysfunction and patient history of testicular sperm extraction) • Gynaecological problems in the participants' partners

Patient characteristics	N=188 infertile people with varicocele and abnormal semen analysis (N=193 randomised but data for n=15 participants who did not complete study not reported)
	
	Human chorionic gonadotrophin (HCG) group (n=91; n=94 initially randomised):
	
	• Mean age (SD): 29.91 (2.67) years
	• Severity of semen abnormalities: not reported
	• Fertility diagnosis:
	  ○ Varicocele: 91/91 (100%)
	• Hypogonadotropic hypogonadism: 0/91 (0%)*
	
	No treatment (n=97; n=99 initially randomised):
	
	• Mean age (SD): 32.79 (3.12) years
	• Severity of semen abnormalities: not reported
	• Fertility diagnosis:
	  ○ Varicocele: 97/97 (100%)
	• Hypogonadotropic hypogonadism: 0/97 (0%)*
	
	* Participants with infertility due to any reason other than varicocele were excluded

Intervention(s)/control	HCG: • HCG, 5000 IU administered intramuscularly every week for 3 consecutive months No treatment: • No medical treatment

	Participants in both groups had an open inguinal varicocelectomy prior to medical treatment
Duration of follow-up	6 months for semen parameters outcomes, 2 years for pregnancy rates
Sources of funding	Not reported
Sample size	N=188 (193 participants randomised): • HCG: n=91 (n=94 initially randomised) • No treatment: n=97 (n=99 initially randomised)
Other information	None

Study arms
Human chorionic gonadotrophin (HCG) (N = 91)

No treatment (N = 97)

Outcomes
Pregnancy rates

Outcome	**Human chorionic gonadotrophin (HCG), N = 91**	**No treatment, N = 97**
Pregnancy rates at 2 years Study does not report how pregnancy was defined; pregnancy reported by participants No of events	n = 56	n = 22

Semen parameters

Outcome	**Human chorionic gonadotrophin (HCG), N = 91**	**No treatment, N = 97**
Sperm concentration (x10^6/ml) at 6 months Mean (SD)	22.2 (4.7)	22.8 (2.6)

Outcome	Human chorionic gonadotrophin (HCG), N = 91	No treatment, N = 97
Higher values are better		
Sperm motility rate (%) at 6 months Mean (SD) *Higher values are better*	56.3 (5.1)	60.1 (7.4)

Critical appraisal with Cochrane RoB 2.0

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(Block randomisation was used but no further information is given about randomisation process or allocation concealment. Percentage of participants with grade II varicocele higher in HCG group that no treatment group, but imbalances compatible with chance)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(No information on blinding of participants or people providing intervention, however nature of interventions mean they likely knew which treatment was received. However, all participants received their allocated interventions)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Only 5 participants dropped out of the study: 3 participants in the HCG group (2 participants lost to follow-up due to poor compliance; 1 participant discontinued the intervention) and 2 participants in the no treatment group (1 participant lost to follow-up due to poor compliance; 1 participant discontinued the intervention))*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(Pregnancy outcomes reported by participants over the phone. Criteria for clinical pregnancy rate not reported in study. Outcome assessors (participants) were likely aware of intervention received but it is unlikely that knowledge of intervention received would influence reporting of pregnancy rates)*

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(No prespecified protocol available. No information about how pregnancy was defined.)*
Overall bias and Directness	Risk of bias judgement	Some concerns *(Some concerns due to lack of information about the randomisation process, measurement of the outcomes and prespecified protocol)*
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	None

Baccetti, 2004

Bibliographic Reference	Baccetti, B.; Piomboni, P.; Bruni, E.; Capitani, S.; Gambera, L.; Moretti, E.; Sterzik, K.; Strehler, E.; Effect of follicle-stimulating hormone on sperm quality and pregnancy rate; Asian Journal of Andrology; 2004; vol. 6 (no. 2); 133-137

Study details

Country/ies where study was carried out	Germany
Study type	Randomised controlled trial (RCT)
Study dates	Not reported
Inclusion criteria	Couples with idiopathic male factor infertility as indicated by combined gynaecological and andrological examinations, meeting the following criteria for the female partners: • No health or fertility problems • No untreatable hormonal irregularities And the following criteria in the male partners: • Normal or low baseline endocrine parameters, including plasma concentrations of FSH, LH, prolactin, 17-estradiol and testosterone

	• No causes of infertility detected by physical examinations, such as reduced testicular size, varicocele, or cryptorchidism • Absence of urinogenital tract infection or inflammation • Unremarkable medical history • Oligo- and/or astheno-zoospermia according to WHO criteria • Failure in at least two IVF or IUI treatment cycles
Exclusion criteria	Participants with plasma concentrations of FSH above 12 mUI/mL

Patient characteristics	N=44 men with idiopathic male factor infertility:
	
	• Mean age (range): Not reported (28-45 years)
	• Severity of semen abnormalities:
	  ○ Non-azoospermic: 44/44 (100%)
	• Fertility diagnosis:
	  ○ Idiopathic oligo- and/or astheno-zoospermia: 44/44 (100%)
	• Hypogonadotropic hypogonadism: 0/44 (0%)*
	
	Participant characteristics not reported separately for each group
	
	*Patients had no known causes of infertility

Intervention(s)/control	Follicle stimulating hormone (FSH): • FSH, 150 IU/day delivered subcutaneously for 12 weeks No treatment: • No treatment given
Duration of follow-up	3 months ("after FSH treatment")
Sources of funding	Not industry funded
Sample size	N=44: • FSH: n=24

	• No treatment: n=20
Other information	Semen parameters outcomes could not be extracted due to insufficient presentation of results: mean and P values are reported for the FSH group but only mean values were reported for the no treatment group. Clinical pregnancy rate is reported in the study as a percentage, so the number of events for the pregnancy rates outcome was therefore converted from percentages to numerical values

Study arms
Follicle stimulating hormone (FSH) (N = 24)

No treatment (N = 20)

Outcomes
Pregnancy rates

Outcome	Follicle stimulating hormone (FSH), N = 24	No treatment, N = 20
Assisted pregnancy rate at 3 months Reported in study as clinical pregnancy rate after ICSI, determined by ultrasound evidence of a foetal sac 6 weeks after embryo transfer. Data reported as percentages and converted to numerical figures No of events	n = 8	n = 4

Critical appraisal with Cochrane RoB 2.0

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(No information reported on randomisation process or allocation concealment. FSH group is slightly larger than no treatment group, but difference is not beyond that compatible with chance)*

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High *(No information reported on blinding of participants or people delivering the intervention, though nature of interventions means it is likely they were aware. No information reported on deviations from the intended intervention, or on analysis used.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Data available for all included participants)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Clinical pregnancy was determined using ultrasound. No information reported on who the outcome assessors were or whether they were blinded, but method of assessing the outcome means data likely could not have been influenced by knowledge of intervention received)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(No prespecified protocol available.)*
Overall bias and Directness	Risk of bias judgement	High *(High risk of bias due to lack of information on deviations from the intended interventions and the randomisation process. Some concerns regarding lack of prespecified protocol available)*
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	None

Cakan, 2009

Bibliographic Reference	Cakan, Murat; Aldemir, Mustafa; Topcuoglu, Murat; Altug, Ugur; Role of testosterone/estradiol ratio in predicting the efficacy of tamoxifen citrate treatment in idiopathic oligoasthenoteratozoospermic men.; Urologia internationalis; 2009; vol. 83 (no. 4); 446-51

Study details

Country/ies where study was carried out	Turkey

Study type	Randomised controlled trial (RCT)
Study dates	June 2001 to January 2006
Inclusion criteria	Men with idiopathic oligoasthenoteratozoospermia ≥2-year history of infertility with their current partner, who partners either: • Had no pathology to cause infertility, OR • Had been treated for infertility
Exclusion criteria	Known or demonstrable causes of oligoasthenoteratozoospermia (clinical or subclinical varicocele, hormonal disorder, infection, stress, epididymopathy, autoimmunity, environmental factors, or on any medications for ≥3 months before the beginning of the study)

Patient characteristics	N=127* men with idiopathic oligoasthenoteratozoospermia
	
	Tamoxifen citrate group (n=103):
	
	• Mean age (SD): 27.3 (4.9) years
	• Severity of semen abnormalities:
	  ○ Non-azoospermic: 103/103 (100%)
	• Fertility diagnosis:
	  ○ Idiopathic oligoasthenoteratozoospermia: 103/103 (100%)
	• Hypogonadotropic hypogonadism: 0/103 (0%)**
	
	No treatment group (n=25):
	
	• Mean age (SD): 26.8 (5.0) years
	• Severity of semen abnormalities:
	  ○ Non-azoospermic: 25/25 (100%)
	• Fertility diagnosis:
	  ○ Idiopathic oligoasthenoteratozoospermia: 25/ 25 (100%)
	• Hypogonadotropic hypogonadism: 0/25 (0%)**

	* Total number of participants reported throughout the study does not match the total of the numbers reported in each group ** People with known or demonstrable causes of infertility, including hormonal disorders, were excluded
Intervention(s)/control	In the first study period, participants were randomised to tamoxifen or no treatment: Tamoxifen citrate: • Tamoxifen citrate, 10mg taken orally twice a day for 25 days every month for 3 months No treatment: • No treatment given In the second study period, participants with a normal testosterone/estradiol (T/E2) ratio continued to receive tamoxifen, while participants with low T/E2 ratios were randomised either to continue with tamoxifen alone as well, or to tamoxifen with additional anastrozole. Only data from the first study phase were extracted
Duration of follow-up	3 months
Sources of funding	Not reported
Sample size	First study phase: N=127*: • Tamoxifen citrate: n=103 • No treatment: n=25 *Total number of participants reported throughout the study does not match the total of the numbers reported in each group
Other information	Means and ranges were reported but not extracted for the outcome sperm concentration, because it is not a primary outcome and the review is data heavy. Data also reported for follicle-stimulating hormone (FSH), however these data not extracted as unlikely to be useful for decision-making. Pregnancy rate is reported in the study as a percentage, so the number of events was therefore converted from percentages

Study arms
Tamoxifen citrate (N = 103)

No treatment (N = 25)

Outcomes
Pregnancy rates

Outcome	Tamoxifen citrate, N = 103	No treatment, N = 25
Pregnancy rate at 3 months Reported as number of partners of participants who were pregnant. Study does not report how these data were collected or how pregnancy was defined No of events	n = 11	n = 0

Hormone parameters

Outcome	Tamoxifen citrate, N = 103	No treatment, N = 25
Testosterone (ng/dl) at 3 months Mean (SD) *Higher values are better*	495.7 (26.1)	407.5 (19.4)
Oestradiol (pg/ml) at 3 months Mean (SD) *Lower values are better*	46.8 (9.3)	29.9 (7.1)

Semen parameters

Outcome	Tamoxifen citrate, , N = 103	No treatment, , N = 25
Sperm motility rate (%) at 3 months Reported in study as sperm motility rate (A+B, %)	37.4 (18.9)	29.6 (15.1)

Outcome	Tamoxifen citrate, , N = 103	No treatment, , N = 25
Mean (SD) *Higher values are better*		

Critical appraisal with Cochrane RoB 2.0

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High *(No information reported on randomisation process or allocation concealment. Large difference in numbers between groups in the first study period indicate a problem with the randomisation process. It is likely this difference was deliberate to enable larger study groups in the second study period, however this is not explained in the study. Some concerns relating to outcomes reported for the second study period due to lack of information about the randomisation process, but numbers between groups are even. However, no information reported regarding differences between patient characteristics at baseline)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Single-blind study; participants were aware of the interventions received. No information on blinding of people providing intervention, but nature of interventions mean they likely knew which treatment was received. However, it is reported that no drug-related serious side effect requiring cessation of medical treatment was observed in the treatment groups, and figure 1 indicates no deviations from the intended interventions)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Outcome data available for all included participants)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Semen parameters were evaluated using World Health Organization criteria (sperm motility) or Kruger strict criteria (sperm morphology) by an examiner who was blinded to treatment received. Testosterone and oestradiol were measured using chemiluminescent immunometric assay. Some concerns for the outcome pregnancy rate, because it is not reported how these data were collected or how pregnancy was defined - it is unclear whether pregnancy rate is defined in the study as an ultrasound scan that has shown at least one fetal*

Section	Question	Answer
		heart beat. It is unlikely that assessment of the outcome pregnancy rates could have been influenced by knowledge of the intervention received)
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(No prespecified protocol was available. No information about how pregnancy was defined or measured)*
Overall bias and Directness	Risk of bias judgement	Some concerns *(Although there is a high risk of bias arising from the randomisation process due to imbalances in numbers between groups, it is likely this difference was deliberate to enable larger study groups in the second study period. Additionally, some minor concerns regarding selection of the reported result, but low risk of bias for all other domains. Some concerns regarding lack of information on measurement of the outcome pregnancy rates)*
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	None

Cavallini, 2013

Bibliographic Reference	Cavallini, G.; Biagiotti, G.; Bolzon, E.; Multivariate analysis to predict letrozole efficacy in improving sperm count of non-obstructive azoospermic and cryptozoospermic patients: A pilot study; Asian Journal of Andrology; 2013; vol. 15 (no. 6); 806-811

Study details

Country/ies where study was carried out	Italy
Study type	Randomised controlled trial (RCT)
Study dates	January 2010 to March 2012
Inclusion criteria	People with normal sperm appearance, consistency, liquefaction, volume, and pH and no chromosomal aberrations, and either of the following:

	• Non-obstructive azoospermia (defined as the absence of sperm in the pellets of 2 centrifuged (300g for 15 min) semen samples collected 7–30 days apart) yielding no spermatozoa with fine needle aspiration, OR • Cryptozoospermia (defined as the presence of sperm in the pellet (but not in the ejaculate) of ≥1 semen sample out of the 2 collected, i.e. with a sperm concentration $<10^3$ ml^{-1}) with testosterone/estradiol ratio <10
Exclusion criteria	• Seminal white blood cell concentration $>10^6$ ml and/or a positive seminal cultural analysis or positive urethral swab chlamydia test • Drug, tobacco, or alcohol abuse • Ongoing medical treatment (gonadotrophins, anabolic steroids, cancer chemotherapy, non-steroidal anti-inflammatory drugs) • Previous cancer radiotherapy or chemotherapy • Palpable varicocele • X-ray exposure in the previous 8 months • Y chromosome microdeletion • Karyotype alterations (such as Klinefelter syndrome)

Patient characteristics	N=45 people with non-obstructive azoospermia or cryptozoospermia (N=52 randomised but data for n=7 participants who did not complete study not reported)
	
	Letrozole group (n=22; n=26 initially randomised)*:
	
	• Mean age (SD): 44 (not reported; range: 37–52) years
	• Severity of semen abnormalities:
	  ○ Azoospermia (non-obstructive): 6/22 (27%)
	  ○ Non-azoospermia: 16/22 (73%)
	• Fertility diagnosis:
	  ○ Previous bilateral cryptorchidism: 3/22 (14%)
	  ○ Previous unilateral cryptorchidism: 5/22 (23%)
	  ○ Idiopathic a- or crypto-zoospermia: 14/22 (64%)
	• Hypogonadotropic hypogonadism: Not reported
	
	Placebo group (n=24; n=26 initially randomised)**:
	
	• Mean age (SD): 45 (not reported; range: 38–53) years
	• Severity of semen abnormalities:

	○ Azoospermia (non-obstructive): 5/24 (21%) ○ Non-azoospermia: 19/24 (79%) • Fertility diagnosis: ○ Previous bilateral cryptorchidism: 4/24 (17%) ○ Previous unilateral cryptorchidism: 5/24 (21%) ○ Idiopathic a- or crypto-zoospermia: 15/24 (63%) • Hypogonadotropic hypogonadism: Not reported * Data for only n=21 participants reported at baseline ** Data for only n=22 participants reported at baseline
Intervention(s)/control	Letrozole: • Letrozole, 2.5mg once a day for 6 months Placebo: • Starch, 100mg once a day for 6 months
Duration of follow-up	6 months
Sources of funding	Not reported
Sample size	N=45 (N=52 randomised): • Letrozole group: n=22 (n=26 initially randomised) • Placebo group: n=24 (n=26 initially randomised)
Other information	Medians and IQRs were reported but not extracted for the following outcomes, because they are not primary outcomes and the review is data heavy: sperm concentration (no. of spermatozoa); progressive motile sperm (%); typical forms using strict criteria (%); testosterone; oestradiol Data also reported for luteinizing hormone (LH), follicle-stimulating hormone (FSH), and prolactin, however these data not extracted as unlikely to be useful for decision-making.

Study arms
Letrozole (N = 22)

Placebo (N = 24)

Outcomes
Pregnancy rates

Outcome	Letrozole, , N = 22	Placebo, , N = 24
Spontaneous pregnancy rate at 6 months Reported as number of natural pregnancies. Study does not report how these data were collected or how pregnancy was defined No of events	n = 0	n = 0

Critical appraisal with Cochrane RoB 2.0

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Randomisation using random number tables and blindness for drug delivery ensured using colour-coded boxes. Minor baseline differences are compatible with chance)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Double-blind study using placebo. All study personnel and participants were blinded to the treatment assignment for the duration of the study: nurses were blinded to the delivery of the boxes containing treatments, and the biologists performing seminal examinations were blinded by assigning each sample with a code number. The review board had access to the unblinded data in case they needed to alert physicians as a result of major side effects, but this was not necessary. Trial authors used a modified intention-to-treat analysis excluding participants with missing outcome data, to improve the robustness of the analysis)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(Four patients (15%) dropped out of the letrozole group due to side effects*

Section	Question	Answer
		(loss of libido: n=2; hair loss: n=1; cutaneous rash: n=1), and 2 patients (9%) were excluded from the placebo group after randomisation because of protocol violations, though these are not detailed. The reasons for dropping out of the active treatment group were linked to side effects, however these are unlikely to be related to the outcome pregnancy rates)
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(It is not reported how data for the outcome pregnancy rates were collected or how pregnancy was defined - it is unclear whether pregnancy rate is defined in the study as an ultrasound scan that has shown at least one fetal heart beat. However, all participants and personnel involved in the trial were blinded)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(No prespecified protocol was available. No information about how pregnancy was defined or measured)*
Overall bias and Directness	Risk of bias judgement	Some concerns *(Some concerns regarding missing outcome data and lack of information on measurement of the outcome and selection of the reported result)*
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	None

Comhaire, 1995

Bibliographic Reference	Comhaire, F; Schoonjans, F; Abdelmassih, R; Gordts, S; Campo, R; Dhont, M; Milingos, S; Gerris, J; Does treatment with testosterone undecanoate improve the in-vitro fertilizing capacity of spermatozoa in patients with idiopathic testicular failure? (results of a double blind study).; Human reproduction (Oxford, England); 1995; vol. 10 (no. 10); 2600-2

Study details

Country/ies where study was carried out	Not reported
Study type	Randomised controlled trial (RCT)
Study dates	Not reported

Inclusion criteria	Couples with primary infertility of ≥12 months who: • Had no pathology in the female partner which could interfere with the ability of oocytes to be fertilized in vitro • Had undergone ≥1 IVF treatment which had failed to result in pregnancy because of a low fertilization rate and ≤1/3 mature oocytes fertilized • Had abnormal semen quality in the male partner (i.e. oligo-and/or astheno-and/or teratozoospermia as defined by the WHO)
Exclusion criteria	Not reported

Patient characteristics	N=64 infertile couples (N=75 initially randomised but n=11 participants who breached the protocol or who did not take the capsule for 3 months were excluded from analysis)
	
	Testosterone undecanoate group (n=30):
	
	• Mean age (SD): not reported. Female partner age (SD): 31 (3.4) years
	• Severity of semen abnormalities:
	  ○ Non-azoospermia: 30/30 (100%)
	• Fertility diagnosis:
	  ○ Oligo- and/or astheno- and/or terato-zoospermia (cause not reported): 30/30 (100%)
	• Hypogonadotropic hypogonadism: Not reported
	
	Placebo group (n=34):
	
	• Mean age (SD): not reported. Female partner age (SD): 30.4 (3.2) years
	• Severity of semen abnormalities:
	  ○ Non-azoospermia: 34/34 (100%)
	• Fertility diagnosis:
	  ○ Oligo- and/or astheno- and/or terato-zoospermia (cause not reported): 34/34 (100%)
	• Hypogonadotropic hypogonadism: Not reported

Intervention(s)/control	Testosterone undecanoate: • Testosterone undecanoate (Andriol), 40mg capsules 3 times a day (for a total of 120mg per day) for 3 months Placebo: • Identically packaged placebo, 3 times a day for 3 months After 3 months of capsule intake, participants in both groups underwent repeat IVF treatment using the same clinical and laboratory techniques as during the first attempt
Duration of follow-up	3 months
Sources of funding	Industry funded
Sample size	N=64 (N=75 initially randomised): • Testosterone undecanoate group: n=30 • Placebo group: n=34
Other information	Clinical pregnancy rate is reported in the study as a percentage, so the number of events for the pregnancy rates outcome was therefore converted from percentages to numerical values. Two participants had spontaneous pregnancies but it is not reported which group these participants were in because they were excluded from the analysis for breaching the protocol (further information is not reported). Data for the following semen parameters outcomes could not be extracted because of insufficient presentation of results (only mean levels at follow-up are reported and no measure of deviation or additional statistics reported): sperm concentration, grade A sperm motility, grade B sperm motility

Study arms
Testosterone undecanoate (N = 30)

Placebo (N = 34)

Outcomes
Pregnancy rates

Outcome	Testosterone undecanoate,, N = 30	Placebo, N = 34
Assisted pregnancy rates at 3 months Reported in study as couples with fertilisation and subsequent pregnancy after IVF. Fertilisation was defined as the occurrence of 2 pronuclei, and pregnancy was documented by echography. Data reported as percentages and converted to numerical figures No of events	n = 5	n = 11

Critical appraisal with Cochrane RoB 2.0

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(No information reported on the randomisation process or allocation concealment. Participants characteristics at baseline do not suggest a difference between groups, but important characteristics such as age of the male participants are not reported so this cannot be assessed)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High *(Double blind trial using placebo. 5/75 couples (7%) who were initially included and randomised were excluded from data analysis because they took their assigned intervention for <3 months; reasons for discontinuation or which group these participants were assigned to are not reported. The number of events for the outcome pregnancy rates is low enough that this could have had a substantial impact on the result)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Data were available for all participants that were not excluded for treatment discontinuation or protocol breaches)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Double blind trial. Pregnancy was confirmed in the study using echography)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(No prespecified protocol available. No semen parameters outcomes could not be extracted because of insufficient presentation of results (only levels at*

Section	Question	Answer
		follow-up are reported and no measure of deviation or additional statistics reported).)
Overall bias and Directness	Risk of bias judgement	High *(High risk of bias due to deviations from the intended interventions. Some concerns related to lack of information about randomisation and bias in the selection of the reported result)*
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	None

Crottaz, 1992

Bibliographic Reference	Crottaz, B.; Senn, A.; Reymond, M.J.; Rey, F.; Germond, M.; Gomez, F.; Follicle-stimulating hormone bioactivity in idiopathic normogonadotropic oligoasthenozoospermia: Double-blind trial with gonadotropin-releasing hormone; Fertility and Sterility; 1992; vol. 57 (no. 5); 1034-1043

Study details

Country/ies where study was carried out	Switzerland
Study type	Randomised controlled trial (RCT)
Study dates	Not reported
Inclusion criteria	Infertile men with idiopathic normogonadotropic oligoasthenozoospermia as the sole etiology of couple infertility: Idiopathic infertility was defined as absence of the following: • History of undescended testes, testicular inflammatory disease, torsion, cancer, or trauma, or exposure to potential testicular noxes • Presence of a varicocele • Recent allergic, acute, febrile, or chronic debilitating diseases • Occult prostatic infection (verified by a normal exfoliative cytology after prostatic massage)

	• Leydig cell dysfunction or androgen insensitivity (verified by normal testosterone values and normal clinical androgenization) • Abnormal basal prolactin Oligoasthenozoospermia was defined as: • <50% spermatozoa with progressive linear motility • <40 X 10^6 motile spermatozoa per ejaculate in ≥3 consecutive analyses ≥1-month apart before entering the study Normogonadotropic was defined as having both basal and GnRH-stimulated (0.1 mg as IV bolus) plasma luteinizing hormone and follicle-stimulating hormone, measured by radioimmunoassay within reference normal values N.B.: despite inclusion criteria, 1 participant with azoospermia was included in the study
Exclusion criteria	Not reported

Patient characteristics	N=28 men with idiopathic normogonadotropic oligoasthenozoospermia (N=39 randomised but data for n=11 participants who did not complete study not reported)
	
	Gonadotrophin-releasing hormone (GnRH) group (n=14; number initially randomised not reported):
	
	• Mean age (SD): 31.7 (1.0) years
	• Severity of semen abnormalities:
	  ○ Azoospermia: 1/14 (7%)
	  ○ Non-azoospermia: 13/14 (93%)
	• Fertility diagnosis:
	  ○ Idiopathic normogonadotropic oligoasthenozoospermia: 14/14 (100%)
	• Hypogonadotropic hypogonadism: 0/14 (0%)*
	
	Placebo group (n=14; number initially randomised not reported):
	
	• Mean age (SD): 32.9 (1.1) years
	• Severity of semen abnormalities:
	  ○ Non-azoospermia: 14/14 (100%)

	• Fertility diagnosis: ○ Idiopathic normogonadotropic oligoasthenozoospermia: 14/14 (100%) • Hypogonadotropic hypogonadism: 0/14 (0%)* * Participants were all normogonadotropic
Intervention(s)/control	GnRH: • GnRH, 0.2mg self-administered using a nasal spray (0.1 mL per puff) every 2 hours from 8:00AM to 8:00PM for 3 months Placebo: • Placebo, self-administered using a nasal spray (0.1 mL per puff) every 2 hours from 8:00AM to 8:00PM for 3 months After the first 3-month phase whereby participants were randomised to the treatments above, participants went 1 month without treatment, and then participants in both initial groups underwent a 3-month period of open GnRH treatment. Only data from the first study phase are extracted because the second phase is non-comparative
Duration of follow-up	1, 2, and 3 months
Sources of funding	Industry funded
Sample size	N=28 (N=39 randomised) • GnRH group: n=14 (number initially randomised not reported) • Placebo group: n=14 (number initially randomised not reported)
Other information	Results for the semen parameters outcomes were reported in graphs and converted using a web plot digitizer as numerical figures not reported in text. Means and SEs were reported for these outcomes and converted to SDs during data extraction Semen parameters data at 1 and 2 months were not included in data extraction due to later data within the short-term period (≤3 months) being reported (at 3 months

	Data also reported for immunoreactive luteinizing hormone (LH), immunoreactive follicle-stimulating hormone (FSH) and bioactive FSH, however these data not extracted as unlikely to be useful for decision-making.

Study arms
Gonadotrophin-releasing hormone (GnRH) (N = 14)

Placebo (N = 14)

Outcomes
Pregnancy rates

Outcome	Gonadotrophin-releasing hormone (GnRH), N = 14	Placebo, N = 14
Pregnancy rate at 3 months Reported as pregnancies during the double-blind study period. Study does not report how these data were collected or how pregnancy was defined No of events	n = 0	n = 3

Semen parameters

Outcome	Gonadotrophin-releasing hormone (GnRH), N = 14	Placebo, N = 14
Total motile sperm count (x10^6) at 3 months Results converted from graph to numerical figures; SEs converted to SDs during data extraction. GnRH SE: 15; placebo SE: 2.9 Mean (SD) *Higher values are better*	28.7 (56.1)	11.6 (10.9)
Sperm concentration (x10^6/ml) at 3 months Results converted from graph to numerical figures; SEs converted to SDs during data extraction. GnRH SE: 12.3; placebo SE: 2.1	30.8 (46)	8.9 (7.9)

Outcome	Gonadotrophin-releasing hormone (GnRH), N = 14	Placebo, N = 14
Mean (SD) *Higher values are better*		
Total sperm count (x10⁶) at 3 months Reported in study as total number of spermatozoa. Results converted from graph to numerical figures; SEs converted to SDs during data extraction. GnRH SE: 43.7; placebo SE: 8.5 Mean (SD) *Higher values are better*	133.4 (163.5)	36.1 (31.8)

Miscarriage rates

Outcome	Gonadotrophin-releasing hormone (GnRH), N = 14	Placebo, N = 14
Miscarriage rate at 3 months Reported in study as spontaneous abortion of pregnancy during the double-blind study period No of events	n = 0	n = 1

Critical appraisal with the Cochrane RoB 2.0

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(No information reported on randomisation process. Interventions were prepared by the manufacturer and the code was not opened until the end of study, so allocation sequence likely concealed. Differences at baseline do not suggest a problem with the randomisation process)*
Domain 2a: Risk of bias due to deviations from the intended	Risk of bias for deviations from the intended	Some concerns *(Double-blind trial using placebo. Some concerns regarding lack of information*

Section	Question	Answer
interventions (effect of assignment to intervention)	interventions (effect of assignment to intervention)	*on analysis used, though this is unlikely to have a substantial impact due to failure to analyse participants in the group they were assigned to, as the open trial phase after the initial blinded study phase meant all participants then received GnRH.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(11/39 participants (28%) dropped out of the study dropped out of the study due to difficulties in compliance. Further information about issues with compliance are not given; it is possible the compliance issues causing missingness in the outcome could therefore be influenced by its true value. It is unclear if missing outcome data are balanced between groups because number of participants initially randomised is not reported, however number of participants in each group at follow-up indicate dop-outs were balanced across groups)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Semen parameters were evaluated using World Health Organization criteria. Some concerns for the outcome pregnancy rates: it is not reported how pregnancy rates data were collected or how pregnancy was defined - it is unclear whether pregnancy rate is defined in the study as an ultrasound scan that has shown at least one fetal heart beat. The study was double-blind so unlikely that assessment of outcomes could have been influenced by knowledge of the intervention received)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(No prespecified protocol was available. No information about how the reported pregnancy rate was defined or measured)*
Overall bias and Directness	Risk of bias judgement	Some concerns *(Some concerns regarding missing outcome data and lack of information on analysis methods, selection of the reported result, and measurement of the outcome pregnancy rates)*
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	None

Farrag, 2015

Bibliographic Reference	Farrag, A.; Sagnella, F.; Pappalardo, S.; Costantini, A.; Lisi, F.; Carfagna, P.; Manna, C.; The use of r-hFSH in treatment of idiopathic male factor infertility before ICSI; European Review for Medical and Pharmacological Sciences; 2015; vol. 19 (no. 12); 2162-2167

Study details

Country/ies where study was carried out	Italy
Study type	Randomised controlled trial (RCT)
Study dates	May 2013 to April 2014
Inclusion criteria	Infertile couples due to idiopathic male factor infertility undergoing ICSI treatment meeting the following criteria: • History of infertility for ≥2 years • Sperm count >10 × 10^6/ml according to World Health Organization • Idiopathic male factor infertility with exclusion of common conditions, such as history of cryptorchidism, postmumps orchitis, testicular torsion or trauma, varicocele, seminal tract infections, antisperm antibodies, karyotypic abnormalities and y-chromosome microdeletions • Normal plasma levels of follicle-stimulating hormone (range, 2-12 IU/L), luteinizing hormone (range, 2-12 IU/L), and testosterone (range, 10-30 nmol/L)
Exclusion criteria	• Clear female factor fertility problems, such as ovulatory disorders, tubal factor, endometriosis, and endocrine abnormalities as evaluated by endocrine evaluation, pelvic ultrasound examination, and hysterosalpingography
Patient characteristics	N=82 male partners of couples with idiopathic male factor infertility undergoing ICSI treatment (N=92 randomised but data for n=10 participants who did not complete study not reported) Recombinant human follicle-stimulating hormone (rhFSH) group (n=36; n=46 initially randomised): • Mean age (SD): 36.9 (5.1) years • Severity of semen abnormalities: ○ Non-azoospermia: 36/36 (100%)

	• Fertility diagnosis:
	  ○ Idiopathic oligozoospermia: 36/36 (100%)
	• Hypogonadotropic hypogonadism: 0/36 (0%)*
	
	No treatment group (n=46):
	
	• Mean age (SD): 38.4 (5.2) years
	• Severity of semen abnormalities:
	  ○ Non-azoospermia: 46/46 (100%)
	• Fertility diagnosis:
	  ○ Idiopathic oligozoospermia: 46/46 (100%)
	• Hypogonadotropic hypogonadism: 0/46 (0%)*
	
	*People with known conditions causing infertility were excluded

Intervention(s)/control	rhFSH: • rhFSH, 150 IU delivered subcutaneously 3 times a week for 3 months No treatment: • No treatment given to male partners Couples in both groups received the following interventions: • Ovarian stimulation • ICSI • Luteal phase support
Duration of follow-up	3 months
Sources of funding	Not reported
Sample size	N=82 (N=92 randomised):

	• rhFSH group: n=36 (n=46 initially randomised) • No treatment group: n=46
Other information	The outcome clinical pregnancy rate was reported as a percentage and converted into numerical figures. It is unclear from the text, but results for the semen parameters outcomes appear to only be reported for the rhFSH group - table VI reports "seminal parameters evaluated before and after treatment in Group A" (rhFSH group). Although the table does have a column for "group B" (no treatment group), this appears to have been mislabeled, as the first column (labelled 'group A') exactly matches the rhFSH group's baseline semen parameters. Because two sets of data at follow-up are not reported, these outcomes have not been extracted

Study arms
Recombinant human follicle stimulating hormone (rhFSH) (N = 36)

No treatment (N = 46)

Outcomes
Pregnancy rates

Outcome	Recombinant human follicle stimulating hormone (rhFSH), N = 36	No treatment, N = 46
Assisted pregnancy rate at 3 months Reported in study as clinical pregnancy after ICSI, confirmed by fetal heart beat on ultrasound. Reported as percentages and converted to numerical figures No of events	n = 15 ; % = 42	n = 9 ; % = 20

Miscarriage rates

Outcome	Recombinant human follicle stimulating hormone (rhFSH), N = 36	No treatment, N = 46
Miscarriage rate at 3 months Reported interchangeably in study as early miscarriage rate and as abortion rate.	n = 1 ; % = 15.7	n = 4 ; % = 43.7

Outcome	Recombinant human follicle stimulating hormone (rhFSH), N = 36	No treatment, N = 46
Reported as percentages and converted to numerical figures, using number of pregnancies in each group as denominators No of events		

Critical appraisal with the Cochrane RoB 2.0

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(No information reported on randomisation process or allocation concealment, but baseline differences do not suggest a problem with the randomisation process)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High *(Information about blinding not reported but participants and personnel likely knew which group they were assigned to due to nature of interventions. Inappropriate analysis (per-protocol) used: 7/46 participants (15%) were excluded from the study post-randomisation because they decided to stop treatment and have ICSI)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High *(10/46 participants (22%) in the rhFSH group were lost to follow-up: 7 discontinued treatment to have ICSI and 3 were lost to follow-up. It is likely that missingness in the outcome depended on its true value because all participants who were lost to follow-up belonged to the treatment group)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Clinical pregnancy was confirmed by fetal heart beat on ultrasound. Some concerns for the outcome miscarriage because this outcome was not defined beyond being 'early' - it is unclear whether miscarriage is defined as loss of a baby before 24 weeks gestational age.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(No prespecified protocol available. Some concerns regarding reporting of pregnancy and miscarriage rates, as only percentages are reported. The percentages reported for miscarriage do not seem to match with participants in*

Section	Question	Answer
		each group, or with number of pregnancies as the denominator. Additionally, semen parameters outcomes could not be extracted because results for both groups do not seem to be reported (though it is not clear if this is a reporting error))
Overall bias and Directness	Risk of bias judgement	High *(High risk of bias due to deviations from the intended interventions and missing outcome data. Some concerns regarding selection of the reported result and lack of information on the randomisation process and on measurement of the outcome miscarriage rate)*
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	None

Foresta, 2005

Bibliographic Reference	Foresta, C.; Bettella, A.; Garolla, A.; Ambrosini, G.; Ferlin, A.; Treatment of male idiopathic infertility with recombinant human follicle-stimulating hormone: A prospective, controlled, randomized clinical study; Fertility and Sterility; 2005; vol. 84 (no. 3); 654-661

Study details

Country/ies where study was carried out	Italy
Study type	Randomised controlled trial (RCT)
Study dates	Not reported
Inclusion criteria	Men with idiopathic oligozoospermia meeting the following criteria: • A history of infertility for ≥2 years • Sperm count ≤10 X10^6/mL on ≥3 separate occasions, according to World Health Organization guidelines • Idiopathic infertility with exclusion of common conditions, such as history of cryptorchidism, postmumps orchitis, testicular torsion or trauma, varicocele, seminal tract infections, antisperm antibodies and Y chromosome microdeletions, karyotypic abnormalities, and CFTR gene mutations

	• Normal plasma levels of follicle-stimulating hormone (range, 1–7 IU/L), luteinizing hormone (range, 2– 6 IU/L), prolactin (range, 15–25 ng/mL), testosterone (range 3–9 ng/mL), and inhibin B (150 pg/mL)
Exclusion criteria	• Clear female factors, such as ovulatory disorders, tubal factor, and endocrine abnormalities as evaluated by endocrine evaluation, pelvic ultrasound examination, and hysterosalpingography

Patient characteristics	N=112 men with idiopathic oligozoospermia (N=128 randomised but data for n=16 participants who did not complete study not reported)
	
	Recombinant human follicle-stimulating hormone (rhFSH) group (n=62; n=65 initially randomised):
	
	• Mean age (SD): 34.2 (4.8) years
	• Severity of semen abnormalities:
	  ○ Non-azoospermia: 62/62 (100%)
	• Fertility diagnosis:
	  ○ Idiopathic oligozoospermia: 62/62 (100%)
	• Hypogonadotropic hypogonadism: 0/62 (0%)*
	
	No treatment group (n=50; n=63 initially randomised):
	
	• Mean age (SD): 34.0 (4.6) years
	• Severity of semen abnormalities:
	  ○ Non-azoospermia: 50/50 (100%)
	• Fertility diagnosis:
	  ○ Idiopathic oligozoospermia: 50/50 (100%)
	• Hypogonadotropic hypogonadism: 0/50 (0%)*
	
	n=40 fertile men were also included as controls but data from these participants were not extracte
	
	*People with known conditions causing infertility were excluded

Intervention(s)/control	rhFSH:

	• rhFSH, 100 IU administered through intramuscular injection on alternate days for 3 months No treatment: • No treatment received After the first study period where participants were randomised to the above treatments, all participants who had not had spontaneous pregnancy underwent ARTs. Only data from the first period are extracted
Duration of follow-up	3 months (immediately after treatment period) and 6 months (3 months after conclusion of treatment)
Sources of funding	Not reported
Sample size	N=112 (N=128 randomised): • rhFSH group: n=62 (n=65 initially randomised) • No treatment group: n=50 (n=63 initially randomised)
Other information	None

Study arms
Recombinant human follicle-stimulating hormone (rhFSH) (N = 62)

No treatment (N = 50)

Outcomes
Pregnancy rates

Outcome	Recombinant human follicle-stimulating hormone (rhFSH), N = 62	No treatment, N = 50
Spontaneous pregnancy rate at 3 months Reported a spontaneous pregnancies and confirmed by measurement of hCG plasma levels No of events	n = 0 ; % = 0	n = 0 ; % = 0

Outcome	Recombinant human follicle-stimulating hormone (rhFSH), N = 62	No treatment, N = 50
Spontaneous pregnancy rate at 6 months Reported a spontaneous pregnancies and confirmed by measurement of hCG plasma levels No of events	n = 6 ; % = 10	n = 2 ; % = 4

Semen parameters

Outcome	Recombinant human follicle-stimulating hormone (rhFSH), N = 62	No treatment, N = 50
Sperm concentration (x10^6/ml) at 3 months Reported interchangeably as sperm concentration and sperm count. Data from responders and non-responders in the rhFSH group reported separately in study and pooled during data extraction Mean (SD) *Higher values are better*	9.7 (8.8)	7.1 (3.5)
Sperm concentration (x10^6/ml) at 6 months Reported interchangeably as sperm concentration and sperm count. Data from responders and non-responders in the rhFSH group reported separately in study and pooled during data extraction Mean (SD) *Higher values are better*	12 (4.2)	8.1 (3.6)
Total sperm count (x10^6) at 3 months Reported in study as total number of sperm. Data from responders and non-responders in the rhFSH group reported separately in study and pooled during data extraction	30 (7.6)	17.3 (6.6)

Outcome	Recombinant human follicle-stimulating hormone (rhFSH), N = 62	No treatment, N = 50
Mean (SD) *Higher values are better*		
Total sperm count (x10^6) at 6 months Reported in study as total number of sperm. Data from responders and non-responders in the rhFSH group reported separately in study and pooled during data extraction Mean (SD) *Higher values are better*	25 (6.5)	17.4 (5.3)

Critical appraisal with Cochrane RoB 2.0

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Participants were randomised by a third-party in a 1:1 ratio with a random number generator. No information reported on allocation concealment. No significant difference between groups at baseline)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(Study reports participants were allocated to their groups in a blinded manner, but further information about blinding not reported. Participants and personnel likely knew which group they were assigned to due to nature of interventions. Inappropriate analysis (per-protocol) used: 1/63 participant (2%) in the rhFSH group was excluded from the study post-randomisation because they discontinued the intervention, but low number means it is unlikely this would have a substantial impact on the result)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High *(2/63 participants (3%) in the no treatment group were lost to follow-up and a further 7/63 participants (11%) in the no treatment group dropped out of the study at the participants' request. The imbalance in participants lost to follow-up indicates missingness in the outcome could depend on its true value)*

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(The personnel analysing semen parameters outcomes was blinded to treatment received by participants, though criteria used are not described. Pregnancies were confirmed by measurement of hCG plasma levels, but not by an ultrasound scan that has shown at least one fetal heart beat)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(No prespecified protocol was available. No information about criteria used to analyse semen parameters)*
Overall bias and Directness	Risk of bias judgement	High *(High risk of bias due to missing outcome data. Some concerns regarding deviations from the intended interventions, selection of the reported result, and lack of information on measurement of the semen parameters outcomes)*
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	None

Foresta, 2009

Bibliographic Reference	Foresta, C.; Selice, R.; Moretti, A.; Pati, M.A.; Carraro, M.; Engl, B.; Garolla, A.; Gonadotropin administration after gonadotropin-releasing-hormone agonist: a therapeutic option in severe testiculopathies; Fertility and Sterility; 2009; vol. 92 (no. 4); 1326-1332

Study details

Country/ies where study was carried out	Italy
Study type	Randomised controlled trial (RCT)
Study dates	Not reported
Inclusion criteria	Men with severe testiculopathy with:

	• Marked oligozoospermia (sperm count <3 x10⁶/ml) due to severe hypospermatogenesis without maturation disturbances (spermatogonial-spermatocyte and spermatidic stage arrest with strong reduction or absence of mature sperm) • High follicle-stimulating hormone plasma levels • A history of infertility for at least 2 years
Exclusion criteria	• Y-chromosome microdeletions • Karyotypic abnormalities • CFTR gene mutations

Patient characteristics	N=90 men with severe testiculopathy (N=87 completed the study):
	
	• Mean age (SD): 34.2 (4.5) years
	• Severity of semen abnormalities:
	  ○ Non-azoospermia: 90/90 (100%)
	• Fertility diagnosis:
	  ○ Cryptorchidism: 20/90 (22%)
	  ○ Varicocele: 18/90 (20%)
	  ○ Post-mumps orchitis: 9/90 (10%)
	  ○ Trauma: 6/90 (7%)
	  ○ Testicular torsion: 3/90 (3%)
	  ○ Idiopathic oligozoospermia*: 34/90 (38%)
	• Hypogonadotropic hypogonadism: Not reported
	
	Participant characteristics not reported separately for each group.
	
	n=32 fertile men were also included as controls but data from these participants are not extracted
	
	*Participants are reported as having idiopathic oligozoospermia, but all oligozoospermia was due to severe hypospermatogenesis

Intervention(s)/control	GnRH-a, FSH + hCG:

	• Gonadotrophin suppression through GnRH-a injection: leuprolide acetate, 3.75 mg delivered intra-muscularly every 30 days for 4 months • 30 days from the first leuprolide administration, recombinant human FSH, 150 IU on alternate days for 3 months • hCG, 2000 IU twice a week for 3 months No treatment: • No treatment received After the first study period where participants were randomised to the above treatments, all participants who had not had spontaneous pregnancy underwent ARTs. Only data from the first period are extracted
Duration of follow-up	1 month (after period of treatment with gonadotrophin succession only) and 4 months (after full treatment period)
Sources of funding	Not reported
Sample size	N=90 (N=87 completed the study): • GnRH-a, FSH + hCG group: n=57 (n=58 initially randomised) • No treatment group: n=30 (n=32 initially randomised):
Other information	None

Study arms
GnRH-a, FSH + hCG (N = 57)
Gonadotrophin releasing-hormone agonist (GnRH-a), follicle-stimulating hormone (FSH) + human chorionic gonadotrophin (hCG)

No treatment (N = 30)

Outcomes
Pregnancy rates

Outcome	GnRH-a, FSH + hCG, N = 57	No treatment, N = 30
Spontaneous pregnancy rate at 1 month Reported as spontaneous pregnancies and confirmed by confirmed by measurement of the woman's b-hCG plasma levels. Treatment group had received only GnRH-a at this follow-up period No of events	n = 0 ; % = 0	n = 0 ; % = 0
Spontaneous pregnancy rate at 4 months Reported as spontaneous pregnancies and confirmed by confirmed by measurement of the woman's b-hCG plasma levels No of events	n = 4 ; % = 7	n = 0 ; % = 0

Semen parameters

Outcome	GnRH-a, FSH + hCG, , N = 57	No treatment, , N = 30
Sperm concentration (x10^6/ml) at 1 month Reported interchangeably as sperm concentration and spermatozoa per ml. Treatment group had received only GnRH-a at this follow-up period Mean (SD) *Higher values are better*	3.2 (1.6)	2 (0.9)
Sperm concentration (x10^6/ml) at 4 months Reported interchangeably as sperm concentration and spermatozoa per ml Mean (SD) *Higher values are better*	6.6 (2.3)	2.3 (1.1)
Total sperm count (x10^6) at 1 month Reported in study as total sperm count (x10^6). Treatment group had received only GnRH-a at this follow-up period	7.8 (2.4)	4.7 (1.9)

Outcome	GnRH-a, FSH + hCG, , N = 57	No treatment, , N = 30
Mean (SD) *Higher values are better*		
Total sperm count (x10⁶) at 4 months Reported in study as total sperm count (x10⁶) Mean (SD) *Higher values are better*	12.3 (3.5)	5.9 (1.5)
Sperm motility rate (%) at 1 month Reported in study as sperm motility (A+B, %). Treatment group had received only GnRH-a at this follow-up period Mean (SD) *Higher values are better*	18.3 (8.6)	16.1 (7.1)
Sperm motility rate (%) at 4 months Reported in study as sperm motility (A+B, %) Mean (SD) *Higher values are better*	28.9 (11.7)	20.2 (9.1)

Critical appraisal with the Cochrane RoB 2.0

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Participants were randomised by a third-party in a 2:1 ratio with a random number generator. No information reported on allocation concealment. Treatment group was larger than no treatment group due to deliberate randomisation in 2:1 ratio. No other significant difference between groups at baseline)*

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(Study reports participants were allocated to their groups in a blinded manner, but further information about blinding not reported. Participants and personnel likely knew which group they were assigned to due to nature of interventions, but no information reported on deviations from interventions)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Data available for nearly all participants)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(The personnel analysing semen parameters outcomes was blinded to treatment received by participants, though criteria used are not described. Pregnancies were confirmed by measurement of hCG plasma levels but not by an ultrasound scan that has shown at least one fetal heart beat)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(No prespecified protocol was available. No information about criteria used to analyse semen parameters)*
Overall bias and Directness	Risk of bias judgement	Some concerns *(Some concerns regarding deviations from the intended interventions, selection of the reported result, and lack of information on measurement of the semen parameters outcomes)*
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	None

Gregoriou, 1993

Bibliographic Reference	Gregoriou, O; Papadias, C; Gargaropoulos, A; Konidaris, S; Kontogeorgi, Z; Kalampokas, E; Treatment of idiopathic infertility with testosterone undecanoate. A double blind study.; Clinical and experimental obstetrics & gynecology; 1993; vol. 20 (no. 1); 9-12

Study details

Country/ies where study was carried out	Greece
Study type	Randomised controlled trial (RCT)
Study dates	Not reported
Inclusion criteria	50 couples admitted to an obstetrics and gynaecology department for primary or secondary subfertility, who: • Had no demonstrable cause of infertility in the female partner (assessed using routine gynaecological investigation, evaluation of follicular and luteal function, and evaluation of tubal patency using hysterosalpingography and diagnostic laparoscopy) • Had idiopathic infertility in the male partner (iatrogenic, systemic, congenital, infectious, autoimmune, varicocele or endocrinologic causes had been excluded after investigation)
Exclusion criteria	Not reported

Patient characteristics	N=50 couples with infertility:
	
	• Mean age (SD): 28.4 (1.1) years
	• Severity of semen abnormalities:
	  ○ Non-azoospermia: 50/50 (100%)
	• Fertility diagnosis:
	  ○ Idiopathic oligoasthenospermia: 50/50 (100%)
	• Hypogonadotropic hypogonadism: 0/50 (0%)*
	
	Participant characteristics were not reported separately for each group
	
	* People with iatrogenic, systemic, congenital, infectious, autoimmune, varicocele or endocrinologic causes of infertility were excluded

Intervention(s)/control	Testosterone undecanoate: • Testosterone undecanoate (Restandol), 40mg capsules 3 times a day (for a total of 120mg per day) for 3 months

	Placebo: • Identically packed placebo capsules 3 times a day for 3 months
Duration of follow-up	3 months
Sources of funding	Not reported
Sample size	N=50: • Testosterone undecanoate group: n=25 • Placebo group: n=25
Other information	Data also reported for luteinizing hormone (LH) and follicle-stimulating hormone (FSH), however these data not extracted as unlikely to be useful for decision-making

Study arms
Testosterone undecanoate (N = 25)

Placebo (N = 25)

Outcomes
Pregnancy rates

Outcome	Testosterone undecanoate, N = 25	Placebo, N = 25
Pregnancy rates at 3 months Study does not report how these data were collected or how pregnancy was defined No of events	n = 4	n = 0

Hormone parameters

Outcome	Testosterone undecanoate, N = 25	Placebo, N = 25
Dihydrotestosterone (ng/ml) at 3 months	145.48 (17.9)	66.12 (12.1)

Outcome	Testosterone undecanoate, N = 25	Placebo, N = 25
Mean (SD) *Higher values are better*		
Total testosterone (ng/ml) at 3 months Mean (SD) *Higher values are better*	7.95 (2.86)	5.95 (4.53)
Oestradiol (pg/ml) at 3 months Mean (SD) *Lower values are better*	28.15 (9.55)	29.1 (7.15)

Semen parameters

Outcome	Testosterone undecanoate, N = 25	Placebo, N = 25
Sperm concentration (x10^6/ml) at 3 months Reported as sperm density (x10^6/ml) Mean (SD) *Higher values are better*	17.95 (8.81)	15.45 (10.15)
Sperm motility rate (%) at 3 months Reported as % of progressive sperm but measurement of x10^6/ml also given in table Mean (SD) *Higher values are better*	20.35 (10.56)	16.84 (10.95)

Miscarriage rates

Outcome	Testosterone undecanoate, N = 25	Placebo, N = 25
Miscarriage rates at 3 months Reported in study as number of pregnancies that were aborted. Study does not report how these data were collected or how abortion was defined No of events	n = 1	n = 0

Critical appraisal with the Cochrane RoB 2.0

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(No information reported on randomisation process or allocation concealment. Reported participant characteristics at baseline do not indicate a problem with the randomisation process, though some important characteristics (such as age of participants) are not reported separately for each group)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Double blind trial using placebo. Minimal information reported about analysis but participants appear to have been analysed according to intervention assigned)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Data available for all included participants)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(It is not reported how data for the outcome pregnancy or miscarriage rates were collected or how pregnancy or abortion was defined - it is unclear whether pregnancy rate is defined in the study as an ultrasound scan that has shown at least one fetal heart beat, and miscarriage rate is reported in the study as number of aborted pregnancies so it is unclear whether this includes loss of a baby before 24 weeks gestational age. Semen parameters were measured using spermiograms, but criteria used to assess results were not reported. However, all participants and personnel involved in the trial were blinded. Low risk of bias for hormone parameters)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(No prespecified protocol was available. No information about how pregnancy*

Section	Question	Answer
		or abortion was defined or measured, or the criteria used to assess sperm parameters. No evidence of selective reporting)
Overall bias and Directness	Risk of bias judgement	Some concerns *(Some concerns relating to lack of information on randomisation procedure, allocation concealment, measurement of the outcomes pregnancy rates and miscarriage rates, and selection of the reported result)*
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	None

Haje, 2015

Bibliographic Reference	Haje, M.; Naoom, K.; Combined tamoxifen and L-carnitine therapies for the treatment of idiopathic male infertility attending intracytoplasmic sperm injection: A randomized controlled trial; International Journal of Infertility and Fetal Medicine; 2015; vol. 6 (no. 1); 20-24

Study details

Country/ies where study was carried out	Iraq
Study type	Randomised controlled trial (RCT)
Study dates	Not reported
Inclusion criteria	Infertile men with idiopathic oligoasthenozoospermia
Exclusion criteria	• Cases with known etiology of leukocytospermia • Altered testicular volume of ≥20ml as depicted by ultrasonography • Varicocele as detected by clinical examination and ultrasonography • Abnormal follicle-stimulating hormone levels • Couples with combined male and female factor infertility
Patient characteristics	N=128 men with idiopathic oligoasthenozoospermia:

	• Mean age (SD): 37.54 (2.46) years
	• Severity of semen abnormalities:
	  ○ Non-azoospermia: 128/128 (100%)
	• Fertility diagnosis:
	  ○ Idiopathic oligoasthenozoospermia: 128/128 (100%)
	• Hypogonadotropic hypogonadism: 0/128 (0%)*
	
	Participant characteristics not reported separately for each group
	
	Two additional group received either L-carnitine only (n=20) or L-carnitine and tamoxifen (n=34), but data were not extracted from these group
	
	* Participants did not have detectable cause of infertility

Intervention(s)/control	Tamoxifen: • Tamoxifen, 20 mg/day for 3 to 6 months Placebo • No details reported Participants in all groups received ICSI following treatment conclusion.
Duration of follow-up	3-6 months
Sources of funding	Not industry funded
Sample size	N=128: • Tamoxifen group: n = 45 • Placebo group: n = 29
Other information	Data reported narratively (p21) for the outcome pregnancy rates do not match the data reported in figure 1 (p23). It is unclear why this difference exists. Data are extracted from the text rather than the figure

Study arms
Tamoxifen only (N = 45)

Placebo (N = 29)

Outcomes
Pregnancy rates

Outcome	Tamoxifen only, N = 45	Placebo, N = 29
Assisted pregnancy rate at 3-6 months Reported as incidence of pregnancy after ICSI. Study does not report how these data were collected or how pregnancy was defined. Data reported as percentages and converted into numerical values No of events	n = 22 ; % = 48.9	n = 6 ; % = 20

Semen parameters

Outcome	Tamoxifen only, N = 45	Placebo, N = 29
Sperm concentration (x10^6/ml) at 3-6 months Reported as sperm count (x10^6/ml) Mean (SD) *Higher values are better*	10.8 (1.8)	8.2 (2.7)
Sperm motility rate (%) at 3-6 months Mean (SD) *Higher values are better*	22 (3.6)	14.9 (5)

Critical appraisal with the Cochrane RoB 2.0

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(No information reported about randomisation process or allocation concealment. Participant baseline characteristics not reported separately for each group)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(Information about blinding of participants or personnel not reported, but use of placebo means participants in the groups of interest were likely unaware which group they were assigned to. No information reported on analysis used)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(No missing outcome data)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(Semen parameters analysed using World Health Organisation criteria, but information on blinding of outcome assessors not reported. Some concerns for the outcome pregnancy rates because it is not reported how these data were collected or how pregnancy was defined - it is unclear whether pregnancy rate is defined in the study as an ultrasound scan that has shown at least one fetal heart beat. It is unlikely that assessment of the outcome pregnancy rates could have been influenced by knowledge of the intervention received)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(No prespecified protocol was available. No information about how pregnancy was defined or measured)*
Overall bias and Directness	Risk of bias judgement	Some concerns *(Some concerns regarding lack of information on randomisation process, deviations from the intended interventions, measurement of the outcome pregnancy rates, and selection of the reported result)*
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	None

Kamischke, 1998

Bibliographic Reference	Kamischke, A.; Behre, H.M.; Bergmann, M.; Simoni, M.; Schafer, T.; Nieschlag, E.; Recombinant human follicle stimulating hormone for treatment of male idiopathic infertility: A randomized, double-blind, placebo-controlled, clinical trial; Human Reproduction; 1998; vol. 13 (no. 3); 596-603

Study details

Country/ies where study was carried out	Germany
Study type	Randomised controlled trial (RCT)
Study dates	March 1994 to November 1996
Inclusion criteria	People >18 years with idiopathic male infertility and: • Infertility for ≥1 year • No acute or history of varicocele, undescended testis or testicular cancer, drug or alcohol abuse or any major systemic disease • No azoospermia and ≥2 semen parameters (motility, concentration, morphology) below WHO criteria • No signs of genital tract infection or immunological infertility • Basal follicle-stimulating hormone concentrations of <12 IU/l and normal luteinizing hormone, prolactin, testosterone, and oestradiol level • Female partners with normal ovulatory cycles
Exclusion criteria	• Intercurrent illnesses • Varicocele • Undescended testis • Abnormal hormone values • Female causes of infertility, including untreatable ovarian dysfunction, known endometriosis or tubal blockage
Patient characteristics	N=65 couples with idiopathic male infertility (N=67 randomised but data for n=2 participants who did not complete study not reported) • Mean age (SD): 32.89 (0.56) years • Severity of semen abnormalities: ○ Non-azoospermia: 66/66 (100%)

	• Fertility diagnosis: ○ Idiopathic abnormal semen parameters: 66/66 (100%) • Hypogonadotropic hypogonadism: 0/66 (0%)* Participant characteristics not reported separately for each group * People with known reasons for their infertility were not included in the study
Intervention(s)/control	rhFSH: • rhFSH, 150 IU with 30 mg saccharose, delivered by subcutaneous injection into abdominal wall daily for 12 weeks • Patients injected themselves after initial instruction by the examiners Placebo: • Placebo containing saccharose alone, delivered by subcutaneous injection into abdominal wall daily for 12 weeks • Patients injected themselves after initial instruction by the examiners
Duration of follow-up	3 months (end of treatment phase) and 6 months (3 months after treatment conclusion) for semen and hormone parameters outcomes. 9 months (6 months after treatment phase) and an undefined period "following the 6 month observation period after treatment" for pregnancy rates outcomes
Sources of funding	Industry funded
Sample size	N=65 (N=67 randomised): • rhFSH group: n=34 • Placebo group: n=31 (n=33 initially randomised)
Other information	Means and SEs were reported for semen parameters outcomes and converted to SDs during data extraction. Pregnancy rate data at 9 months were not included in data extraction due to later data within the short-term period (>3 months to ≤12 months) being reported (>9 months). The following semen parameters outcomes were reported at 3 and

	6 months but not extracted as overall normal sperm morphology was a preferred outcome for decision making: normal sperm head; normal nucleus; normal acrosome; normal axonem Data also reported for luteinizing hormone (LH), follicle-stimulating hormone (FSH) and inhibin B, however these data not extracted as unlikely to be useful for decision-making

Study arms
Recombinant human follicle stimulating hormone (rhFSH) (N = 34)

Placebo (N = 31)

Outcomes
Pregnancy rates

Outcome	Recombinant human follicle stimulating hormone (rhFSH), N = 31	Placebo, N = 30
Pregnancy rate at >9 months Reported as number of induced pregnancies (spontaneous or assisted) within or 6 months after the treatment phase, or following the 6 month observation period after treatment, confirmed by ultrasound and human chorionic gonadotrophin concentration increase. Exact follow-up period not reported No of events	n = 8	n = 10
Spontaneous pregnancy rate at >9 months Reported as number of spontaneous induced pregnancies following the 6 month observation period after treatment, confirmed by ultrasound and human chorionic gonadotrophin concentration increase. Exact follow-up period not reported No of events	n = 3	n = 0

Hormone parameters

Outcome	Recombinant human follicle stimulating hormone (rhFSH), N = 34	Placebo, N = 31
Testosterone (nmol/l) at 3 months SEs converted to SDs during data extraction. rhFSH SE: 1; placebo SE: 0.7 Mean (SD) *Higher values are better*	19.7 (5.8)	16.3 (3.9)
Testosterone (nmol/l) at 6 months SEs converted to SDs during data extraction. rhFSH SE: 0.8; placebo SE: 0.7 Mean (SD) *Higher values are better*	17.5 (4.7)	14.9 (3.9)
Oestradiol (pmol/l) at 3 months SEs converted to SDs during data extraction. rhFSH SE: 2.7; placebo SE: 2.4 Mean (SD) *Lower values are better*	59.6 (15.7)	55 (13.4)
Oestradiol (pmol/l) at 6 months SEs converted to SDs during data extraction. rhFSH SE: 2.2; placebo SE: 2.3 Mean (SD) *Lower values are better*	57.9 (12.8)	51.6 (12.8)

Semen parameters

Outcome	Recombinant human follicle stimulating hormone (rhFSH), N = 34	Placebo, N = 31
Sperm motility rate (%) at 3 months Reported as sperm motility (A+B, %). SEs converted to SDs during data extraction. rhFSH SE: 2.8; placebo SE: 3 Mean (SD) *Higher values are better*	30.5 (16.3)	35.4 (16.7)
Sperm motility rate (%) at 6 months Reported as sperm motility (A+B, %). SEs converted to SDs during data extraction. rhFSH SE: 2.9; placebo SE: 2.9 Mean (SD) *Higher values are better*	33 (16.9)	32.1 (16.1)
Sperm concentration (x10^6/ml) at 3 months SEs converted to SDs during data extraction. rhFSH SE: 2.1; placebo SE: 2.1 Mean (SD) *Higher values are better*	9.9 (12.2)	11.2 (11.7)
Sperm concentration (x10^6/ml) at 6 months SEs converted to SDs during data extraction. rhFSH SE: 2.1; placebo SE: 1.9 Mean (SD) *Higher values are better*	11.1 (12.2)	10.3 (10.6)

Critical appraisal with the Cochrane RoB 2.0

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Randomisation is described as "third party true randomization" but further information is not provided. Personnel were blinded to treatment allocation using a code. No significant differences between participants at baseline)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Double-blind study using placebo)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Only 1/65 participants (2%) had missing outcome data because they dropped out for personal reasons. 1 participant was excluded because a semen analysis test revealed immunological fertility which had previously been missed. Pregnancy outcomes data were not available for 4/65 participants (6%) because of later endoscopically confirmed tubal blockage (n=3) or pregnancy prior to treatment start (n=1). Some concerns for the following semen parameters outcomes because only 18/34 participants (53%) in the rhFSH group and 13/31 participants (42%) in the placebo group had outcome data: normal sperm head; normal nucleus; normal acrosome; normal axonem; sperm quality index. It is unlikely missingness in the outcome depended on its true value because numbers are balanced between groups. Low number of participants with results is due to the fact that results were only available for participants who had electron microscopy data which was possible to analyse at all three time points)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Semen parameters outcomes were assessed using semen light microscopy (analysed according to WHO guidelines) or electron microscopy (analysed according to Bartoov). Hormone assays were assessed according to WHO guidelines. Pregnancies were confirmed by ultrasound and human chorionic gonadotrophin concentration increase. Outcome assessors were blind to treatment received)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(No prespecified protocol was available. Authors note that there were data for ejaculate volume, seminal markers for the epididymis, prostate and seminal*

Section	Question	Answer
		vesicles remained unchanged throughout all examinations, but these were not reported because they remained unchanged throughout all examinations)
Overall bias and Directness	Risk of bias judgement	Low *(Very minor concerns relating to selection of the reported result and missing outcome data for the semen parameters outcome sperm quality index)*
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	Some concerns for the semen parameters outcome sperm quality index

Knuth, 1987

Bibliographic Reference	Knuth, U.A.; Honigl, W.; Bals-Pratsch, M.; Schleicher, G.; Nieschlag, E.; Treatment of severe oligospermia with human chorionic gonadotropin/human menopausal gonadotropin: A placebo-controlled, double blind trial; Journal of Clinical Endocrinology and Metabolism; 1987; vol. 65 (no. 6); 1081-1087

Study details

Country/ies where study was carried out	Germany
Study type	Randomised controlled trial (RCT)
Study dates	Not reported
Inclusion criteria	Infertile men meeting the following criteria: • Spouses had no recognisable causes of infertility and normal ovulatory function • Normal tubal patency • Sperm counts between 0.1-10 x10^6/ml on ≥2 previous occasions • Normal serum luteinizing hormone, follicle-stimulating hormone, and testosterone values • No other treatment received for at least 6 months
Exclusion criteria	Men with known causes of infertility

Patient characteristics	N=37 infertile men (N=39 randomised but data for n=2 participants who did not complete study not reported)
	
	Human chorionic gonadotrophin (HCG) + human menopausal gonadotrophin (HMG) group (n=17; number initially randomised not reported):
	
	• Mean age (SD): 31.1 (3.6) years
	• Severity of semen abnormalities: Not reported
	• Fertility diagnosis:
	  ○ Idiopathic oligozoospermia: 17/17 (100%)
	• Hypogonadotropic hypogonadism: 0/17 (0%)*
	
	Placebo group (n=20; number initially randomised not reported):
	
	• Mean age (SD): 33.2 (6.5) years
	• Severity of semen abnormalities: Not reported
	• Fertility diagnosis:
	  ○ Idiopathic oligozoospermia: 20/20 (100%)
	• Hypogonadotropic hypogonadism: 0/20 (0%)*
	
	* People with known causes of infertility were excluded

Intervention(s)/control	HCG + HMG: • HCG, 2500 IU delivered by intramuscular injection on Mondays and Fridays for 13 weeks • HMG, 150 IU delivered by intramuscular injection on Mondays, Wednesdays, and Fridays for 13 weeks Placebo: • Sodium chloride was injected on the same days as the HCG and HMG group for 13 weeks

	In both groups, injections were delivered by each participant's GP
Duration of follow-up	3, 4, 5, and 6 months for semen and hormone parameters outcomes; 9 months for pregnancy outcomes (6 months after cessation of treatment)
Sources of funding	Not reported
Sample size	N=37 (N=39 randomised): • HCG + HMG group: n=17 (number initially randomised not reported) • Placebo group: n=20 (number initially randomised not reported)
Other information	Results for the hormone parameter outcome oestradiol levels are only reported at 3 months (at treatment cessation); authors only note they are similar at all times after the end of treatment. Data for oestradiol levels at 3 months could not be extracted as it is not clear which dataset belongs to each group. Semen and hormone parameters data at 4 and 5 months were not included in data extraction due to later data within the medium-term period (>3 months to ≤12 months) being reported (at 6 months) Data also reported for immunoreactive luteinizing hormone (LH) and immunoreactive follicle-stimulating hormone (FSH), however these data not extracted as unlikely to be useful for decision-making. Results for semen and hormone parameters outcomes were reported in graphs and converted using a web plot digitizer as numerical figures not reported in text. Means and SEs were reported for these outcomes and converted to SDs during data extraction

Study arms
Human chorionic gonadotrophin (HCG) + human menopausal gonadotrophin (HMG) (N = 17)

Placebo (N = 20)

Outcomes
Pregnancy rates

Outcome	Human chorionic gonadotrophin (HCG) + human menopausal gonadotrophin (HMG), N = 17	Placebo, N = 20
Pregnancy rate at 9 months Study does not report how these data were collected or how pregnancy was defined No of events	n = 2	n = 0

Hormone parameters

Outcome	Human chorionic gonadotrophin (HCG) + human menopausal gonadotrophin (HMG), N = 17	Placebo, N = 20
Testosterone (nmol/l) at 3 months Results converted from graph to numerical figures; SEs converted to SDs during data extraction. HCG + HMG SE: 1.7; placebo SE: 1.3 Mean (SD) *Higher values are better*	9.8 (7)	13.6 (5.8)
Testosterone (nmol/l) at 6 months Results converted from graph to numerical figures; SEs converted to SDs during data extraction. HCG + HMG SE: 1.3; placebo SE: 1.3 Mean (SD) *Higher values are better*	13.5 (5.4)	14.7 (5.8)

Semen parameters

Outcome	Human chorionic gonadotrophin (HCG) + human menopausal gonadotrophin (HMG), N = 17	Placebo, N = 20
Sperm concentration (x10^6/ml) at 3 months Results converted from graph to numerical figures; SEs converted to SDs during data extraction. HCG + HMG SE: 1.1; placebo SE: 1.3	3.8 (4.5)	4.8 (5.8)

Outcome	Human chorionic gonadotrophin (HCG) + human menopausal gonadotrophin (HMG), N = 17	Placebo, N = 20
Mean (SD) *Higher values are better*		
Sperm concentration (x10^6/ml) at 6 months Results converted from graph to numerical figures; SEs converted to SDs during data extraction. HCG + HMG SE: 1.1; placebo SE: 1.6 Mean (SD) *Higher values are better*	3.7 (4.5)	5 (7.2)
Sperm motility rate (%) at 3 months Results converted from graph to numerical figures; SEs converted to SDs during data extraction. HCG + HMG SE: 6.4; placebo SE: 3.8 Mean (SD) *Higher values are better*	34.8 (26.4)	36.9 (17)
Sperm motility rate (%) at 6 months Results converted from graph to numerical figures; SEs converted to SDs during data extraction. HCG + HMG SE: 6.1; placebo SE: 4 Standardised Mean (SD) *Higher values are better*	33.9 (25.2)	27.5 (17.9)

Critical appraisal with the Cochrane RoB 2.0

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(No information reported on randomisation process or allocation sequence, but differences at baseline do not suggest a problem with the randomisation process)*

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Double-blind study using placebo. 2/39 participants (5%) were excluded post-randomisation due to a febrile illness, to avoid biasing the result)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Data available for nearly all participants)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Semen parameters outcomes assessed using WHO criteria; hormone parameters assessed using radioimmunoassay. Some concerns for the outcome pregnancy rates: it is not reported how pregnancy rates data were collected or how pregnancy was defined - it is unclear whether pregnancy rate is defined in the study as an ultrasound scan that has shown at least one fetal heart beat. The study was double-blind so unlikely that assessment of outcomes could have been influenced by knowledge of the intervention received)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(No prespecified protocol was available. No information about how the reported pregnancy rate was defined or measured)*
Overall bias and Directness	Risk of bias judgement	Some concerns *(Some concerns regarding lack of information on randomisation process, measurement of the outcome pregnancy rates, and selection of the reported result)*
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	None

Krause, 1992

Bibliographic Reference	Krause, W.; Holland-Moritz, H.; Schramm, P.; Treatment of idiopathic oligozoospermia with tamoxifen - A randomized controlled study; International Journal of Andrology; 1992; vol. 15 (no. 1); 14-18

Study details

Country/ies where study was carried out	Germany
Study type	Randomised controlled trial (RCT)
Study dates	Not reported
Inclusion criteria	Men with idiopathic oligozoospermia, defined as sperm count between 2 and 20 x10^6ml, sperm motility rate between 20% and 50%, and sperm morphology of between 50% and 80% abnormal sperm
Exclusion criteria	Varicocele; history of maldescended testicles; history of genital inflammation; severe general diseases

Patient characteristics	N=76 men with idiopathic oligozoospermia
	
	Tamoxifen group (n=39):
	
	• Mean age (SD): 31 years (not reported)
	• Severity of semen abnormalities:
	  ○ Non-azoospermia: 39/39 (100%)
	• Fertility diagnosis:
	  ○ Idiopathic oligozoospermia: 39/39 (100%)
	• Hypogonadotropic hypogonadism: 0/39 (0%)*
	
	Placebo group (n=37):
	
	• Mean age (SD): 28.5 years (not reported)
	• Severity of semen abnormalities:
	  ○ Non-azoospermia: 37/37 (100%)
	• Fertility diagnosis:
	  ○ Idiopathic oligozoospermia: 37/37 (100%)
	• Hypogonadotropic hypogonadism: 0/37 (0%)*
	
	* Participants had unknown causes of infertility

Intervention(s)/control	Tamoxifen:

	• Tamoxifen 30mg/day for 3 months Placebo: • Placebo for 3 months, no further details reported
Duration of follow-up	3 months (end of treatment) and at least 3 months after the end of treatment
Sources of funding	Not reported
Sample size	N=76 (N=35 completed the assessment): • Tamoxifen group: n=39 (n=17 completed the assessment) • Placebo group: n=37 (n=18 completed the assessment)
Other information	Data also reported for luteinizing hormone (LH) and follicle-stimulating hormone (FSH), however, these data not extracted as unlikely to be useful for decision-making

Study arms
Tamoxifen (N = 39)

Placebo (N = 37)

Outcomes
Pregnancy rates

Outcome	Tamoxifen, N = 39	Placebo, N = 37
Spontaneous pregnancy rate at 7 months Reported as cumulative number of spontaneous pregnancies after treatment (pregnancies occurred 1-7 months after the end of treatment). Study does not report how these data were collected or how pregnancy was defined. ITT analysis No of events	n = 5	n = 3

Hormone parameters

Outcome	Tamoxifen, N = 39	Placebo, N = 37
Testosterone (ng/ml) at 3 months Reported as mean serum testosterone level Mean (SD) *Higher values are better*	7.9 (3.6)	5.6 (2)

Hormone parameters (cont.)

Outcome	Tamoxifen, N = 17	Placebo, N = 18
Testosterone at 6 months Reported as mean serum testosterone level (ng/ml) Mean (SD) *Higher values are better*	7.3 (3.7)	7.4 (2.2)

Semen parameters

Outcome	Tamoxifen, N = 39	Placebo, N = 37
Sperm concentration (x10^6/ml) at 3 months Reported as sperm count (x10^6/ml) Mean (SD) *Higher values are better*	11.4 (13.7)	9.3 (8.8)
Sperm motility rate (%) at 3 months Mean (SD) *Higher values are better*	38.8 (21.9)	35 (21)

Semen parameters (cont.)

Outcome	Tamoxifen, , N = 17	Placebo, , N = 18
Sperm concentration (x10⁶/ml) at 6 months Reported as sperm count (x10⁶/ml) Mean (SD) *Higher values are better*	14.1 (14.4)	10.9 (15.7)
Sperm motility rate (%) at 6 months Mean (SD) *Higher values are better*	33.8 (21.1)	40 (25.4)

Critical appraisal with the Cochrane RoB 2.0

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(Paper reports that participants were assigned to conditions 'following a previously randomized design'. However, no information is provided about sequence generation or allocation concealment. Visual comparison of baseline values between arms suggests broadly similar groups, but statistical comparison between participants assigned to tamoxifen or placebo at baseline not reported)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(Trial included placebo so likely that participants were not aware of the assigned intervention during the trial. However, the blinding of intervention administrators (and of allocation concealment) is unclear.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(ITT analysis available for endpoint (but not post-intervention follow-up) assessment)*

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Semen parameters were evaluated using World Health Organization criteria. Some concerns for the pregnancy rate outcome (because it is not reported how data collected or how pregnancy was defined). Blinding of outcome assessors not reported. However, it was judged unlikely that the measurement was inappropriate or would differ between groups, or that the assessment of outcome was influenced by knowledge of the intervention received)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(No prespecified protocol was available. No information about how pregnancy was defined or measured)*
Overall bias and Directness	Risk of bias judgement	Some concerns *(Some concerns about bias arising from the randomisation process, due to deviations from the intended interventions, and selection of the reported result)*
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	Some concerns about the measurement of the outcome for pregnancy rate as it is not clear how data were collected or how pregnancy was defined

Maier, 1988

Bibliographic Reference	Maier, U.; Hienert, G.; Tamoxifen and testolactone in therapy of oligozoospermia: Results of a randomized study; European Urology; 1988; vol. 14 (no. 6); 447-449

Study details

Country/ies where study was carried out	Austria
Study type	Randomised controlled trial (RCT)
Study dates	Not reported
Inclusion criteria	Men in infertile partnerships with: • Mild oligoasthenozoospermia (classified according to Eliasson) • Sperm density 10-19 x10^6/ml

	• 2-hour sperm motility between 20 and 49%
Exclusion criteria	• Varicocele • Chronic adnexal infection • Hypogonadism

Patient characteristics	N=40 men with mild oligoasthenozoospermia:
	
	• Mean age (SD): Not reported
	• Severity of semen abnormalities:
	  ○ Non-azoospermia: 40/40 (100%)
	• Fertility diagnosis:
	  ○ Oligoasthenozoospermia (cause not reported): 40/40 (100%)
	• Hypogonadotropic hypogonadism: 0/40 (0%)*
	
	Participant characteristics not reported separately for each grou
	
	* People with hypogonadism were excluded

Intervention(s)/control	Tamoxifen: • Tamoxifen, 10 mg 3 times a day for 3 months Tamoxifen + testolactone: • Tamoxifen, 10mg 3 times a day for 3 months • Testolactone, 50mg 3 times a day for 3 months
Duration of follow-up	3 months. Semen analysis was also carried out at 6 weeks but these data do not appear to be reported
Sources of funding	Not reported
Sample size	N=40: • Tamoxifen group: n=20

	• Tamoxifen + testolactone group: n=20
Other information	Data also reported for luteinizing hormone (LH) and follicle-stimulating hormone (FSH), however these data not extracted as unlikely to be useful for decision-making Data for the following semen and hormone parameters outcomes could not be extracted because of insufficient presentation of results (only changes in levels from baseline are reported and no measure of deviation or additional statistics reported): sperm density, sperm motility, sperm morphology, testosterone

Study arms
Tamoxifen (N = 20)

Tamoxifen + testolactone (N = 20)

Outcomes
Pregnancy rates

Outcome	Tamoxifen, N = 20	Tamoxifen + testolactone, N = 20
Pregnancy rate at 3 months Reported as number of induced pregnancies/ gravidities. Study does not report how these data were collected or how pregnancy was defined No of events	n = 3	n = 3

Hormone parameters

Outcome	Tamoxifen, N = 20	Tamoxifen + testolactone, N = 20
Oestradiol levels at 3 months Unit of measurement not reported Mean (SD) *Lower values are better*	49.8 (14.2)	40.2 (6.2)

Critical appraisal with the Cochrane RoB 2.0

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(No information reported on randomisation process, allocation concealment, or baseline participant characteristics)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High *(No information about blinding, deviations from the intended interventions, or analysis used. Participants likely knew which group they were assigned to due to the nature of interventions (2 drugs vs 1))*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High *(No information reported on loss to follow-up or missing outcome data)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(Hormone parameters assessed using radioimmunoassay, but no information reported on blinding of outcome assessors. It is not reported how pregnancy rates data were collected or how pregnancy was defined - it is unclear whether pregnancy rate is defined in the study as an ultrasound scan that has shown at least one fetal heart beat. It is unlikely that assessment of the outcome pregnancy rates could have been influenced by knowledge of the intervention received)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	High *(No prespecified protocol available. Multiple semen and hormone parameters outcomes could not be extracted because of insufficient presentation of results (only changes in levels from baseline are reported and no measure of deviation or additional statistics reported): sperm density and testosterone. Additionally, for the following outcomes, no data were reported, only that there was no significant change from baseline: sperm motility, sperm morphology. Results for the outcome oestradiol levels are reported as means and SDs at follow-up, but these kinds of data are not reported for any other semen or hormone parameters outcomes. It is also reported that spermiograms were assessed at 6 and 12 weeks follow-up, but only one set of results are presented)*
Overall bias and Directness	Risk of bias judgement	High *(High risk of bias due to selection of the reported result and lack of information on the randomisation process, deviations from the intended interventions, missing outcome data, or measurement of the outcome)*

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	None

Matorras, 1997

Bibliographic Reference	Matorras, R.; Perez, C.; Corcostegui, B.; Pijoan, J.I.; Ramon, O.; Delgado, P.; Rodriguez-Escudero, F.J.; Treatment of the male with follicle-stimulating hormone in intrauterine insemination with husband's spermatozoa: A randomized study; Human Reproduction; 1997; vol. 12 (no. 1); 24-28

Study details

Country/ies where study was carried out	Spain
Study type	Randomised controlled trial (RCT)
Study dates	January 1991 to December 1994
Inclusion criteria	Couples undergoing intrauterine insemination (IUI) due to male subfertility with the following: • Some subnormal parameters of the seminogram but >2 x10^6/ml motile spermatozoa obtained after semen preparation with Percoll • Infertility history >2 years
Exclusion criteria	Low concentration of serum FSH (<5 IU/m)

Patient characteristics	N=148 subfertile men:
	• Fertility diagnosis:
	  ○ Asthenoteratozoospermia (cause not reported): 109/148 (74%)
	  ○ Oligoasthenozoospermia (cause not reported): 19/148 (13%)
	  ○ Asthenozoospermia (cause not reported): 9/148 (6%)
	  ○ Teratozoospermia (cause not reported): 3/148 (2%)
	  ○ Oligoteratozoospermia (cause not reported): 8/148 (5%)

	Follicle-stimulating hormone (FSH) group (n=68):
	
	• Mean age (SD): 34.06 (3.16) years
	• Severity of semen abnormalities:
	  ○ Non-azoospermic: 68/68 (100%)
	• Fertility diagnosis: Not reported separately for each group
	• Hypogonadotropic hypogonadism: Not reported
	
	Non-FSH group (n=80):
	
	• Mean age (SD): 34.63 (4.28) years
	• Severity of semen abnormalities:
	  ○ Non-azoospermic: 80/80 (100%)
	• Fertility diagnosis: Not reported separately for each group
	• Hypogonadotropic hypogonadism: Not reported

Intervention(s)/control	FSH: • FSH, 150 IU administered intramuscularly or subcutaneously 3 times a week, starting 3 months before the beginning of IUI cycles and maintained until the 5th IUI cycle Non-FSH: • IUI without treatment of the male partner Participants in both groups underwent IUI (for a total of 6 IUI cycles if pregnancy was not obtained)
Duration of follow-up	4 years
Sources of funding	Not reported
Sample size	N=148:

	• FSH group: n=68 • Non-FSH group: n=80
Other information	None

Study arms
FSH group (N = 68)

Non-FSH group (N = 80)

Outcomes
Pregnancy rate per cycle

Outcome	**FSH group, N = 209**	**Non-FSH group, N = 288**
Pregnancy rate (per IUI cycle) at 4 years Pregnancy defined by the visualization of a gestational sac at week 6–7 of amenorrhoea, for all initially randomised (not excluding non-IUI pregnancies) No of events	n = 26 ; % = 12.44	n = 29 ; % = 10.07

Pregnancy rate per woman

Outcome	**FSH group, N = 68**	**Non-FSH group, N = 80**
Pregnancy rate (per woman) at 4 years Pregnancy defined by the visualization of a gestational sac at week 6–7 of amenorrhoea, for all initially randomised (not excluding non-IUI pregnancies) No of events	n = 36 ; % = 52.94	n = 31 ; % = 38.75

Assisted pregnancy rate per cycle

Outcome	FSH group, N = 193	Non-FSH group, N = 288
Assisted pregnancy rate (per IUI cycle) at 4 years Pregnancy defined by the visualization of a gestational sac at week 6–7 of amenorrhoea, for IUI-assisted pregnancies only No of events	n = 26 ; % = 13.47	n = 29 ; % = 10.07

Assisted pregnancy rate per woman

Outcome	FSH group, N = 58	Non-FSH group, N = 78
Assisted pregnancy rate (per woman) at 4 years Pregnancy defined by the visualization of a gestational sac at week 6–7 of amenorrhoea, for IUI-assisted pregnancies only No of events	n = 26 ; % = 44.83	n = 29 ; % = 37.18

Critical appraisal with the Cochrane RoB 2.0

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(Participants assigned to conditions based on a random numbers table, however, allocation concealment is unclear)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(Participants and intervention administrators were aware of the assigned intervention, and there was no information about deviations from the intended intervention that arose because of experimental context)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	High *(Participants and intervention administrators aware of assigned intervention, unclear if non-protocol interventions balanced across groups, and the intervention was changed halfway through the study period (with participants starting treatment during the first 2 years of the trial receiving pure urinary FSH administered intramuscularly, and participants starting treatment during*

Section	Question	Answer
		the last 2 years of the trial receiving highly purified FSH administered subcutaneously))
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Pregnancy defined by the visualization of a gestational sac at week 6–7 of amenorrhoea. It was judged likely that outcome assessors were aware of the intervention received, but considered unlikely that the assessment of outcome was influenced by knowledge of the intervention received)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(No prespecified protocol was available. Data not extractable for semen parameters as not reported (unclear if measured) for the non-FSH group)*
Overall bias and Directness	Risk of bias judgement	High *(High risk of bias for deviations from the intended interventions (effect of adhering to intervention). Some concerns about the randomisation process, deviations from the intended interventions (effect of assignment to intervention), and selection of the reported result)*
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	None

Matsumiya, 1998

Bibliographic Reference	Matsumiya, K.; Kitamura, M.; Kishikawa, H.; Kondoh, N.; Fujiwara, Y.; Namiki, M.; Okuyama, A.; A prospective comparative trial of a gonadotropin-releasing hormone analogue with clomiphene citrate for the treatment of oligoasthenozoospermia; International Journal of Urology; 1998; vol. 5 (no. 4); 361-363

Study details

Country/ies where study was carried out	Japan
Study type	Randomised controlled trial (RCT)

Study dates	January to December 1995
Inclusion criteria	Men with newly-diagnosed idiopathic normogonadotropic oligoasthenozoospermia with: • Sperm densities of 5 to 30 X 10^6/mL • Serum follicle-stimulating hormone levels below the normal upper limit
Exclusion criteria	• Organic disorders such as varicocele or hyperprolactinaemia

Patient characteristics	N=44 men with idiopathic normogonadotropic oligoasthenozoospermia
	
	Gonadotrophin releasing hormone (GnRH) analogue group (n=23):
	
	• Mean age (SD): 33.1 (4.5) years
	• Severity of semen abnormalities:
	  ○ Non-azoospermic: 23/23 (100%)
	• Fertility diagnosis:
	  ○ Idiopathic normogonadotropic oligoasthenozoospermia: 23/23 (100%)
	• Hypogonadotropic hypogonadism: 0/23 (0%)*
	
	Clomiphene citrate group (n=21):
	
	• Mean age (SD): 31.7 (4.1) years
	• Severity of semen abnormalities:
	  ○ Non-azoospermic: 21/21 (100%)
	• Fertility diagnosis:
	  ○ Idiopathic normogonadotropic oligoasthenozoospermia: 21/21 (100%)
	• Hypogonadotropic hypogonadism: 0/23 (0%)*
	
	* Participants were all normogonadotropic

Intervention(s)/control	GnRH analogue:

	• GnRH analogue (buserelin acetate), 15µg (original concentration diluted to 10% with sterile saline, since 1 spray of Suprecur contained 150µg of GnRHa) once a day intranasally for ≥3 months Clomiphene citrate: • Clomiphene citrate, 50 mg administrated orally every day for ≥3 months
Duration of follow-up	3 months
Sources of funding	Not reported
Sample size	N=44: • GnRH analogue group: n=23 • Clomiphene citrate group: n=21
Other information	None

Study arms
Gonadotrophin-releasing hormone analogue (GnRH analogue) (N = 23)

Clomiphene citrate (N = 21)

Outcomes
Pregnancy rates

Outcome	Gonadotrophin-releasing hormone analogue (GnRH analogue), N = 23	Clomiphene citrate, N = 21
Pregnancy rate at 3 months Reported in study as total number of pregnancies (spontaneous or assisted). Study does not report how these data were collected or how pregnancy was defined No of events	n = 3	n = 0

Outcome	Gonadotrophin-releasing hormone analogue (GnRH analogue), N = 23	Clomiphene citrate, N = 21
Spontaneous pregnancy rate at 3 months Reported in study as number of spontaneous pregnancies. Study does not report how these data were collected or how pregnancy was defined No of events	n = 1	n = 0

Semen parameters

Outcome	Gonadotrophin-releasing hormone analogue (GnRH analogue), N = 23	Clomiphene citrate, N = 21
Sperm concentration (x10^6/ml) at 3 months Reported as sperm density (x10^6/ml) Mean (SD) *Higher values are better*	26.9 (16.3)	21.5 (14.6)
Sperm motility rate (%) at 3 months Mean (SD) *Higher values are better*	43.9 (17.8)	39.9 (22.1)

Critical appraisal with the Cochrane RoB 2.0

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(Participants were assigned to interventions on an alternating basis. No information reported on allocation concealment, but differences in participant characteristics at baseline do not indicate a problem with the randomisation process)*

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(Information about blinding not reported but participants likely knew which group they were assigned to due to nature of interventions (delivered intranasally or orally). No information on deviations from intended interventions, but appropriate analysis used)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Data available for all participants)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Semen parameters were evaluated using World Health Organization criteria. Some concerns for the outcome pregnancy rate, because it is not reported how these data were collected or how pregnancy was defined - it is unclear whether pregnancy rate is defined in the study as an ultrasound scan that has shown at least one fetal heart beat. It is unlikely that assessment of the outcome pregnancy rates could have been influenced by knowledge of the intervention received)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(No prespecified protocol was available. No information about how pregnancy was defined or measured)*
Overall bias and Directness	Risk of bias judgement	Some concerns *(Some concerns due to lack of information on the randomisation process, deviations from the intended interventions, measurement of the pregnancy rates outcomes, and selection of the reported result)*
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	None

Micic, 1985

Bibliographic Reference	Micic, S.; Dotlic, R.; Evaluation of sperm parameters in clinical trial with clomiphene citrate of oligospermic men; Journal of Urology; 1985; vol. 133 (no. 2); 221-222

Study details

Country/ies where study was carried out	Serbia (Yugoslavia at time of study)
Study type	Randomised controlled trial (RCT)
Study dates	Not reported
Inclusion criteria	Men with idiopathic oligozoospermia and infertile marriages for >2 years
Exclusion criteria	Not reported

Patient characteristics	N=101 men with idiopathic oligozoospermia:
	
	• Mean age (SD): Not reported
	• Severity of semen abnormalities:
	  ○ Non-azoospermic: 101/101 (100%)
	• Fertility diagnosis:
	  ○ Idiopathic oligozoospermia: 101/101 (100%)
	• Hypogonadotropic hypogonadism: 0/101 (0%)*
	
	Participant characteristics not reported separately for each group
	
	* Participants had unknown cause of infertility

Intervention(s)/control	Clomiphene citrate: • Clomiphene citrate, 50 mg daily for 6 to 9 months No treatment: • No treatment received
Duration of follow-up	6 to 9 months
Sources of funding	Not reported
Sample size	N=101: • Clomiphene citrate: n=56

	• No treatment: n=45
Other information	Data also reported for follicle-stimulating hormone (FSH), however these data not extracted as unlikely to be useful for decision-making

Study arms
Clomiphene citrate (N = 56)

No treatment (N = 45)

Outcomes
Pregnancy rates

Outcome	Clomiphene citrate, N = 56	No treatment, N = 45
Pregnancy rate at 6-9 months Study does not report how these data were collected or how pregnancy was defined No of events	n = 7	n = 0

Semen parameters

Outcome	Clomiphene citrate, N = 56	No treatment, N = 45
Sperm concentration (x10^6/ml) at 6-9 months Reported as sperm density (x10^6/ml) Mean (SD) *Higher values are better*	16 (2.1)	8.3 (2.2)
Sperm motility rate (%) at 6-9 months Reported in study as percentage of motile sperm Mean (SD) *Higher values are better*	36.5 (9.5)	24.6 (10.1)

Critical appraisal with the Cochrane RoB 2.0

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(No information reported on randomisation process or allocation concealment. Ages of participants not reported at baseline but rest of participant characteristics do not indicate a problem with the randomisation process)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High *(No information about blinding, deviations from the intended interventions, or analysis used. Participants likely knew which group they were assigned to due to the nature of interventions)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High *(No information reported on loss to follow-up or missing outcome data)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High *(No information reported on how semen parameters outcomes were assessed, or on blinding of outcome assessors. Some concerns for the outcome pregnancy rates: is not reported how pregnancy rates data were collected or how pregnancy was defined - it is unclear whether pregnancy rate is defined in the study as an ultrasound scan that has shown at least one fetal heart beat. It is unlikely that assessment of pregnancy rates could have been influenced by knowledge of the intervention received)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(No prespecified protocol available and no information reported on how the outcomes were defined or measured)*
Overall bias and Directness	Risk of bias judgement	High *(High risk of bias due to lack of information on the randomisation process, deviations from the intended interventions, missing outcome data, or measurement of the outcome. Some concerns regarding selection of the reported result)*
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	None

Paradisi, 2006

Bibliographic Reference	Paradisi, R.; Busacchi, P.; Seracchioli, R.; Porcu, E.; Venturoli, S.; Effects of high doses of recombinant human follicle-stimulating hormone in the treatment of male factor infertility: results of a pilot study; Fertility and Sterility; 2006; vol. 86 (no. 3); 728-731

Study details

Country/ies where study was carried out	Italy
Study type	Randomised controlled trial (RCT)
Study dates	Not reported
Inclusion criteria	Men with: • Idiopathic oligoasthenozoospermia (in the moderate to severe range with sperm concentration between 1 and 15 x10^6/ml) • History of unexplained male factor infertility for at least 2 years • No indication of hormonal (normal basal FSH and T values), infective (negative spermioculture), or physical causes for infertility • Female partner has no endocrine and/or obstructive disorders
Exclusion criteria	• Testicular tumor • Hypergonadotropic or hypogonadotropic hypogonadism • Isolated gonadotrophin deficiency • Hyperprolactinemia • Severe scrotal varicocele • History of cryptorchidism • Leucocytospermia • Acute orchitis or other genital infections • Positivity to seminal sperm antibodies • Presence of y-chromosome microdeletions • Obesity • Any systemic severe chronic illness

Patient characteristics	N=30 men with idiopathic oligoasthenozoospermia
	
	Recombinant human FSH (rhFSH) group (n=15)
	
	• Mean age (SD): Not reported
	• Severity of semen abnormalities:
	  ○ Non-azoospermic: 15/15 (100%)
	• Fertility diagnosis:
	  ○ Idiopathic oligoasthenozoospermia: 15/15 (100%)
	• Hypogonadotropic hypogonadism: 0/15 (0%)*
	
	Placebo group (n=15)
	
	• Mean age (SD): Not reported
	• Severity of semen abnormalities:
	  ○ Non-azoospermic: 15/15 (100%)
	• Fertility diagnosis:
	  ○ Idiopathic oligoasthenozoospermia: 15/15 (100%)
	• Hypogonadotropic hypogonadism: 0/15 (0%)*
	
	* People with hypogonadotropic hypogonadism were excluded

Intervention(s)/control	rhFSH: • rhFSH, 300 IU (2 vials of 150 IU lyophilized FSH with 30mg saccharose) administered by subcutaneous injection every other day for at least 4 months Placebo: • Matching placebo (2 vials containing 30mg saccharose-only) administered by subcutaneous injection every other day for at least 4 months
Duration of follow-up	4 months for semen and hormonal parameters; >4 months ('in the months after treatment') for clinical pregnancy

Sources of funding	Partly funded by industry
Sample size	N=30: • Recombinant human FSH (rhFSH) group: n=15 • Placebo group: n=15
Other information	Data also reported for luteinizing hormone (LH), follicle-stimulating hormone (FSH), and prolactin, however these data not extracted as unlikely to be useful for decision-making

Study arms
Recombinant human FSH (rhFSH) (N = 15)

Placebo (N = 15)

Outcomes
Live birth and pregnancy rates

Outcome	Recombinant human FSH (rhFSH), N = 15	Placebo, N = 15
Live birth rate at >4 months Study reports that all pregnancies went to term successfully No of events	n = 4	n = 0
Spontaneous pregnancy rate at >4 months Reported as cumulative number of spontaneous pregnancies after treatment. Study does not report how these data were collected or how pregnancy was defined. ITT analysis No of events	n = 4	n = 0

Hormone parameters

Outcome	Recombinant human FSH (rhFSH), N = 15	Placebo, N = 15
Testosterone (µg/l) at 4 months Reported as testosterone (ng/ml) Mean (SD) *Higher values are better*	4.7 (1.7)	4.9 (1.5)
Free testosterone (µg/l) at 4 months Reported as free testosterone (ng/ml) Mean (SD) *Higher values are better*	17.5 (5)	17.4 (4.2)

Semen parameters

Outcome	Recombinant human FSH (rhFSH), N = 15	Placebo, N = 15
Sperm concentration (x10^6/ml) at 4 months Mean (SD) *Higher values are better*	16.1 (11.1)	7.5 (4.6)
Total sperm count (x10^6) at 4 months Reported as total sperm number (x10^6/ejaculate) Mean (SD) *Higher values are better*	46.6 (31.6)	24 (15.3)
Sperm motility rate (%) at 4 months Reported separately in study as 2 outcomes: percentage of forward progression up of sperm with rapid linear movement (type 1 motility), and percentage of	34 (10.77)	28.9 (16.69)

Outcome	Recombinant human FSH (rhFSH), N = 15	Placebo, N = 15
forward progression up of sperm with slow linear movement (type 2 motility); results combined for the purpose of this review. Mean type 1 sperm motility rate (SD) for rhFSH and placebo groups, respectively (%): 11.3 (4.4); 9.3 (5.6). Mean type 2 sperm motility rate (SD) for rhFSH and placebo groups, respectively (%): 22.7 (5.6); 19.6 (9.9) Mean (SD) *Higher values are better*		

Critical appraisal with the Cochrane RoB 2.0

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Groups were matched on age, weight and height but were assigned using a computer-generated randomisation list. The method of allocation concealment is unclear, but paper reports that assignment was 'blinded for examiners'. Visual inspection of baseline values suggests there are probably not significant baseline differences between drug and placebo arms and there does not appear to be a problem with the randomisation process)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Double-blind study using placebo)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Semen parameters were evaluated using World Health Organization criteria. Some concerns for the pregnancy rate outcome because it is not reported how data collected or how pregnancy was defined - it is unclear whether pregnancy rate is defined in the study as an ultrasound scan that has shown at least one*

Section	Question	Answer
		fetal heart beat. Blinding of outcome assessors not reported; however, it was judged unlikely that the measurement was inappropriate or would differ between groups, or that the assessment of outcome was influenced by knowledge of the intervention received)
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(No prespecified protocol was available. Timepoint for measurements is also unclear as paper reports 'post-therapy' for semen and hormonal parameters, and 'the months after treatment' for the pregnancy/birth outcome.)*
Overall bias and Directness	Risk of bias judgement	Some concerns *(Some concerns regarding selection of the reported result and measurement of the outcome pregnancy rates)*
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	None

Pusch, 1989

Bibliographic Reference	Pusch, H H; Oral treatment of oligozoospermia with testosterone-undecanoate: results of a double-blind-placebo-controlled trial.; Andrologia; 1989; vol. 21 (no. 1); 76-82

Study details

Country/ies where study was carried out	Austria
Study type	Randomised controlled trial (RCT)
Study dates	Not reported
Inclusion criteria	Healthy men aged <30 years attending an obstetrics and gynaecology hospital, who had: • Sperm density <40 x10^6/ml • Normal follicle stimulating hormone (FSH) and luteinising hormone (LH) levels • Normal or low-normal serum-testosterone values

Exclusion criteria	• Suspected prostatic or mammary carcinoma • Receiving or had received other drugs for improving their fertility, or medications for other reasons • Autoagglutination in the ejaculates • Known causes of infertility (e.g. varicocele or a history of inflammatory affections of the genital tract) • Partner aged >30 years

Patient characteristics	N=60 normogonadotropic oligozoospermic men:
	
	• Mean age (SD): not reported. All men were aged <30 years
	• Severity of semen abnormalities:
	  ○ Non-azoospermic: 60/60 (100%)
	• Fertility diagnosis:
	  ○ Idiopathic normogonadotropic oligozoospermia: 60/60 (100%)
	• Hypogonadotropic hypogonadism: 0/60 (0%)*
	
	Participant characteristics were not reported separately for each group
	
	* Participants were all normogonadotropic

Intervention(s)/control	Testosterone undecanoate: • Testosterone undecanoate, 40mg capsules 3 times per day (for a total of 120mg per day) for 3 months Placebo: • Identical placebo capsule. Further details not reported
Duration of follow-up	12 weeks (immediately following treatment period) and 18 weeks (6 weeks after finishing treatment) for semen parameters outcomes; 12 weeks only for hormone parameters; 18 weeks only for pregnancy and miscarriage rates
Sources of funding	Not reported
Sample size	N=60: • Testosterone undecanoate group: n=30

	• Placebo group: n=30
Other information	The following semen parameters outcomes were reported in the study at 12 and 18 weeks but not extracted as overall sperm morphology were preferred outcomes for decision making: sperm morphology: head; sperm morphology: midpiece; sperm morphology: tail. Data also reported for LH, FSH, prolactin, serum glutamic-oxaloacetic transaminase (SGOT), and serum glutamic pyruvic transaminase (SGPT), however these data not extracted as unlikely to be useful for decision-making

Study arms
Testosterone undecanoate (N = 30)

Placebo (N = 30)

Outcomes
Pregnancy rates

Outcome	Testosterone undecanoate, N = 30	Placebo, N = 30
Pregnancy rates at 4 months Study does not report how these data were collected or how pregnancy was defined No of events	n = 6	n = 4

Hormone parameters

Outcome	Testosterone undecanoate, N = 29	Placebo, N = 2
Free testosterone (pg/ml) at 3 months Mean (SD) *Higher values are better*	23.6 (11.23)	22.21 (4.73)
Total testosterone (ng/ml) at 3 months	6.65 (3.57)	4.48 (1.63)

Outcome	Testosterone undecanoate, N = 29	Placebo, N = 2
Mean (SD) *Higher values are better*		
Oestradiol (pg/ml) at 3 months Mean (SD) *Lower values are better*	26.19 (8.2)	29.02 (18.38)

Semen parameters

Outcome	Testosterone undecanoate, N = 29	Placebo, N = 28
Sperm concentration (x10^6/ml) at 3 months Reported as sperm density (x10^6/ml) Mean (SD) *Higher values are better*	15.33 (10.1)	19.76 (10.61)
Sperm motility rate (%) at 3 months Reported as percent of progressive motile sperm Mean (SD) *Higher values are better*	15.3 (10.3)	19.5 (11.9)

Semen parameters (cont.)

Outcome	Testosterone undecanoate, N = 25	Placebo, N = 28
Sperm concentration (x10^6/ml) at 4 months Reported as sperm density (x10^6/ml)	17.83 (15.08)	25.72 (20.98)

Outcome	Testosterone undecanoate, N = 25	Placebo, N = 28
Mean (SD) *Higher values are better*		
Sperm motility rate (%) at 4 months Reported as percent of progressive motile sperm Mean (SD) *Higher values are better*	19.2 (11.43)	22.14 (12.43)

Miscarriage rates

Outcome	Testosterone undecanoate, N = 30	Placebo, N = 30
Miscarriage rates at 4 months Reported in study as number of pregnancies that were aborted. Study does not report how these data were collected or how abortion was defined No of events	n = 0	n = 1

Critical appraisal with the Cochrane RoB 2.0

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(No information reported on randomisation process or allocation concealment. Reported participant characteristics at baseline do not indicate a problem with the randomisation process, though some important characteristics (such as age of participants) are not reported)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Double-blind trial using placebo. Minimal information reported about analysis but participants appear to have been analysed according to intervention assigned)*

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Missing outcome data for 3/60 participants (5%) at 12 weeks follow-up, with missing data distributed evenly between groups. It is not clear from the text, but pregnancy and miscarriage rates appear to be reported for all included participants. High risk of bias for semen parameters outcomes at 18 weeks only because of missing outcome data for 7/60 participants (12%: 2/30 in placebo group (7%) and 5/30 in the testosterone undecanoate group (17%)). Missingness in the value likely depended on its true outcome because 2 participants in the testosterone undecanoate group did not attend the final spermiogram due to pregnancy or because they had decided to adopt)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(It is not reported how data for the outcome pregnancy or miscarriage rates were collected or how pregnancy or abortion was defined - it is unclear whether pregnancy rate is defined in the study as an ultrasound scan that has shown at least one fetal heart beat, and miscarriage rate is reported in the study as number of aborted pregnancies so it is unclear whether this includes loss of a baby before 24 weeks gestational age. Semen parameters were measured using spermiograms, but criteria used to assess results were not reported. However, all participants and personnel involved in the trial were blinded. Low risk of bias for hormone parameters)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(No prespecified protocol was available. No information about how pregnancy or abortion was defined or measured, or the criteria used to assess sperm parameters. No evidence of selective reporting)*
Overall bias and Directness	Risk of bias judgement	Some concerns *(Some concerns due to lack of information on randomisation process or allocation concealment, measurement of the outcomes pregnancy and miscarriage rates and semen parameters, and selection of the reported result. High risk of bias for missing outcome data for semen parameters outcomes at 18 weeks only)*
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	High overall risk of bias for semen parameters outcomes at 18 weeks only due to missing outcome data

Selice, 2011

Bibliographic Reference	Selice, R.; Garolla, A.; Pengo, M.; Caretta, N.; Ferlin, A.; Foresta, C.; The response to fsh treatment in oligozoospermic men depends on fsh receptor gene polymorphisms; International Journal of Andrology; 2011; vol. 34 (no. 4part1); 306-312

Study details

Country/ies where study was carried out	Italy
Study type	Randomised controlled trial (RCT)
Study dates	January 2006 to October 2008
Inclusion criteria	Oligozoospermic men with: • ≥1 year of infertility • Sperm count <20 x10⁶/ml (based on at least 2 semen analyses separated by an interval of 3 months) • Normal plasma levels of FSH (within the 1–8 IU/l range), luteinizing hormone (within the 2–6 IU/l range), testosterone (within the 10–29 nmol/l range), prolactin (within the 10–25 ng/ml range) and inhibin B (>100 pg/ml) • Testicular cytology characterized by hypospermatogenesis without maturative arrest (defined as reduced number of germ cells which are in normal relative percentages)
Exclusion criteria	• Hypogonadotropic hypogonadism • Abuse of androgenic (anabolic) steroids • Received treatment with chemotherapeutic agents or radiotherapy • Karyotype abnormalities or y-chromosome long arm microdeletions
Patient characteristics	N=105 men with oligozoospermia Recombinant follicle-stimulating hormone (rFSH) group (n=70): • Mean age (SD): Not reported • Severity of semen abnormalities: ○ Non-azoospermia: 70/70 (100%)

	• Fertility diagnosis:
	  ○ Oligozoospermia (cause not reported*): 70/70 (100%)
	• Hypogonadotropic hypogonadism: 0/70 (0%)**
	
	No treatment group (n=35):
	
	• Mean age (SD): Not reported
	• Severity of semen abnormalities:
	  ○ Non-azoospermia: 35/35 (100%)
	• Fertility diagnosis:
	  ○ Oligozoospermia (cause not reported*): 35/35 (100%)
	• Hypogonadotropic hypogonadism: 0/35 (0%)*
	
	*All oligozoospermia was due to hypospermatogenesis, but cause not reported
	
	** People with hypogonadotropic hypogonadism were excluded

Intervention(s)/control	rFSH: • rFSH, 150 IU 3 times per week for 3 months No treatment: • No treatment given for 3 months
Duration of follow-up	3 months (at end of treatment period) for semen and hormonal parameters; 6 months for clinical pregnancy (including 3 month post-treatment period)
Sources of funding	Not reported
Sample size	N=105: • rFSH: n=70

	• No treatment: n=35
Other information	Data also reported for luteinizing hormone (LH) and follicle-stimulating hormone (FSH), inhibin B, and testicular volume, however, these data not extracted as unlikely to be useful for decision-making

Study arms
Recombinant follicle-stimulating hormone (rFSH) (N = 70)

No treatment (N = 35)

Outcomes
Pregnancy rates

Outcome	Recombinant follicle-stimulating hormone (rFSH), N = 70	No treatment, N = 35
Spontaneous pregnancy rate at 6 months Reported as cumulative number of spontaneous pregnancies during and after treatment. Study does not report how these data were collected or how pregnancy was defined. ITT analysis No of events	n = 10 ; % = 14.8	n = 2 ; % = 4.6

Hormone parameters

Outcome	Recombinant follicle-stimulating hormone (rFSH), N = 70	No treatment, N = 35
Testosterone (nmol/l) at 3 months Mean (SD) *Higher values are better*	16.2 (5.8)	16.4 (5.9)
Oestradiol (pmol/l) at 3 months Mean (SD)	93.3 (52.9)	92.4 (43.2)

Outcome	Recombinant follicle-stimulating hormone (rFSH), N = 70	No treatment, N = 35
Lower values are better		

Semen parameters

Outcome	Recombinant follicle-stimulating hormone (rFSH), N = 70	No treatment, N = 35
Sperm concentration (x10^6/ml) at 3 months Mean (SD) *Higher values are better*	8.6 (11.3)	4.1 (4.2)
Total sperm count (x10^6) at 3 months Mean (SD) *Higher values are better*	24 (28.1)	11.7 (11.9)
Sperm motility rate (%) at 3 months Reported in study as forward (A+B) motility (%) Mean (SD) *Higher values are better*	25.5 (17.7)	21.6 (16.9)
Total motile sperm count (x10^6) at 3 months Mean (SD) *Higher values are better*	8.6 (12.1)	3.3 (6)

Critical appraisal with the Cochrane RoB 2.0

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Participants assigned to conditions based on random number generator and allocation concealed (central allocation). No significant baseline differences were found between arms indicating that there does not appear to be a problem with the randomisation process)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Non-blind, but no deviations from the intended intervention and analysis appropriate (ITT))*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Data analysed for all randomised participants (ITT))*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Semen parameters were evaluated using World Health Organization criteria and hormonal parameters evaluated by commercial electrochemiluminescence immunoassay methods. Some concerns for the pregnancy rate outcome because it is not reported how data collected or how pregnancy was defined - it is unclear whether pregnancy rate is defined in the study as an ultrasound scan that has shown at least one fetal heart beat. Blinding of outcome assessors not reported, and likely to be aware of whether participants assigned to treatment or no treatment groups. However, it was judged unlikely that the measurement was inappropriate or would differ between groups, or that the assessment of outcome was influenced by knowledge of the intervention received)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(No prespecified protocol was available. No information about how pregnancy was defined or measured)*
Overall bias and Directness	Risk of bias judgement	Some concerns *(Some concerns regarding selection of the reported result and lack of information on measurement of the outcome pregnancy rates)*
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	None

Sokol, 1988

Bibliographic Reference	Sokol, R.Z.; Steiner, B.S.; Bustillo, M.; Petersen, G.; Swerdloff, R.S.; A controlled comparison of the efficacy of clomiphene citrate in male infertility; Fertility and Sterility; 1988; vol. 49 (no. 5); 865-870

Study details

Country/ies where study was carried out	USA
Study type	Randomised controlled trial (RCT)
Study dates	Not reported
Inclusion criteria	Oligospermic men (sperm count ranged between 0.5-20 x10^6/ml based on 3 semen analyses) meeting the following criteria: • Diagnosis of infertility (had not achieved pregnancy after 12 months of regular unprotected sexual intercourse) • Female partner was presumed to be fertile based on clinical history (including menstrual history), physical examination (including basal body temperature), normal progesterone levels, and where performed a normal hysterosalpingogram (18 women) and/or laparoscopy (11 women)
Exclusion criteria	Major systemic or psychiatric illness; abnormal sperm morphology (based on 3 semen analyses); sperm motility ≤10% (based on 3 semen analyses); abnormal hormonal parameters (for luteinizing hormone, follicle-stimulating hormone, testosterone, and prolactin)

Patient characteristics	N=20 men with oligozoospermia (N=23 randomised but data for n=3 participants lost to follow-up not reported):
	
	• Mean age (range): Not reported (23-49 years)
	• Severity of semen abnormalities:
	  ○ Non-azoospermia: 23/23 (100%)
	• Fertility diagnosis:
	  ○ Oligozoospermia (cause not reported): 23/23 (100%)
	• Hypogonadotropic hypogonadism: Not reported
	
	Participant characteristics not reported separately for each group

Intervention(s)/control	Clomiphene citrate: • Clomiphene citrate, 25mg per day for 12 months Placebo: • Placebo, 1 tablet per day for 12 months
Duration of follow-up	12 month treatment period. This was preceded by a 3-month control period during which blood and semen samples were collected monthly
Sources of funding	Not industry funded
Sample size	N=20 (N=23 initially randomised): • Clomiphene group: n=11 (n randomised not reported) • Placebo group: n=9 (n randomised not reported)
Other information	Data also reported for luteinizing hormone (LH) and follicle-stimulating hormone (FSH), and for stimulated responses of LH, FSH, and testosterone to GnRH stimulation testing, however, these data not extracted as unlikely to be useful for decision-making.

Study arms
Clomiphene (N = 11)

Placebo (N = 9)

Outcomes
Pregnancy rates

Outcome	Clomiphene, N = 11	Placebo, N = 9
Spontaneous pregnancy rate at 12 months Reported as cumulative number of spontaneous pregnancies during treatment. Study does not report how these data were collected or how pregnancy was defined. Data only available for completers	n = 1 ; % = 9.09	n = 4 ; % = 44.44

Outcome	Clomiphene, N = 11	Placebo, N = 9
No of events		

Hormone parameters

Outcome	Clomiphene, N = 11	Placebo, N = 9
Change in oestradiol from baseline (pg/ml) at 12 months Mean (SD) *Lower values are better*	15.88 (20.49)	-6.78 (8.24)
Change in testosterone from baseline (ng/dl) at 12 months Mean (SD) *Higher values are better*	473.19 (276.47)	8.66 (146.18)

Semen parameters

Outcome	Clomiphene, N = 11	Placebo, N = 9
Change in sperm motility rate from baseline (%) at 12 months Data available for n=10 in clomiphene group and n=9 in placebo group Mean (SD) *Higher values are better*	-0.46 (15.7)	6.8 (9.2)
Change in total sperm count from baseline ($x10^6$) at 12 months Mean (SD) *Higher values are better*	37.4 (116.5)	26 (43.5)

Critical appraisal with the Cochrane RoB 2.0

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Participants assigned to conditions based on a random numbers table and allocation was double-blind (with identical-appearing tablets). No statistically significant difference between groups at baseline for clinical variables, indicating that there does not appear to be a problem with the randomisation process)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Double-blind study using placebo)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High *(Data available for between 65% and 87% of randomised participants across outcomes. No reasons for missing data provided and no methods used to impute missing data. The number of participants randomised by arm is not reported (baseline data only reported for completers) so differences between arms in terms of dropout rate and reasons for discontinuation is unclear, also not clear why there are different rates of missing data across outcomes)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Semen parameters were evaluated using World Health Organization criteria. Some concerns for the pregnancy rate outcome because it is not reported how data collected or how pregnancy was defined - it is unclear whether pregnancy rate is defined in the study as an ultrasound scan that has shown at least one fetal heart beat. Blinding of outcome assessors not reported. However, it was judged unlikely that the measurement was inappropriate or would differ between groups, or that the assessment of outcome was influenced by knowledge of the intervention received)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(No prespecified protocol was available. No information about how pregnancy was defined or measured. No justification for reporting continuous outcomes based on change from baseline to mean during the treatment period.)*
Overall bias and Directness	Risk of bias judgement	High *(High risk of bias for missing outcome data, some concerns regarding*

Section	Question	Answer
		selection of the reported result and lack of information on measurement of the outcome pregnancy rates)
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	None

Srivannaboon, 1992

Bibliographic Reference	Srivannaboon, S.; Dhall, G.I.; De Krester, D.M.; Hargreave, T.B.; Comhaire, F.H.; Padron, R.S.; Mas, J.; Hingorani, V.; Miranda, C.; Cooke, I.D.; Vernon-Parry, J.; Hagenfeldt, K.; Sas, M.; Resch, B.A.; Ladjimi, A.; Bourkhris, R.; Farley, T.M.M.; Rowe, P.J.; Hazelden, C.; A double-blind trial of clomiphene citrate for the treatment of idiopathic male infertility; International Journal of Andrology; 1992; vol. 15 (no. 4); 299-307

Study details

Country/ies where study was carried out	11 centres in: Australia; Belgium; Cuba; Hungary; India; Sweden; Switzerland; Thailand; Tunisia; UK
Study type	Randomised controlled trial (RCT)
Study dates	Study initiated in 1981, no further detail on dates reported
Inclusion criteria	Men with idiopathic oligozoospermia or asthenozoospermia (defined as low sperm concentration <20 million ml-1 and/or poor sperm motility <50% progressive motility in the best of 2 semen samples); female partner had no demonstrable abnormality or was under successful treatment for a minor endocrine problem
Exclusion criteria	Not reported
Patient characteristics	N=141 men with idiopathic oligozoospermia or asthenozoospermia (N=190 randomised before diagnosis and later found to be ineligible, only data for eligible participants reported) • Mean age (SD): 30.4 (4.2) years Clomiphene group (n=70) • Mean age (SD): 30.3 (4.4) years

	• Severity of semen abnormalities:
	  ○ Non-azoospermia: 70/70 (100%)
	• Fertility diagnosis:
	  ○ Idiopathic oligo- or astheno-zoospermia: 70/70 (100%)
	• Hypogonadotropic hypogonadism: 0/70 (0%)*
	
	Placebo group (n=71)
	
	• Mean age (SD): 30.5 (4.1) years
	• Severity of semen abnormalities:
	  ○ Non-azoospermia: 71/71 (100%)
	• Fertility diagnosis:
	  ○ Idiopathic oligo- or astheno-zoospermia: 71/71 (100%)
	• Hypogonadotropic hypogonadism: 0/71 (0%)*
	
	* Participants had no detected aetiological factors causing infertility

Intervention(s)/control	Clomiphene citrate: • Clomiphene citrate, 25mg per day Placebo: • Placebo for 6 months, no further details reported
Duration of follow-up	8 months (2 months after the end of treatment)
Sources of funding	Not industry funded
Sample size	N=141 (N=78 completed trial): • Clomiphene group: n=70 (n=44 completed trial) • Placebo group: n=71 (n=34 completed trial)

Other information	Study initiated by the World Health Organization (WHO), and on this basis assumed no industry funding

Study arms
Clomiphene (N = 70)

Placebo (N = 71)

Outcomes
Pregnancy rates

Outcome	Clomiphene , N = 70	Placebo, N = 71
Spontaneous pregnancy rate at 8 months Reported as cumulative number of spontaneous pregnancies after treatment. Study does not report how these data were collected or how pregnancy was defined. Data entered for ITT analysis assuming those who did not complete did not get pregnant. 1 pregnancy from each arm not included as the time of conception is estimated before first tablet taken No of events	n = 6	n = 5

Critical appraisal with the Cochrane RoB 2.0

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Limited detail on randomised sequence generation, although allocation sequence concealed (sequentially numbered drug containers, and central allocation). A number of participants were randomised prior to confirmation of diagnosis and were later found to be ineligible (49/190). Although, no significant baseline differences were found between drug and placebo arms for the eligible participants (141/190) indicating that there does not appear to be a problem with the randomisation process.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Double-blind study using placebo)*

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(The only extractable outcome is pregnancy rate, and it is not clear how these data were collected or how pregnancy was defined; however, it was judged unlikely that the measurement was inappropriate or would differ between groups, or that the assessment of outcome was influenced by knowledge of the intervention received)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(No prespecified protocol was available. Data not extractable for semen or hormonal parameters as no measure of variance is reported)*
Overall bias and Directness	Risk of bias judgement	Some concerns *(Some concerns regarding selection of the reported result)*
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	None

Zhao, 2019

Bibliographic Reference	Zhao, N.; Lu, X.-L.; Li, J.-T.; Zhang, J.-M.; Treatment of idiopathic oligozoospermia with combined human chorionic gonadotropin/human menopausal gonadotrophin: A randomised, double-blinded, placebo-controlled clinical study; Andrologia; 2019; vol. 51 (no. 6); e13271

Study details

Country/ies where study was carried out	China
Study type	Randomised controlled trial (RCT)
Study dates	June 2015 and September 2017
Inclusion criteria	Infertile men with idiopathic oligozoospermia with:

	• Sperm concentration consistently below 15 x10⁶/ml • Infertility for ≥1 year • No medical treatment in the previous 6 months • No presence of varicocele • No smoking • No infection of the accessory sex glands • No identifiable cytogenetic abnormalities • Partners with regular ovulation, no anatomic abnormalities, and no abnormal fallopian tube anatomy
Exclusion criteria	Not reported

Patient characteristics	N=316 infertile men with idiopathic oligozoospermia
	
	Human chorionic gonadotrophin (HCG) + human menopausal gonadotrophin (HMG) group (n=158):
	
	• Mean age (SE):
	  ○ Lower-level group (inhibin B level <92 pg/ml): 31.96 (3.62)
	  ○ Medium-level group (92 pg/ml < inhibin B level <316 pg/ml): 33.31 (4.16)
	  ○ Higher-level group (inhibin B level >316 pg/ml): 32.45 (3.81)
	• Severity of semen abnormalities:
	  ○ Non-azoospermia: 158/158 (100%)
	• Fertility diagnosis:
	  ○ Idiopathic oligozoospermia: 158/158 (100%)
	• Hypogonadotropic hypogonadism: 0/158 (0%)*
	
	Placebo group (n=158):
	
	• Mean age (SE):
	  ○ Lower-level group (inhibin B level <92 pg/ml): 33.93 (4.15)
	  ○ Medium-level group (92 pg/ml < inhibin B level <316 pg/ml): 32.34 (3.92)

	○ Higher-level group (inhibin B level >316 pg/ml): 31.96 (2.96) • Severity of semen abnormalities: ○ Non-azoospermia: 158/158 (100%) • Fertility diagnosis: ○ Idiopathic oligozoospermia: 158/158 (100%) • Hypogonadotropic hypogonadism: 0/158 (0%)* * Participants had no known cause of infertility
Intervention(s)/control	HCG + HMG: • HCG, 2000 IU through intramuscular injection twice a week for 3 months • HMG, 150 IU through intramuscular injection 3 times a week for 3 months Placebo: • Intramuscular injections of physiological saline solution for 3 months
Duration of follow-up	1, 2, and 3 months for semen parameters; 3 months only for pregnancy rates
Sources of funding	Not reported
Sample size	N=316: • HCG + HMG group: n=158 • Placebo group: n=158
Other information	Results for semen and hormone parameters outcomes were reported separately for each group according to whether participants had low (inhibin B level <92 pg/ml), medium (92 pg/ml < inhibin B level <316 pg/ml), or high levels (inhibin B level >316 pg/ml) of inhibin B. Means and SEs were reported for these outcomes; data were converted to SDs and combined during data extraction Data also reported for follicle-stimulating hormone (FSH) and inhibin B, however these data not extracted as unlikely to be useful for decision-making

	Semen and hormone parameters data at 1 and 2 months were not included in data extraction due to later data within the short-term period (≤3 months) being reported (at 3 months)

Study arms
Human chorionic gonadotrophin + human menopausal gonadotrophin (N = 158)

Placebo (N = 158)

Outcomes
Pregnancy rates

Outcome	Human chorionic gonadotrophin + human menopausal gonadotrophin, N = 158	Placebo, N = 158
Spontaneous pregnancy rate at 3 months Reported as number of spontaneous pregnancies. Pregnancy was reported by participants by phone and confirmed through date of last normal menstrual period, serum human chorionic gonadotropin level and ultrasound confirmation of clinical pregnancy. Clinical pregnancy was defined as the presence of a gestational sac and foetal heart rate motion on transvaginal ultrasound scanning No of events	n = 41	n = 12

Hormone parameters

Outcome	Human chorionic gonadotrophin + human menopausal gonadotrophin, N = 158	Placebo, N = 158
Testosterone (µg/l) at 3 months SEs converted to SDs and combined during data extraction. HCG + HMG SEs (low, medium, and high level inhibin B): 0.49, 0.58, and 0.59; placebo SEs (low, medium, and high level inhibin B): 0.46, 0.53, and 0.49 Mean (SD) *Higher values are better*	5.1 (5.1)	4.2 (4.6)

Semen parameters

Outcome	Human chorionic gonadotrophin + human menopausal gonadotrophin, N = 158	Placebo, N = 158
Sperm concentration (x10⁶/ml) at 3 months Reported as sperm count (x10⁶/ml). SEs converted to SDs and combined during data extraction. HCG + HMG SEs (low, medium, and high level inhibin B): 2.02, 2.21, and 2.33; placebo SEs (low, medium, and high level inhibin B): 1.89, 1.69, and 2.13 Mean (SD) *Higher values are better*	16.3 (20.84)	11.6 (15.3)
Sperm motility rate (%) at 3 months Reported as rate of forward motile spermatozoa (%). SEs converted to SDs and combined during data extraction. HCG + HMG SEs (low, medium, and high level inhibin B): 2.86, 3.68, and 3.26; placebo SEs (low, medium, and high level inhibin B): 3.26, 3.16, and 3.14 Mean (SD) *Higher values are better*	31.1 (32.1)	24.1 (27.8)
Total motile sperm count (x10⁶) at 3 months Reported as total motile sperm number. SEs converted to SDs and combined during data extraction. HCG + HMG SEs (low, medium, and high level inhibin B): 2.38, 2.85, and 2.52; placebo SEs (low, medium, and high level inhibin B): 2.68, 2.21, and 1.78 Mean (SD) *Higher values are better*	18.8 (25)	13.9 (19.7)

Critical appraisal with the Cochrane RoB 2.0

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Randomisation was done using a random number table, and allocation sequence produced by the statistician delivered to a pharmacist so the reproduction specialist in this study could not know about the results of allocation table. No significant difference between groups at baseline)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Double blind study using placebo)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(No information reported on missing data, but results appear to be available for all participants based on number of participants with pregnancy rate data at 3 months follow-up)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Semen parameters outcomes were assessed using WHO guidelines, and the hormone parameter outcome testosterone measured by enzyme-linked immunosorbent assay. Pregnancy was reported by participants by phone and confirmed through date of last normal menstrual period, serum human chorionic gonadotrophin level and ultrasound confirmation of clinical pregnancy. Clinical pregnancy was defined as the presence of a gestational sac and foetal heart rate motion on transvaginal ultrasound scanning. Details about the blinding of outcome assessors not reported for semen and hormone parameters but study was double-blind)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(No prespecified protocol available)*
Overall bias and Directness	Risk of bias judgement	Low *(Very minor concerns relating to selection of the reported result)*
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	None

Appendix E Forest plots

Forest plots for review question: What is the effectiveness of hormone treatment in male factor fertility problems?

This section includes forest plots only for outcomes that are meta-analysed. Outcomes from single studies are not presented here; the quality assessment for such outcomes is provided in the GRADE profiles in appendix F.

Participants with impaired or reduced semen parameters (non-azoospermia) only

Figure 2: Anti-oestrogen vs placebo, spontaneous pregnancy rate in med term

Study or Subgroup	Anti-oestrogen Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Krause 1992	5	39	3	37	24.7%	1.58 [0.41, 6.15]
Sokol 1988	1	11	4	9	35.4%	0.20 [0.03, 1.52]
Srivannaboon 1992	6	70	5	71	39.9%	1.22 [0.39, 3.81]
Total (95% CI)		**120**		**117**	**100.0%**	**0.95 [0.45, 2.01]**
Total events	12		12			

Heterogeneity: Chi² = 2.97, df = 2 (P = 0.23); I² = 33%

Test for overall effect: Z = 0.14 (P = 0.89)

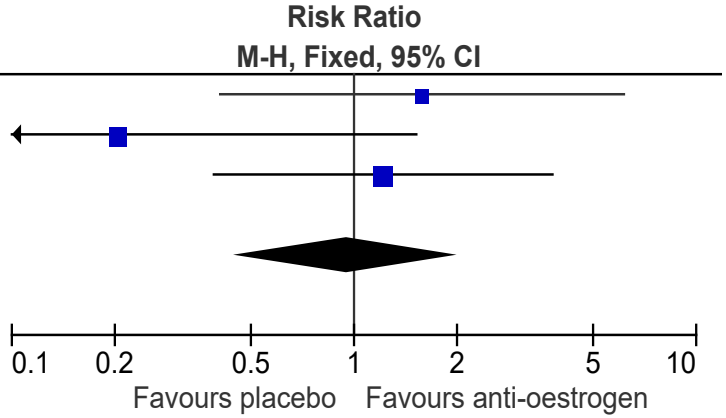


Figure 3: Anti-oestrogen vs placebo, sperm concentration (x10⁶/ml) in med term

Study or Subgroup	Anti-oestrogen Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Haje 2015	10.8	1.8	45	8.2	2.7	29	98.8%	2.60 [1.49, 3.71]
Krause 1992	14.1	14.4	17	10.9	15.7	18	1.2%	3.20 [-6.77, 13.17]
Total (95% CI)			**62**			**47**	**100.0%**	**2.61 [1.50, 3.72]**

Heterogeneity: Chi² = 0.01, df = 1 (P = 0.91); I² = 0%
Test for overall effect: Z = 4.61 (P < 0.00001)

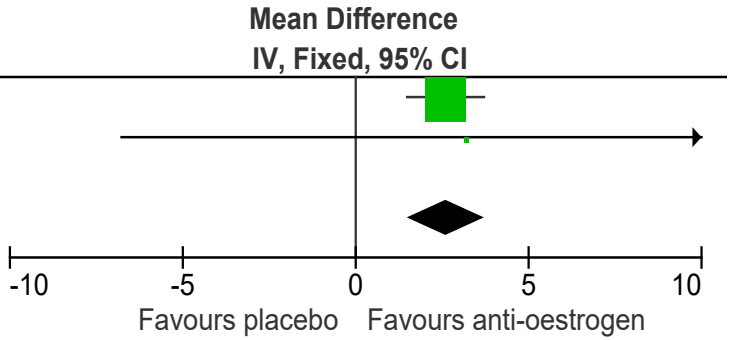


Figure 4: Anti-oestrogen vs placebo, sperm motility rate (%) in med term

Study or Subgroup	Anti-oestrogen Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Haje 2015	22	3.6	45	14.9	5	29	98.2%	7.10 [5.00, 9.20]
Krause 1992	33.8	21.1	17	40	25.4	18	1.8%	-6.20 [-21.64, 9.24]
Total (95% CI)			**62**			**47**	**100.0%**	**6.86 [4.78, 8.94]**

Heterogeneity: Chi² = 2.80, df = 1 (P = 0.09); I² = 64%
Test for overall effect: Z = 6.45 (P < 0.00001)

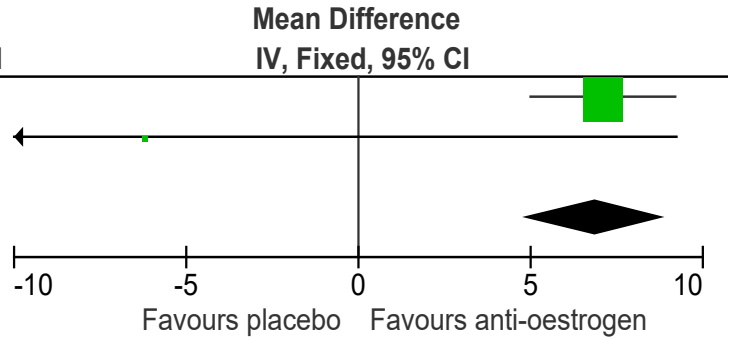


Figure 5: Gonadotrophin therapy vs no treatment, spontaneous pregnancy rate in short term

	Gonadotrophin therapy		No treatment			Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Foresta 2005	0	62	0	50	58.5%	0.00 [-0.03, 0.03]
Foresta 2009	0	57	0	30	41.5%	0.00 [-0.05, 0.05]
Total (95% CI)		**119**		**80**	**100.0%**	**0.00 [-0.03, 0.03]**
Total events	0		0			

Heterogeneity: Chi² = 0.00, df = 1 (P = 1.00); I² = 0%

Test for overall effect: Z = 0.00 (P = 1.00)

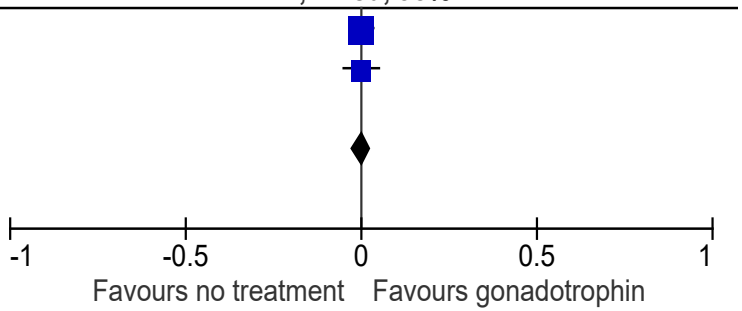


Figure 6: Gonadotrophin therapy vs no treatment, spontaneous pregnancy rate in med term (Non-azoospermic participants only)

	Gonadotrophin therapy		No treatment			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Foresta 2005	6	62	2	50	40.0%	2.42 [0.51, 11.47]
Foresta 2009	4	57	0	30	11.8%	4.81 [0.27, 86.47]
Selice 2011	10	70	2	35	48.2%	2.50 [0.58, 10.80]
Total (95% CI)		**189**		**115**	**100.0%**	**2.74 [1.01, 7.45]**
Total events	20		4			

Heterogeneity: Chi² = 0.19, df = 2 (P = 0.91); I² = 0%

Test for overall effect: Z = 1.98 (P = 0.05)

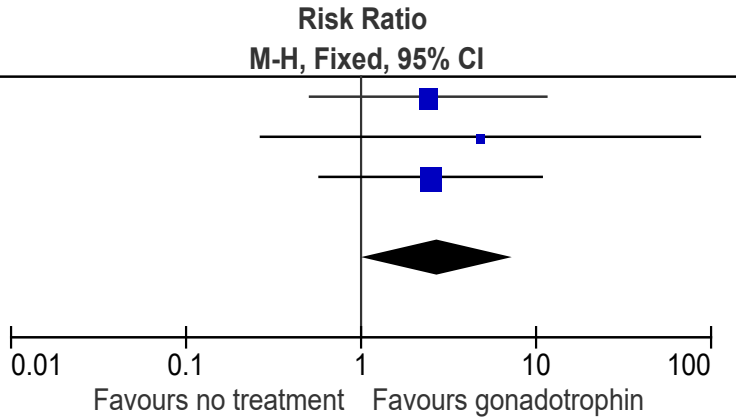


Figure 7: Gonadotrophin therapy vs no treatment, assisted pregnancy rate in short term

Study or Subgroup	Gonadotrophin therapy Events	Total	No treatment Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Baccetti 2004	8	24	4	20	35.6%	1.67 [0.59, 4.73]
Farrag 2015	15	36	9	46	64.4%	2.13 [1.06, 4.30]
Total (95% CI)		**60**		**66**	**100.0%**	**1.96 [1.10, 3.52]**
Total events	23		13			

Heterogeneity: Chi² = 0.15, df = 1 (P = 0.70); I² = 0%

Test for overall effect: Z = 2.28 (P = 0.02)

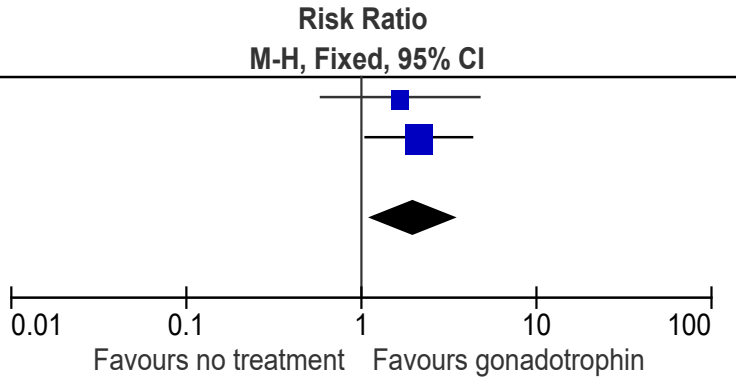


Figure 8: Gonadotrophin therapy vs no treatment, total sperm count (x10⁶) in short term

Study or Subgroup	Gonadotrophin therapy Mean	SD	Total	No treatment Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
6.13.2 Various fertility diagnoses (cryptorchidism; varicocele; post-mumps orchitis; trauma; testicular torsion; idiopathic oligozoospermia)								
Foresta 2009	7.8	2.4	57	4.7	1.9	30	87.9%	3.10 [2.18, 4.02]
Subtotal (95% CI)			**57**			**30**	**87.9%**	**3.10 [2.18, 4.02]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 6.59 (P < 0.00001)								
6.13.3 Idiopathic oligozoospermia								
Foresta 2005	30	7.6	62	17.3	6.6	50	10.8%	12.70 [10.07, 15.33]
Subtotal (95% CI)			**62**			**50**	**10.8%**	**12.70 [10.07, 15.33]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 9.46 (P < 0.00001)								
6.13.4 Oligozoospermia (cause not reported)								
Selice 2011	24	28.1	70	11.7	11.9	35	1.3%	12.30 [4.63, 19.97]
Subtotal (95% CI)			**70**			**35**	**1.3%**	**12.30 [4.63, 19.97]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.14 (P = 0.002)								
Total (95% CI)			**189**			**115**	**100.0%**	**4.25 [3.39, 5.12]**
Heterogeneity: Chi² = 49.81, df = 2 (P < 0.00001); I² = 96%								
Test for overall effect: Z = 9.64 (P < 0.00001)								
Test for subgroup differences: Chi² = 49.81, df = 2 (P < 0.00001), I² = 96.0%								

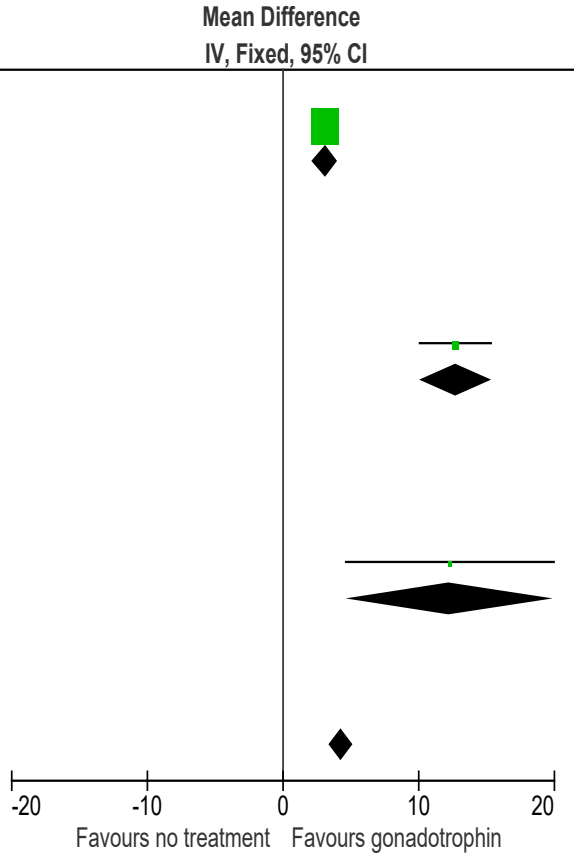


Figure 9: Gonadotrophin therapy vs no treatment, total sperm count (x10⁶) in med term

Study or Subgroup	Gonadotrophin therapy Mean	SD	Total	No treatment Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Foresta 2005	25	6.5	62	17.4	5.3	50	18.9%	7.60 [5.41, 9.79]
Foresta 2009	12.3	3.5	57	5.9	1.5	30	81.1%	6.40 [5.34, 7.46]
Total (95% CI)			**119**			**80**	**100.0%**	**6.63 [5.68, 7.58]**

Heterogeneity: Chi² = 0.94, df = 1 (P = 0.33); I² = 0%

Test for overall effect: Z = 13.67 (P < 0.00001)

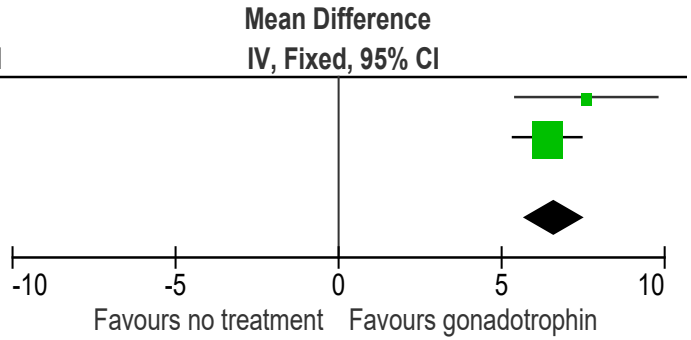


Figure 10: Gonadotrophin therapy vs no treatment, sperm concentration (x10⁶/ml) in short term

Study or Subgroup	Gonadotrophin therapy Mean	SD	Total	No treatment Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
6.16.2 Various fertility diagnoses (cryptorchidism; varicocele; post-mumps orchitis; trauma; testicular torsion; idiopathic oligozoospermia)								
Foresta 2009	3.2	1.6	57	2	0.9	30	92.7%	1.20 [0.67, 1.73]
Subtotal (95% CI)			**57**			**30**	**92.7%**	**1.20 [0.67, 1.73]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.47 (P < 0.00001)								
6.16.3 Idiopathic oligozoospermia								
Foresta 2005	9.7	8.8	62	7.1	3.5	50	4.5%	2.60 [0.20, 5.00]
Subtotal (95% CI)			**62**			**50**	**4.5%**	**2.60 [0.20, 5.00]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.13 (P = 0.03)								
6.16.4 Oligozoospermia (cause not reported)								
Selice 2011	8.6	11.3	70	4.1	4.2	35	2.9%	4.50 [1.51, 7.49]
Subtotal (95% CI)			**70**			**35**	**2.9%**	**4.50 [1.51, 7.49]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.95 (P = 0.003)								
Total (95% CI)			**189**			**115**	**100.0%**	**1.36 [0.85, 1.86]**
Heterogeneity: Chi² = 5.62, df = 2 (P = 0.06); I² = 64%								
Test for overall effect: Z = 5.26 (P < 0.00001)								
Test for subgroup differences: Chi² = 5.62, df = 2 (P = 0.06), I² = 64.4%								

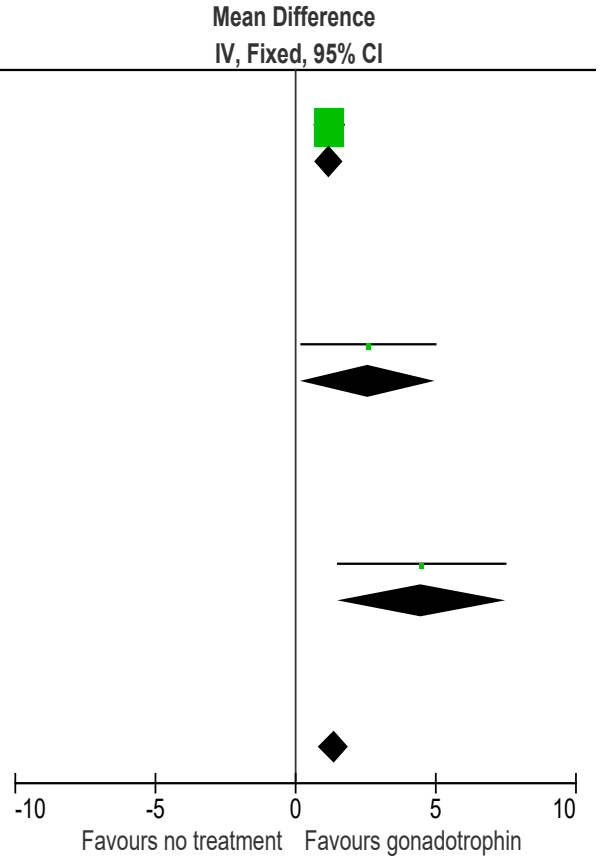


Figure 11: Gonadotrophin therapy vs no treatment, sperm concentration (x10⁶/ml) in med term - Non-azoospermic participants only

Study or Subgroup	Gonadotrophin therapy Mean	SD	Total	No treatment Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Foresta 2005	12	4.2	62	8.1	3.6	50	19.7%	3.90 [2.45, 5.35]
Foresta 2009	6.6	2.3	57	2.3	1.1	30	80.3%	4.30 [3.58, 5.02]
Total (95% CI)			**119**			**80**	**100.0%**	**4.22 [3.58, 4.86]**

Heterogeneity: Chi² = 0.24, df = 1 (P = 0.63); I² = 0%
Test for overall effect: Z = 12.91 (P < 0.00001)

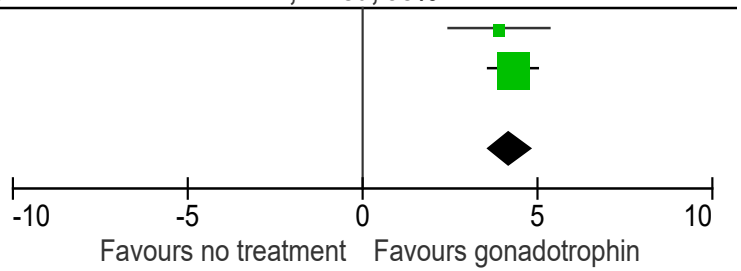


Figure 12: Gonadotrophin therapy vs no treatment, sperm motility rate (%) in short term

Study or Subgroup	Gonadotrophin therapy Mean	SD	Total	No treatment Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Foresta 2009	18.3	8.6	57	16.1	7.1	30	80.9%	2.20 [-1.18, 5.58]
Selice 2011	25.5	17.7	70	21.6	16.9	35	19.1%	3.90 [-3.07, 10.87]
Total (95% CI)			**127**			**65**	**100.0%**	**2.52 [-0.52, 5.57]**

Heterogeneity: Chi² = 0.19, df = 1 (P = 0.67); I² = 0%
Test for overall effect: Z = 1.63 (P = 0.10)

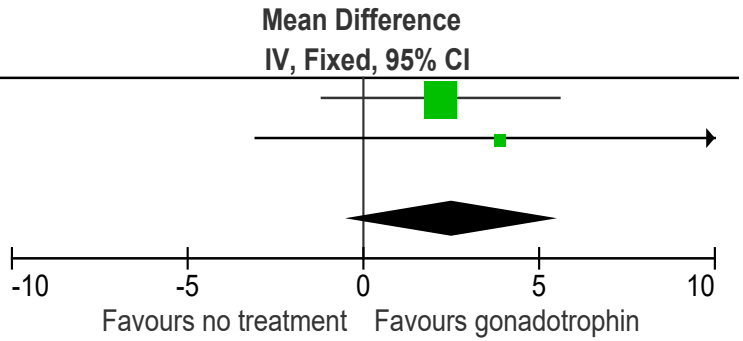


Figure 13: Gonadotrophin therapy vs placebo, spontaneous pregnancy rate in med term

Study or Subgroup	Gonadotrophin therapy Events	Total	Placebo Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Kamischke 1998	3	31	0	30	44.7%	7.66 [0.77, 76.54]
Paradisi 2006	4	15	0	15	55.3%	9.31 [1.17, 73.75]
Total (95% CI)		**46**		**45**	**100.0%**	**8.53 [1.83, 39.76]**
Total events	7		0			

Heterogeneity: Chi² = 0.02, df = 1 (P = 0.90); I² = 0%

Test for overall effect: Z = 2.73 (P = 0.006)

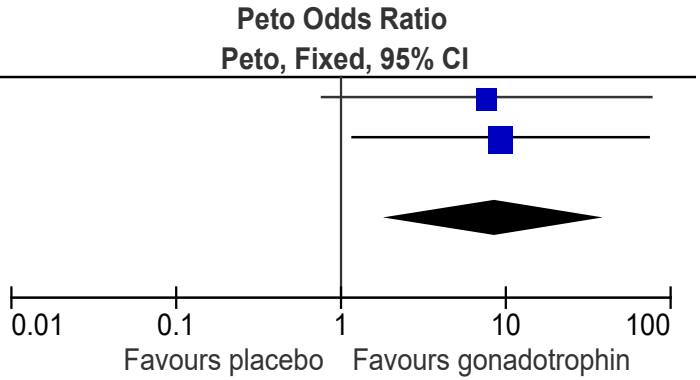


Figure 14: Gonadotrophin therapy vs placebo, sperm concentration (x10⁶/ml) in short term - Non-azoospermic participants only

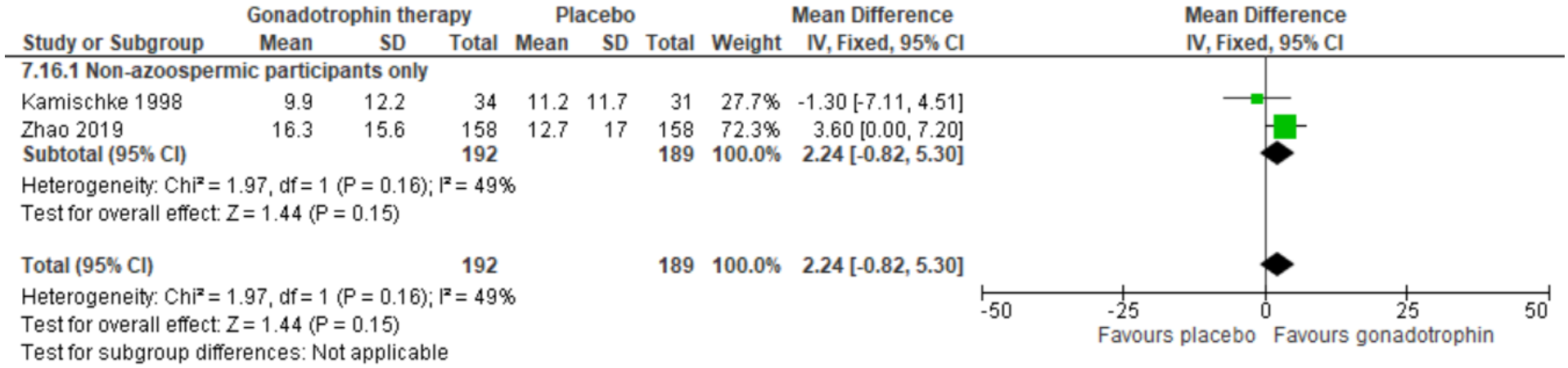


Figure 15: Gonadotrophin therapy vs placebo, sperm concentration (x10⁶/ml) in med term - Non-azoospermic participants only

Study or Subgroup	Gonadotrophin therapy Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
7.17.1 Non-azoospermic participants, mean participant age <45								
Kamischke 1998	11.1	12.2	34	10.3	10.6	31	54.6%	0.80 [-4.74, 6.34]
Subtotal (95% CI)			**34**			**31**	**54.6%**	**0.80 [-4.74, 6.34]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.28 (P = 0.78)								
7.17.2 Non-azoospermic participants, participant age not reported								
Paradisi 2006	16.1	11.1	15	7.5	4.6	15	45.4%	8.60 [2.52, 14.68]
Subtotal (95% CI)			**15**			**15**	**45.4%**	**8.60 [2.52, 14.68]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.77 (P = 0.006)								
Total (95% CI)			**49**			**46**	**100.0%**	**4.34 [0.24, 8.44]**
Heterogeneity: Chi² = 3.45, df = 1 (P = 0.06); I² = 71%								
Test for overall effect: Z = 2.08 (P = 0.04)								
Test for subgroup differences: Chi² = 3.45, df = 1 (P = 0.06), I² = 71.0%								

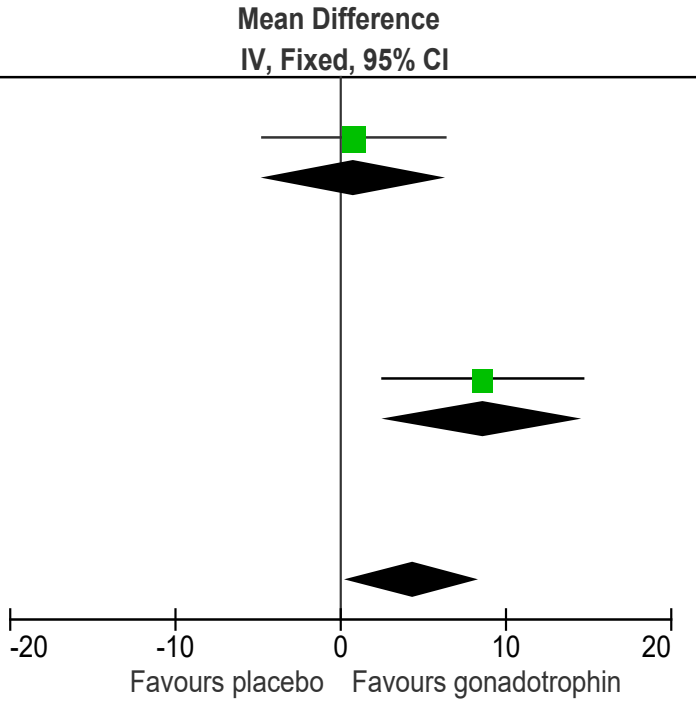


Figure 16: Gonadotrophin therapy vs placebo, sperm motility rate (%) in short term - Non-azoospermic participants only

Study or Subgroup	Gonadotrophin therapy Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Kamischke 1998	30.5	16.3	34	35.4	16.7	31	40.4%	-4.90 [-12.94, 3.14]
Zhao 2019	31.1	32.1	158	24.1	27.8	158	59.6%	7.00 [0.38, 13.62]
Total (95% CI)			**192**			**189**	**100.0%**	**2.19 [-2.92, 7.30]**
Heterogeneity: Chi² = 5.02, df = 1 (P = 0.03); I² = 80%								
Test for overall effect: Z = 0.84 (P = 0.40)								

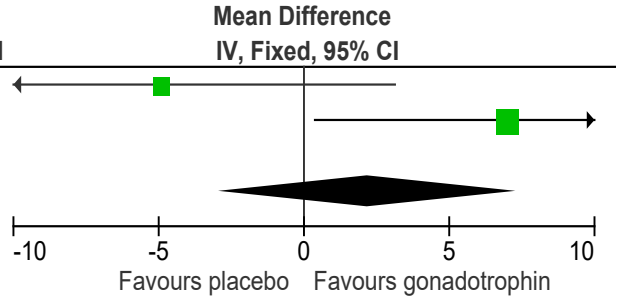


Figure 17: Gonadotrophin therapy vs placebo, sperm motility rate (%) in med term - Non-azoospermic participants only

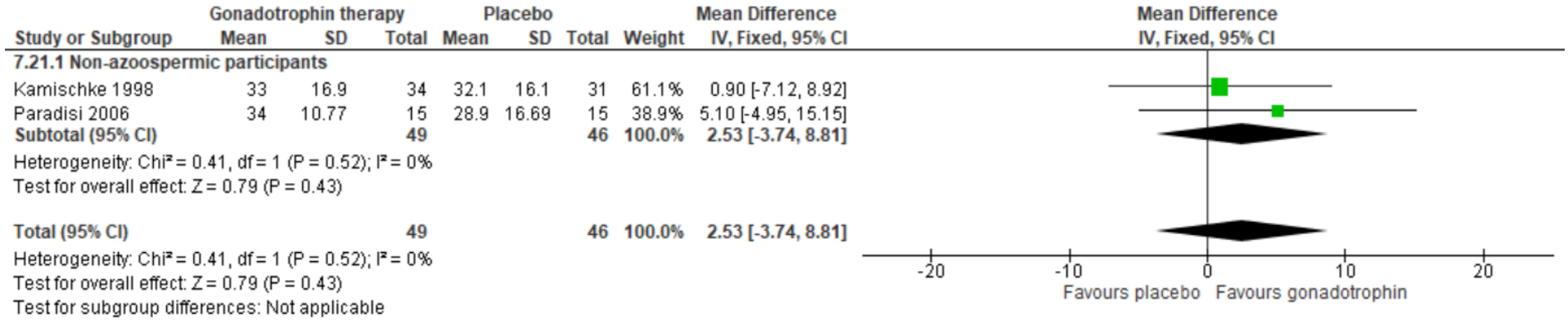


Figure 18: Androgen vs placebo, pregnancy rate in short term – Non-azoospermic participants only

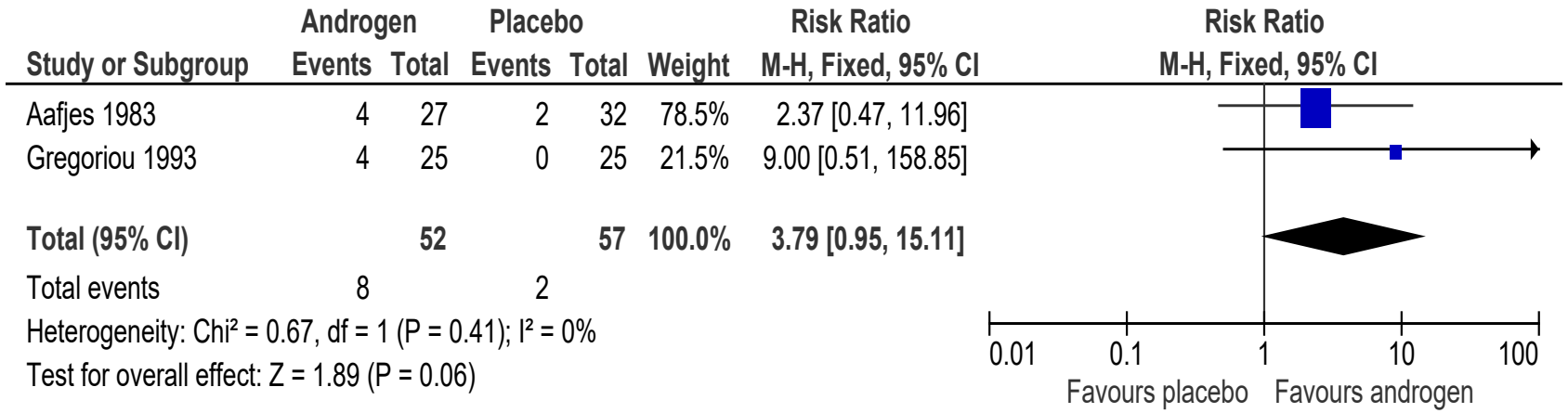


Figure 19: Androgen vs placebo, total testosterone (ng/ml) in short term

Study or Subgroup	Androgen Mean	Androgen SD	Androgen Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Gregoriou 1993	7.95	2.86	25	5.95	4.53	25	31.8%	2.00 [-0.10, 4.10]
Pusch 1989	6.65	3.57	29	4.48	1.63	28	68.2%	2.17 [0.74, 3.60]
Total (95% CI)			**54**			**53**	**100.0%**	**2.12 [0.93, 3.30]**

Heterogeneity: Chi² = 0.02, df = 1 (P = 0.90); I² = 0%
Test for overall effect: Z = 3.50 (P = 0.0005)

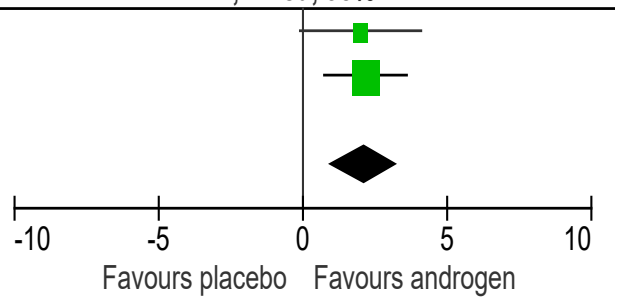


Figure 20: Androgen vs placebo, total oestradiol (pg/ml) in short term

Study or Subgroup	Androgen Mean	Androgen SD	Androgen Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Gregoriou 1993	28.15	9.55	25	29.1	7.15	25	71.6%	-0.95 [-5.63, 3.73]
Pusch 1989	26.19	8.2	29	29.02	18.38	28	28.4%	-2.83 [-10.26, 4.60]
Total (95% CI)			**54**			**53**	**100.0%**	**-1.48 [-5.44, 2.48]**

Heterogeneity: Chi² = 0.18, df = 1 (P = 0.67); I² = 0%
Test for overall effect: Z = 0.73 (P = 0.46)

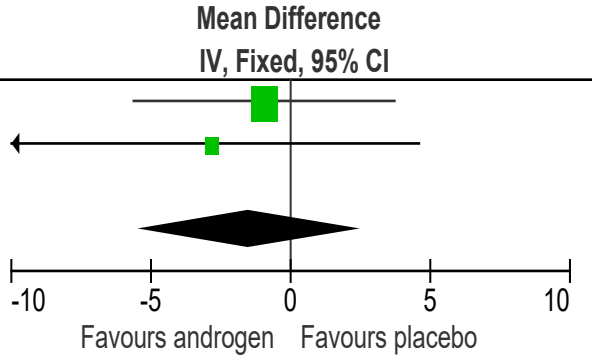


Figure 21: Androgen vs placebo, sperm concentration (x10⁶/ml) in short term

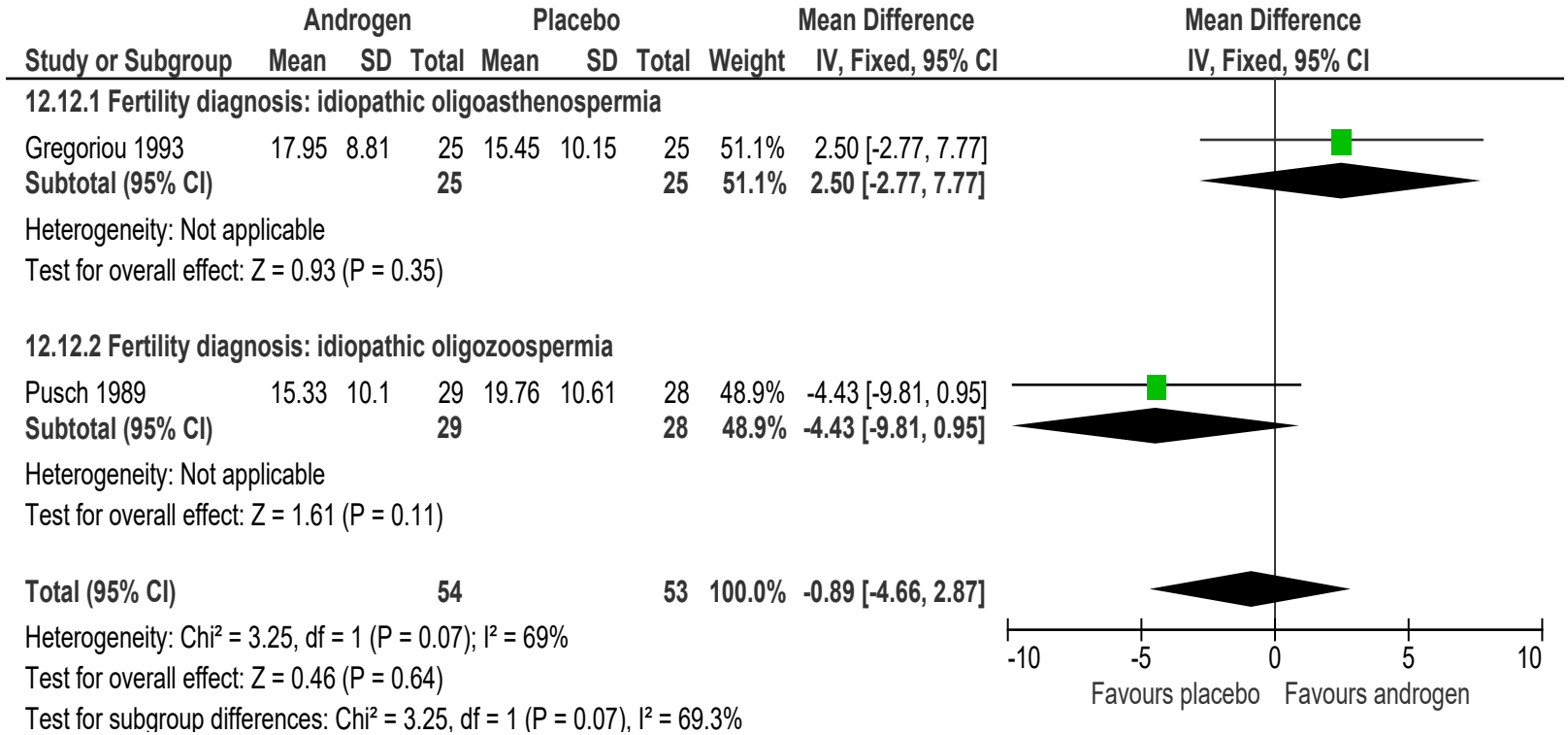
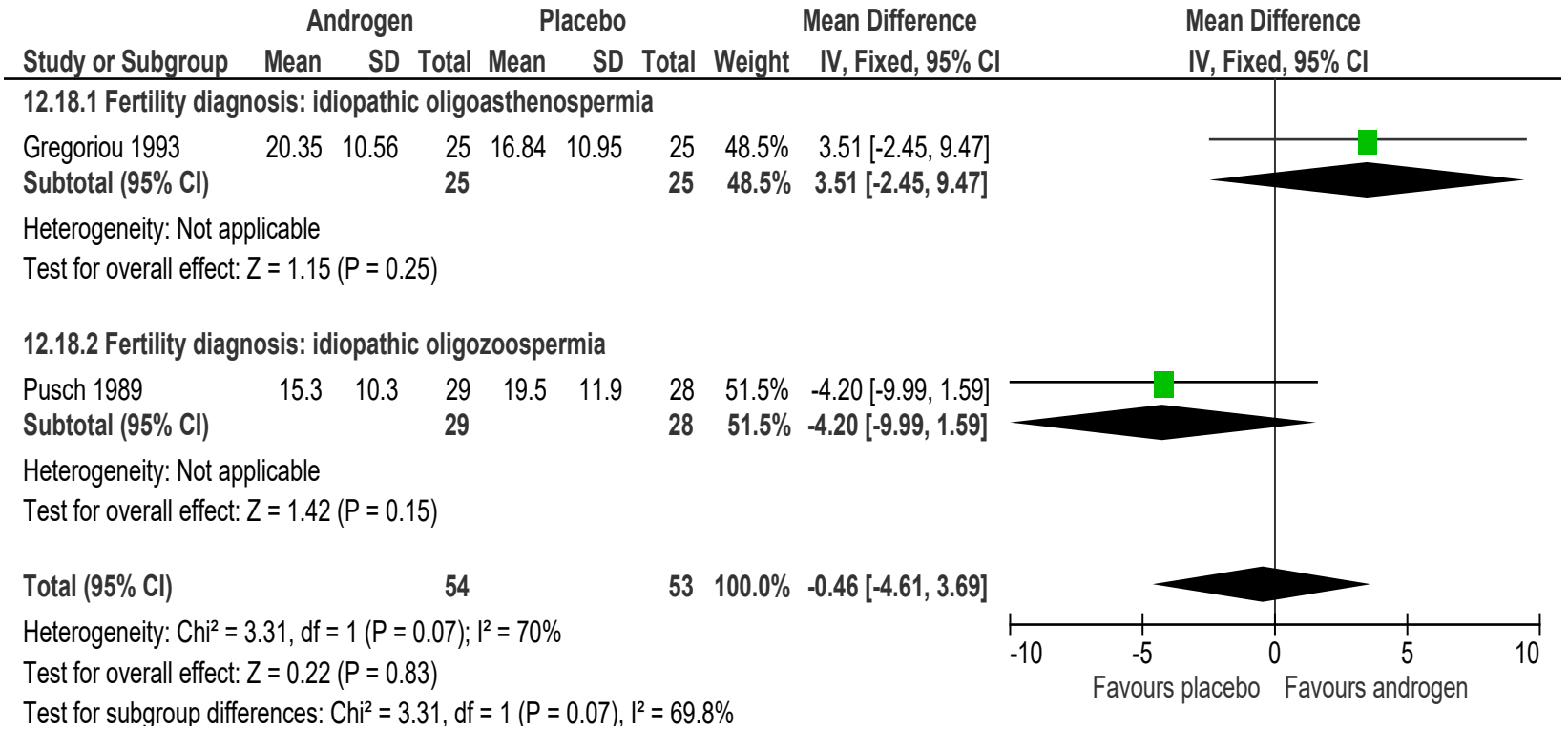


Figure 22: Androgen vs placebo, sperm motility rate (%) in short term



Appendix F GRADE tables

GRADE tables for review question: What is the effectiveness of hormone treatment in male factor fertility problems?

Participants with semen abnormalities (non-azoospermia) only

Table 5: Evidence profile for comparison between anti-oestrogen and no treatment: participants with semen abnormalities (non-azoospermia) only

Quality assessment							No of participants		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Anti-oestrogen	No treatment	Relative (95% CI)	Absolute		
Pregnancy rate in short term (Pregnancy not defined)												
1 (Cakan 2009)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	11/103 (10.7%)	0/25 (0%)	POR 3.85 (0.82 to 18.21)	-	LOW	CRITICAL
Pregnancy rate in med term (Pregnancy not defined)												
1 (Micic 1985)	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	7/56 (12.5%)	0/45 (0%)	POR 6.81 (1.46 to 31.69)	-	LOW	CRITICAL
Testosterone (ng/dl) in short term (Better indicated by higher values)												
1 (Cakan 2009)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	103	25	-	MD 88.2 higher (79.08 to 97.32 higher)	MODERATE	IMPORTANT
Oestradiol (pg/ml) in short term (Better indicated by lower values)												
1 (Cakan 2009)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	103	25	-	MD 16.9 higher (13.59 to 20.21 higher)	MODERATE	IMPORTANT
Sperm concentration ($x10^6$/ml) in med term (Better indicated by higher values)												
1 (Micic 1985)	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	56	45	-	MD 7.7 higher (6.85 to 8.55 higher)	LOW	IMPORTANT
Sperm motility rate (%) in short term (Better indicated by higher values)												
1 (Cakan 2009)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	103	25	-	MD 7.8 higher (0.85 to 14.75 higher)	LOW	IMPORTANT
Sperm motility rate (%) in med term (Better indicated by higher values)												
1 (Micic 1985)	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	56	45	-	MD 11.9 higher (8.04 to 15.76 higher)	LOW	IMPORTANT

CI: confidence intervals; MD: mean difference; MID: minimally important difference; POR: peto odds ratio; RoB: risk of bias; SD: standard deviation

[1] Serious risk of bias in the evidence contributing to the outcomes as per RoB 2

[2] 95% CI crosses 1 MID

[3] Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2

[4] 95% CI crosses 1 MID (±0.5x control group SD, for sperm motility rate in short term = 7.55)

Table 6: Evidence profile for comparison between anti-oestrogen and placebo: participants with semen abnormalities (non-azoospermia) only

Quality assessment							No of participants		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Anti-oestrogen	Placebo	Relative (95% CI)	Absolute		
Assisted pregnancy rate in med term												
1 (Haje 2015)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	22/45 (48.9%)	6/29 (20.7%)	RR 2.36 (1.09 to 5.12)	281 more per 1000 (from 19 more to 852 more)	LOW	CRITICAL
Spontaneous pregnancy rate in med term												
3[a]	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	12/120 (10%)	12/117 (10.3%)	RR 0.95 (0.45 to 2.01)	5 fewer per 1000 (from 56 fewer to 104 more)	VERY LOW	CRITICAL
Change in testosterone from baseline (ng/dl) in med term (Better indicated by higher values)												
1 (Sokol 1988)	randomised trials	very serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	11	9	-	MD 464.53 higher (275.28 to 653.78 higher)	LOW	IMPORTANT
Testosterone (µg/l) in short term (Better indicated by higher values)												
1 (Krause 1992)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[5]	none	39	37	-	MD 2.3 higher (0.92 to 3.68 higher)	LOW	IMPORTANT
Testosterone (µg/l) in med term (Better indicated by higher values)												
1 (Krause 1992)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[5]	none	17	18	-	MD 0.1 lower (2.13 lower to 1.93 higher)	LOW	IMPORTANT
Change in oestradiol from baseline (pg/ml) in med term (Better indicated by lower values)												
1 (Sokol 1988)	randomised trials	very serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	11	9	-	MD 22.66 higher (9.41 to 35.91 higher)	LOW	IMPORTANT
Change in total sperm count from baseline ($x10^6$) in med term (Better indicated by higher values)												
1 (Sokol 1988)	randomised trials	very serious[4]	no serious inconsistency	no serious indirectness	very serious[6]	none	11	9	-	MD 11.4 higher (63.08 lower to 85.88 higher)	VERY LOW	IMPORTANT
Sperm concentration ($x10^6$/ml) in short term (Better indicated by higher values)												
1 (Krause 1992)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[5]	none	39	37	-	MD 2.1 higher (3.05 lower to 7.25 higher)	LOW	IMPORTANT
Sperm concentration ($x10^6$/ml) in med term (Better indicated by higher values)												
2[b]	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	62	47	-	MD 2.61 higher (1.5 to 3.72 higher)	MODERATE	IMPORTANT
Change in sperm motility rate (%) from baseline in med term (Better indicated by higher values)												
1 (Sokol 1988)	randomised trials	very serious[4]	no serious inconsistency	no serious indirectness	very serious[6]	none	10	9	-	MD 7.26 lower (18.7 lower to 4.18 higher)	VERY LOW	IMPORTANT
Sperm motility rate (%) in short term (Better indicated by higher values)												
1 (Krause 1992)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[5]	none	39	37	-	MD 3.8 higher (5.85 lower to 13.45 higher)	LOW	IMPORTANT
Sperm motility rate (%) in med term (Better indicated by higher values)												

2[b]	randomised trials	serious[1]	serious[7]	no serious indirectness	no serious imprecision	none	62	47	-	MD 6.86 higher (4.78 to 8.94 higher)	VERY LOW	IMPORTANT

CI: confidence intervals; MD: mean difference; MID: minimally important difference; RoB: risk of bias; RR: risk ratio; SD: standard deviation
[a] Krause 1992, Sokol 1988, Srivannaboon 1992
[b] Haje 2015, Krause 1992
[1] Serious risk of bias in the evidence contributing to the outcomes as per RoB 2
[2] 95% CI crosses 1 MID
[3] 95% CI crosses 2 MIDs
[4] Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2
[5] 95% CI crosses 1 MID (±0.5x control group SD, for testosterone in short term = 1; for testosterone in med term = 1.1; for sperm concentration in short term = 4.4; for sperm motility in short term = 10.5; for sperm motility in med term = 7.6)
[6] 95% CI crosses 2 MIDs (±0.5x control group SD, for change in total sperm count from baseline = 21.75; for change in sperm motility rate from baseline = 4.6)
[7] Serious heterogeneity (>50%) unexplained by subgroup analysis

Table 7: Evidence profile for comparison between anti-oestrogen + androgen and placebo: participants with semen abnormalities (non-azoospermia) only

Quality assessment							No of participants		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Anti-oestrogen + androgen	Placebo	Relative (95% CI)	Absolute		
Spontaneous pregnancy rate in short term												
1 (Adamopoulos 2003)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	4/88 (4.5%)	9/87 (10.3%)	RR 0.44 (0.14 to 1.37)	58 fewer per 1000 (from 89 fewer to 38 more)	VERY LOW	CRITICAL
Spontaneous pregnancy rate in med term												
1 (Adamopoulos 2003)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	36/88 (40.9%)	11/87 (12.6%)	RR 3.24 (1.76 to 5.94)	283 more per 1000 (from 96 more to 625 more)	MODERATE	CRITICAL
Sperm motility rate (%) in short term (Better indicated by higher values)												
1 (Adamopoulos 2003)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	88	87	-	MD 5.6 higher (0.32 to 10.88 higher)	LOW	IMPORTANT
Sperm motility rate (%) in med term (Better indicated by higher values)												
1 (Adamopoulos 2003)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	88	87	-	MD 10.9 higher (6.68 to 15.12 higher)	LOW	IMPORTANT

CI: confidence intervals; MD: mean difference; MID: minimally important difference; RoB: risk of bias; RR: risk ratio; SD: standard deviation
[1] Serious risk of bias in the evidence contributing to the outcomes as per RoB 2
[2] 95% CI crosses 2 MIDs
[3] 95% CI crosses 1 MID (±0.5x control group SD, for sperm motility rate in short term = 9.95; for sperm motility rate in med term = 7.65

Table 8: Evidence profile for comparison between aromatase inhibitor and no treatment: participants with semen abnormalities (non-azoospermia) only

Quality assessment							No of participants		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aromatase inhibitor	No treatment	Relative (95% CI)	Absolute		
Pregnancy rate in short term (Number of induced pregnancies/ gravidities)												
1 (Maier 1988)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	3/20 (15%)	3/20 (15%)	RR 1 (0.23 to 4.37)	0 fewer per 1000 (from 116 fewer to 506 more)	VERY LOW	CRITICAL
Oestradiol (pg/ml) in short term (Better indicated by lower values)												
1 (Maier 1988)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	20	20	-	MD 9.6 lower (16.39 to 2.81 lower)	VERY LOW	IMPORTANT

CI: confidence intervals; MD: mean difference; MID: minimally important difference; RoB: risk of bias; RR: risk ratio; SD: standard deviation
[1] Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2
[2] 95% CI crosses 2 MIDs
[3] 95% CI crosses 1 MID (±0.5x control group SD, for oestradiol = 7.1)

Table 9: Evidence profile for comparison between gonadotrophin therapy and no treatment: participants with semen abnormalities (non-azoospermia) only

Quality assessment							No of participants		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Gonadotrophin therapy	No treatment	Relative (95% CI)	Absolute		
Spontaneous pregnancy rate in short term												
2[a]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	0/119 (0%)	0/80 (0%)	RD 0.00 (-0.03 to 0.03)	-	VERY LOW	CRITICAL
Spontaneous pregnancy rate in med term - Non-azoospermic participants only												
3[b]	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	20/189 (10.5%)	4/115 (3.5%)	RR 2.74 (1.01 to 7.45)	61 more per 1000 (from 0 more to 224 more)	LOW	CRITICAL
Assisted pregnancy rate in short term												
2[c]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[4]	none	23/60 (38.3%)	13/66 (19.7%)	RR 1.96 (1.1 to 3.52)	189 more per 1000 (from 20 more to 496 more)	VERY LOW	CRITICAL
Pregnancy rate (per IUI cycle) in long term												
1 (Matorras 1997)	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[5]	none	26/209 (12.4%)	29/288 (10.1%)	RR 1.24 (0.75 to 2.03)	24 more per 1000 (from 25 fewer to 104 more)	VERY LOW	CRITICAL
Pregnancy rate (per woman) in long term												
1 (Matorras 1997)	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[4]	none	36/68 (52.9%)	31/80 (38.8%)	RR 1.37 (0.96 to 1.95)	143 more per 1000 (from 16 fewer to 368 more)	VERY LOW	CRITICAL

Assisted pregnancy rate (per IUI cycle) in long term												
1 (Matorras 1997)	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[4]	none	26/193 (13.5%)	29/288 (10.1%)	RR 1.34 (0.81 to 2.2)	34 more per 1000 (from 19 fewer to 121 more)	VERY LOW	CRITICAL
Assisted pregnancy rate (per woman) in long term												
1 (Matorras 1997)	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[4]	none	26/58 (44.8%)	29/78 (37.2%)	RR 1.21 (0.8 to 1.81)	78 more per 1000 (from 74 fewer to 301 more)	VERY LOW	CRITICAL
Testosterone (nmol/l) in short term (Better indicated by higher values)												
1 (Selice 2011)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	70	35	-	MD 0.2 lower (2.58 lower to 2.18 higher)	MODERATE	IMPORTANT
Oestradiol (pmol/l) in short term (Better indicated by lower values)												
1 (Selice 2011)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	70	35	-	MD 0.9 higher (18.03 lower to 19.83 higher)	MODERATE	IMPORTANT
Total sperm count ($x10^6$) in short term (Better indicated by higher values)												
3[b]	randomised trials	serious[1]	very serious[6]	no serious indirectness	no serious imprecision	none	189	115	-	MD 4.25 higher (3.39 to 5.12 higher)	VERY LOW	IMPORTANT
Total sperm count ($x10^6$) in short term - Various fertility diagnoses (cryptorchidism; varicocele; post-mumps orchitis; trauma; testicular torsion; idiopathic oligozoospermia) (Better indicated by higher values)												
1 (Foresta 2009)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	57	30	-	MD 3.1 higher (2.18 to 4.02 higher)	MODERATE	IMPORTANT
Total sperm count ($x10^6$) in short term - Idiopathic oligozoospermia (Better indicated by higher values)												
1 (Foresta 2005)	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	62	50	-	MD 12.7 higher (10.07 to 15.33 higher)	LOW	IMPORTANT
Total sperm count ($x10^6$) in short term - Oligozoospermia (cause not reported) (Better indicated by higher values)												
1 (Selice 2011)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[7]	none	70	35	-	MD 12.3 higher (4.63 to 19.97 higher)	LOW	IMPORTANT
Total sperm count ($x10^6$) in med term (Better indicated by higher values)												
2[a]	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	119	80	-	MD 6.63 higher (5.68 to 7.58 higher)	MODERATE	IMPORTANT
Sperm concentration ($x10^6$/ml) in short term (Better indicated by higher values)												
3[b]	randomised trials	serious[1]	serious[8]	no serious indirectness	very serious[9]	none	189	115	-	MD 1.36 higher (0.85 to 1.86 higher)	VERY LOW	IMPORTANT
Sperm concentration ($x10^6$/ml) in short term - Various fertility diagnoses (cryptorchidism; varicocele; post-mumps orchitis; trauma; testicular torsion; idiopathic oligozoospermia) (Better indicated by higher values)												
1 (Foresta 2009)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	57	30	-	MD 1.2 higher (0.67 to 1.73 higher)	MODERATE	IMPORTANT
Sperm concentration ($x10^6$/ml) in short term - Idiopathic oligozoospermia (Better indicated by higher values)												
1 (Foresta 2005)	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[7]	none	62	50	-	MD 2.6 higher (0.2 to 5 higher)	VERY LOW	IMPORTANT
Sperm concentration ($x10^6$/ml) in short term - Oligozoospermia (cause not reported) (Better indicated by higher values)												

1 (Selice 2011)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[7]	none	70	35	-	MD 4.5 higher (1.51 to 7.49 higher)	LOW	IMPORTANT
Sperm concentration (x10^6/ml) in med term - Non-azoospermic participants only (Better indicated by higher values)												
2[a]	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	119	80	-	MD 4.22 higher (3.58 to 4.86 higher)	MODERATE	IMPORTANT
Total motile sperm count (x10^6) in short term (Better indicated by higher values)												
1 (Selice 2011)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[7]	none	70	35	-	MD 5.3 higher (1.84 to 8.76 higher)	LOW	IMPORTANT
Sperm motility rate (%) in short term (Better indicated by higher values)												
2[d]	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[7]	none	127	65	-	MD 2.52 higher (0.52 lower to 5.57 higher)	LOW	IMPORTANT
Sperm motility rate (%) in med term - Non-azoospermic participants only (Better indicated by higher values)												
1 (Foresta 2009)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[7]	none	57	30	-	MD 8.7 higher (4.25 to 13.15 higher)	LOW	IMPORTANT
Miscarriage rate in short term												
1 (Farrag 2015)	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[5]	none	1/36 (2.8%)	4/46 (8.7%)	RR 0.32 (0.03 to 2.43)	59 fewer per 1000 (from 84 fewer to 124 more)	VERY LOW	IMPORTANT

CI: confidence intervals; IUI: intrauterine insemination; MD: mean difference; MID: minimally important difference; POR: peto odds ratio; RD: risk difference; RoB: risk of bias; RR: risk ratio; SD: standard deviation

[a] Foresta 2005, Foresta 2009

[b] Foresta 2005, Foresta 2009, Selice 2011

[c] Baccetti 2004, Farrag 2015

[d] Foresta 2009, Selice 2011

[1] Serious risk of bias in the evidence contributing to the outcomes as per RoB 2

[2] Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2

[3] Sample size <200

[4] 95% CI crosses 1 MID

[5] 95% CI crosses 2 MIDs

[6] Very serious heterogeneity (>80%), explained by subgroup analysis (see rows beneath)

[7] 95% CI crosses 1 MID (±0.5x control group SD, for total sperm count in short term (fertility diagnosis not reported) = 5.95; sperm concentration in short term (idiopathic infertility) = 1.95; sperm concentation in short term (fertility diagnosis not reported) = 2.1; total motile sperm count in short term = 3; sperm motility rate in short term = 4.49; sperm motility rate in med term (non-azoospermic participants) = 4.55;)

[8] Serious heterogeneity (>50%), explained by subgroup analysis (see rows beneath)

[9] 95% CI crosses 2 MIDs (±0.5x control group SD, for sperm concentration in short term = 0.56)

Table 10: Evidence profile for comparison between gonadotrophin therapy and placebo: participants with semen abnormalities (non-azoospermia) only

Quality assessment							No of participants		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Gonadotrophin therapy	Placebo	Relative (95% CI)	Absolute		
Live birth rate in med term												

1 (Paradisi 2006)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	4/15 (26.7%)	0/15 (0%)	POR 9.31 (1.17 to 73.75)	-	VERY LOW	CRITICAL
Pregnancy rate in med term (Pregnancy reported as induced pregnancies (spontaneous or assisted))												
1 (Kamischke 1998)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	reporting bias[3]	8/31 (25.8%)	10/30 (33.3%)	RR 0.77 (0.35 to 1.69)	77 fewer per 1000 (from 217 fewer to 230 more)	LOW	CRITICAL
Spontaneous pregnancy rate in short term												
1 (Zhao 2019)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	41/158 (25.9%)	12/158 (7.6%)	RR 3.42 (1.87 to 6.25)	184 more per 1000 (from 66 more to 399 more)	HIGH	CRITICAL
Spontaneous pregnancy rate in med term												
2[a]	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[3]	7/46 (15.2%)	0/45 (0%)	POR 8.53 (1.83 to 39.76)	-	LOW	CRITICAL
Testosterone (µg/l) in short term (Better indicated by higher values)												
1 (Zhao 2019)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	158	158	-	MD 0.9 higher (0.17 lower to 1.97 higher)	HIGH	IMPORTANT
Testosterone (µg/l) in med term (Better indicated by higher values)												
1 (Paradisi 2006)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[5]	reporting bias[3]	15	15	-	MD 0.2 lower (1.35 lower to 0.95 higher)	VERY LOW	IMPORTANT
Testosterone (nmol/l) in short term - Non-azoospermic participants only (Better indicated by higher values)												
1 (Kamischke 1998)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[6]	reporting bias[3]	34	31	-	MD 3.4 higher (1.02 to 5.78 higher)	LOW	IMPORTANT
Testosterone (nmol/l) in med term – Non-azoospermic participants only (Better indicated by higher values)												
1 (Kamischke 1998)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[6]	reporting bias[3]	34	31	-	MD 2.6 higher (0.51 to 4.69 higher)	LOW	IMPORTANT
Free testosterone (µg/l) in med term (Better indicated by higher values)												
1 (Paradisi 2006)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[5]	reporting bias[3]	15	15	-	MD 0.1 higher (3.2 lower to 3.4 higher)	VERY LOW	IMPORTANT
Oestradiol (pmol/l) in short term (Better indicated by lower values)												
1 (Kamischke 1998)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[6]	reporting bias[3]	34	31	-	MD 4.6 higher (2.48 lower to 11.68 higher)	LOW	IMPORTANT
Oestradiol (pmol/l) in med term (Better indicated by lower values)												
1 (Kamischke 1998)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[6]	reporting bias[3]	34	31	-	MD 6.3 higher (0.07 to 12.53 higher)	LOW	IMPORTANT
Sperm concentration (x10^6/ml) in short term - Non-azoospermic participants only (Better indicated by higher values)												
2[b]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	192	189	-	MD 2.24 higher (0.82 lower to 5.3 higher)	HIGH	IMPORTANT
Sperm concentration (x10^6/ml) in med term – Non-azoospermic participants only (Better indicated by higher values)												

2[a]	randomised trials	no serious risk of bias	serious[7]	no serious indirectness	serious[6]	none	49	46	-	MD 4.34 higher (0.24 higher to 8.44 higher)	LOW	IMPORTANT
Sperm concentration (x10^6/ml) in med term – Non-azoospermic participants only, mean participant age <45 (Better indicated by higher values)												
1 (Kamischke 1998)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[6]	none	34	31	-	MD 0.80 higher (4.74 lower to 6.34 higher)	MODERATE	IMPORTANT
Sperm concentration (x10^6/ml) in med term - Non-azoospermic participants only, participant age not reported (Better indicated by higher values)												
1 (Paradisi 2006)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[3]	15	15	-	MD 8.6 higher (2.52 to 14.68 higher)	LOW	IMPORTANT
Total sperm count (x10^6) in med term (Better indicated by higher values)												
1 (Paradisi 2006)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[6]	reporting bias[3]	15	15	-	MD 22.6 higher (4.83 to 40.37 higher)	VERY LOW	IMPORTANT
Total motile sperm count (x10^6) in short term - Non-azoospermic participants only (Better indicated by higher values)												
1 (Zhao 2019)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[6]	none	158	158	-	MD 4.9 higher (0.06 lower to 9.86 higher)	MODERATE	IMPORTANT
Sperm motility rate (%) in short term - Non-azoospermic participants only (Better indicated by higher values)												
2[b]	randomised trials	no serious risk of bias	very serious[8]	no serious indirectness	no serious imprecision	none	192	189	-	MD 2.19 higher (2.92 lower to 7.30 higher)	LOW	IMPORTANT
Sperm motility rate (%) in med term - Non-azoospermic participants only (Better indicated by higher values)												
2[a]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[6]	reporting bias[3]	49	46	-	MD 2.53 higher (3.74 lower to 8.81 higher)	LOW	IMPORTANT

CI: confidence intervals; MD: mean difference; MID: minimally important difference; POR: peto odds ratio; RoB: risk of bias; RR: risk ratio; SD: standard deviation

[a] Kamischke 1998, Paradisi 2006

[b] Kamischke 1998, Zhao 2019

[1] Serious risk of bias in the evidence contributing to the outcomes as per RoB 2

[2] Number of events <150

[3] Publication bias suspected due to majority of studies being industry funded

[4] 95% CI crosses 2 MIDs

[5] 95% CI crosses 2 MIDs (±0.5x control group SD, for testosterone (µg/l) in med term = 0.75; free testosterone (µg/l) in med term = 2.1)

[6] 95% CI crosses 1 MID (±0.5x control group SD, for testosterone (nmol/l) in short term (non-azoospermic participants only) = 1.95; testosterone (nmol/l) in med term (non-azoospermic participants only) = 1.95; oestradiol in short term = 6.7; oestradiol in med term = 6.4; sperm concentration in med term (non-azoospermic participants only) = 3.85; sperm concentration in med term (non-azoospermic participants only, mean participant age <45) = 5.3; total sperm count in med term = 7.65; total motile sperm count in short term (non-azoospermic participants only) = 9.85; sperm motility rate in med term (non-azoospermic participants only) = 8.16;)

[7] Serious heterogeneity (>50%), explained by subgroup analysis (see rows beneath)

[8] Very serious heterogeneity (>80%) unexplained by subgroup analysis

Table 11: Evidence profile for comparison between gonadotrophin therapy and anti-oestrogen: participants with semen abnormalities (non-azoospermia) only

Quality assessment							No of participants		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Gonadotrophin therapy	Anti-oestrogen	Relative (95% CI)	Absolute		
Pregnancy rate in short term (Total number of pregnancies (spontaneous or assisted))												
1 (Matsumiya 1998)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	3/23 (13%)	0/21 (0%)	POR 7.44 (0.73 to 75.68)	-	VERY LOW	CRITICAL
Spontaneous pregnancy rate in short term												
1 (Matsumiya 1998)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/23 (4.3%)	0/21 (0%)	POR 6.77 (0.13 to 342.76)	-	VERY LOW	CRITICAL
Sperm concentration ($x10^6$/ml) in short term (Better indicated by higher values)												
1 (Matsumiya 1998)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	23	21	-	MD 5.4 higher (3.73 lower to 14.53 higher)	LOW	IMPORTANT
Sperm motility rate (%) in short term (Better indicated by higher values)												
1 (Matsumiya 1998)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	23	21	-	MD 4 higher (7.93 lower to 15.93 higher)	LOW	IMPORTANT

CI: confidence intervals; MD: mean difference; MID: minimally important difference; POR: peto odds ratio; RoB: risk of bias; SD: standard deviation
[1] Serious risk of bias in the evidence contributing to the outcomes as per RoB 2
[2] 95% CI crosses 2 MIDs
[3] 95% CI crosses 1 MID (±0.5x control group SD, for sperm concentration in short term = 7.3; sperm motility rate in short term = 11.05)

Table 12: Evidence profile for comparison between androgen and placebo: participants with semen abnormalities (non-azoospermia) only

Quality assessment							No of participants		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Androgen	Placebo	Relative (95% CI)	Absolute		
Pregnancy rate in short term (Pregnancy not defined) – Non-azoospermic participants only												
2[a]	randomised trials	very serious[4]	no serious inconsistency	no serious indirectness	serious[2]	none	8/52 (15.4%)	2/57 (3.5%)	RR 3.79 (0.95 to 15.11)	98 more per 1000 (from 2 less to 495 more)	VERY LOW	CRITICAL
Pregnancy rate in med term (Pregnancy not defined)												
1 (Pusch 1989)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	6/30 (20%)	4/30 (13.3%)	RR 1.5 (0.47 to 4.78)	67 more per 1000 (from 71 fewer to 504 more)	VERY LOW	CRITICAL
Assisted pregnancy rate in med term												
1 (Comhaire 1995)	randomised trials	very serious[4]	no serious inconsistency	no serious indirectness	very serious[3]	reporting bias[5]	5/30 (16.7%)	11/34 (32.4%)	RR 0.52 (0.2 to 1.31)	155 fewer per 1000 (from 259 fewer to 100 more)	VERY LOW	CRITICAL

Dihydrotestosterone (ng/ml) in short term (Better indicated by higher values)												
1 (Gregoriou 1993)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	25	25	-	MD 79.36 higher (70.89 to 87.83 higher)	MODERATE	IMPORTANT
Free testosterone (pg/ml) in short term (Better indicated by higher values)												
1 (Pusch 1989)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[6]	none	29	28	-	MD 1.39 higher (3.06 lower to 5.84 higher)	VERY LOW	IMPORTANT
Total testosterone (ng/ml) in short term (Better indicated by higher values)												
2[b]	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[7]	none	54	53	-	MD 2.12 higher (0.93 to 3.3 higher)	LOW	IMPORTANT
Oestradiol (pg/ml) in short term (Better indicated by lower values)												
2[b]	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[7]	none	54	53	-	MD 1.48 lower (5.44 lower to 2.48 higher)	LOW	IMPORTANT
Sperm concentration ($x10^6$/ml) in short term (Better indicated by higher values)												
2[b]	randomised trials	serious[1]	serious[8]	no serious indirectness	no serious imprecision	none	54	53	-	MD 0.89 lower (4.66 lower to 2.87 higher)	LOW	IMPORTANT
Sperm concentration ($x10^6$/ml) in short term - Fertility diagnosis: idiopathic oligoasthenospermia (Better indicated by higher values)												
1 (Gregoriou 1993)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[7]	none	25	25	-	MD 2.5 higher (2.77 lower to 7.77 higher)	LOW	IMPORTANT
Sperm concentration ($x10^6$/ml) in short term - Fertility diagnosis: idiopathic oligozoospermia (Better indicated by higher values)												
1 (Pusch 1989)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[7]	none	29	28	-	MD 4.43 lower (9.81 lower to 0.95 higher)	LOW	IMPORTANT
Sperm concentration ($x10^6$/ml) in med term (Better indicated by higher values)												
1 (Pusch 1989)	randomised trials	very serious[4]	no serious inconsistency	no serious indirectness	serious[7]	none	25	28	-	MD 7.89 lower (17.65 lower to 1.87 higher)	VERY LOW	IMPORTANT
Sperm motility rate (%) in short term (Better indicated by higher values)												
2[b]	randomised trials	serious[1]	serious[8]	no serious indirectness	no serious imprecision	none	54	53	-	MD 0.46 lower (4.61 lower to 3.69 higher)	LOW	IMPORTANT
Sperm motility rate (%) in short term - Fertility diagnosis: idiopathic oligoasthenospermia (Better indicated by higher values)												
1 (Gregoriou 1993)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[7]	none	25	25	-	MD 3.51 higher (2.45 lower to 9.47 higher)	LOW	IMPORTANT
Sperm motility rate (%) in short term - Fertility diagnosis: idiopathic oligozoospermia (Better indicated by higher values)												
1 (Pusch 1989)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[7]	none	29	28	-	MD 4.2 lower (9.99 lower to 1.59 higher)	LOW	IMPORTANT
Sperm motility rate (%) in med term (Better indicated by higher values)												
1 (Pusch 1989)	randomised trials	very serious[4]	no serious inconsistency	no serious indirectness	serious[7]	none	25	28	-	MD 2.94 lower (9.36 lower to 3.48 higher)	VERY LOW	IMPORTANT
Miscarriage rate in short term												
1 (Gregoriou 1993)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/25 (4%)	0/25 (0%)	POR 7.39 (0.15 to 372.38)	-	VERY LOW	IMPORTANT
Miscarriage rate in med term												
1 (Pusch 1989)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	0/30 (0%)	1/30 (3.3%)	POR 0.14 (0 to 6.82)	-	VERY LOW	IMPORTANT

CI: confidence intervals; MD: mean difference; MID: minimally important difference; POR: peto odds ratio; RoB: risk of bias; RR: risk ratio; SD: standard deviation
[a] Aafjes 1983, Gregoriou 1993
[b] Gregoriou 1993, Pusch 1989
[1] Serious risk of bias in the evidence contributing to the outcomes as per RoB 2
[2] 95% CI crosses 1 MID
[3] 95% CI crosses 2 MIDs
[4] Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2
[5] Publication bias suspected due to majority of studies being industry funded
[6] 95% CI crosses 2 MIDs (±0.5x control group SD, for free testosterone (pg/ml) in short term = 2.37)
[7] 95% CI crosses 1 MID (±0.5x control group SD, for total testosterone (ng/ml) in short term = 1.28; oestradiol (pg/ml) in short term = 5.17; sperm concentration (x10^6/ml) in short term (fertility diagnosis: idiopathic oligoasthenospermia) = 5.08; sperm concentration (x10^6/ml) in short term (fertility diagnosis: idiopathic oligozoospermia) = 5.31; sperm concentration (x10^6/ml) in med term = 10.49; sperm motility rate (%) in short term (fertility diagnosis: idiopathic oligoasthenospermia) = 5.48; sperm motility rate (%) in short term (fertility diagnosis: idiopathic oligozoospermia) = 5.95; sperm motility rate (%) in med term = 6.21)
[8] Serious heterogeneity (>50%), explained by subgroup analysis (see rows beneath)

Mixed population - participants with semen abnormalities (non-azoospermia) or azoospermia

Table 13: Evidence profile for comparison between aromatase inhibitor and placebo: participants with semen abnormalities (non-azoospermia) or azoospermia

Quality assessment							No of participants		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aromatase inhibitor	Placebo	Relative (95% CI)	Absolute		
Spontaneous pregnancy rate in med term - Azoospermic and non-azoospermic participants												
1 (Cavallini 2013)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/22 (0%)	0/24 (0%)	RD 0.00 (-0.08 to 0.08)	-	VERY LOW	CRITICAL

CI: confidence intervals; RD: risk difference; RoB: risk of bias
[1] Serious risk of bias in the evidence contributing to the outcomes as per RoB 2
[2] Sample size <200

Table 14: Evidence profile for comparison between gonadotrophin therapy and placebo: participants with semen abnormalities (non-azoospermia) or azoospermia

Quality assessment							No of participants		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Gonadotrophin therapy	Placebo	Relative (95% CI)	Absolute		
Pregnancy rate in short term - Azoospermic and non-azoospermic participants (Pregnancy not defined)												
1 (Crottaz 1992)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	reporting bias[2]	0/14 (0%)	3/14 (21.4%)	POR 0.12 (0.01 to 1.21)	-	VERY LOW	CRITICAL
Sperm concentration (x10^6/ml) in short term - Azoospermic and non-azoospermic participants (Better indicated by higher values)												

1 (Crottaz 1992)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[6]	reporting bias[2]	14	14	-	MD 21.9 higher (2.55 lower to 46.35 higher)	VERY LOW	IMPORTANT
Total sperm count (x10^6) in short term - Azoospermic and non-azoospermic participants (Better indicated by higher values)												
1 (Crottaz 1992)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[6]	reporting bias[2]	14	14	-	MD 97.3 higher (10.05 to 184.55 higher)	VERY LOW	IMPORTANT
Total motile sperm count (x10^6) in short term - Azoospermic and non-azoospermic participants (Better indicated by higher values)												
1 (Crottaz 1992)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[5]	reporting bias[2]	14	14	-	MD 17.1 higher (12.84 lower to 47.04 higher)	VERY LOW	IMPORTANT
Miscarriage rate in short term - Azoospermic and non-azoospermic participants												
1 (Crottaz 1992)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	reporting bias[2]	0/14 (0%)	1/14 (7.1%)	POR 0.14 (0 to 6.82)	-	VERY LOW	IMPORTANT

CI: confidence intervals; MD: mean difference; MID: minimally important difference; POR: peto odds ratio; RoB: risk of bias; RR: risk ratio; SD: standard deviation
[1] Serious risk of bias in the evidence contributing to the outcomes as per RoB 2
[2] Publication bias suspected due to majority of studies being industry funded
[3] 95% CI crosses 1 MID
[4] 95% CI crosses 2 MIDs
[5] 95% CI crosses 2 MIDs (±0.5x control group SD, for total motile sperm count in short term (azoospermic and non-azoospermic participants) = 5.45)
[6] 95% CI crosses 1 MID (±0.5x control group SD, for sperm concentration in short term (azoospermic and non-azoospermic participants) = 3.95; total sperm count in short term (azoospermic and non-azoospermic participants) = 15.9)

Participants' severity of semen abnormality not reported

Table 15: Evidence profile for comparison between gonadotrophin therapy and no treatment: participants' severity of semen abnormality not reported

Quality assessment							No of participants		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Gonadotrophin therapy**	**No treatment**	**Relative (95% CI)**	**Absolute**		
Pregnancy rate in long term (Pregnancy not defined) - Severity of semen abnormalities not reported												
1 (Babak 2018)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	56/91 (61.5%)	22/97 (22.7%)	RR 2.71 (1.82 to 4.05)	388 more per 1000 (from 186 more to 692 more)	MODERATE	CRITICAL
Spontaneous pregnancy rate in med term - Severity of semen abnormalities not reported												
1 (Amirzargar 2012)	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	40/78 (51.3%)	0/35 (0%)	POR 9.23 (4.03 to 21.18)	-	LOW	CRITICAL
Spontaneous or assisted pregnancy rate in med term - Severity of semen abnormalities not reported												
1 (Amirzargar 2012)	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	40/78 (51.3%)	15/35 (42.9%)	RR 1.20 (0.77 to 1.86	86 more per 1000 (from 99 fewer to 369 more)	VERY LOW	CRITICAL
Number of participants with sperm concentration >20x10^6/mL in med term - Severity of semen abnormalities not reported												

1 (Amirzargar 2012)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	38/78 (48.7%)	20/35 (57.1%)	RR 0.85 (0.59 to 1.23)	86 fewer per 1000 (from 234 fewer to 131 more)	HIGH	IMPORTANT
Sperm concentration (x10^6/ml) in med term - Severity of semen abnormalities not reported (Better indicated by higher values)												
1 (Babak 2018)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	91	97	-	MD 0.6 lower (1.7 lower to 0.5 higher)	LOW	IMPORTANT
Number of participants with sperm motility rate >50% in med term - Severity of semen abnormalities not reported												
1 (Amirzargar 2012)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	40/78 (51.3%)	18/35 (51.4%)	RR 1 (0.68 to 1.47)	0 fewer per 1000 (from 165 fewer to 242 more)	LOW	IMPORTANT
Sperm motility rate (%) in med term - Severity of semen abnormalities not reported (Better indicated by higher values)												
1 (Babak 2018)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	91	97	-	MD 3.8 lower (5.61 to 1.99 lower)	LOW	IMPORTANT

CI: confidence intervals; IUI: intrauterine insemination; MD: mean difference; MID: minimally important difference; POR: peto odds ratio; RD: risk difference; RoB: risk of bias; RR: risk ratio; SD: standard deviation

[1] Serious risk of bias in the evidence contributing to the outcomes as per RoB 2

[2] Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2

[3] 95% CI crosses 2 MIDs

[4] 95% CI crosses 1 MID (±0.5x control group SD, for sperm concentration in med term (severity of semen abnormalities not reported) = 1.3; sperm motility rate in med term (severity of semen abnormalities not reported) = 3.7)

Table 16: Evidence profile for comparison between gonadotrophin therapy and placebo: participants' severity of semen abnormality not reported

Quality assessment							No of participants		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Gonadotrophin therapy**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Pregnancy rate in med term - Severity of semen abnormalities not reported (Pregnancy not defined)												
1 (Knuth 1987)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/17 (11.8%)	0/20 (0%)	POR 9.38 (0.56 to 157.44)	-	VERY LOW	CRITICAL
Testosterone (nmol/l) in short term - Severity of semen abnormalities not reported (Better indicated by higher values)												
1 (Knuth 1987)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	17	20	-	MD 3.8 lower (7.99 lower to 0.39 higher)	LOW	IMPORTANT
Testosterone (nmol/l) in med term - Severity of semen abnormalities not reported (Better indicated by higher values)												
1 (Knuth 1987)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	17	20	-	MD 1.2 lower (4.81 lower to 2.41 higher)	LOW	IMPORTANT
Sperm concentration (x10^6/ml) in short term - Severity of semen abnormalities not reported (Better indicated by higher values)												
1 (Knuth 1987)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	17	20	-	MD 1.00 lower (4.32 lower to 2.32 higher)	LOW	IMPORTANT
Sperm concentration (x10^6/ml) in med term - Severity of semen abnormalities not reported (Better indicated by higher values)												

1 (Knuth 1987)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	17	20	-	MD 1.30 lower (5.11 lower to 2.51 higher)	LOW	IMPORTANT
Sperm motility rate (%) in short term - Severity of semen abnormalities not reported (Better indicated by higher values)												
1 (Knuth 1987)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	17	20	-	MD 2.10 lower (16.69 lower to 12.49 higher)	VERY LOW	IMPORTANT
Sperm motility rate (%) in med term - Severity of semen abnormalities not reported (Better indicated by higher values)												
1 (Knuth 1987)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	17	20	-	MD 6.40 higher (7.92 lower to 20.72 higher)	LOW	IMPORTANT

CI: confidence intervals; MD: mean difference; MID: minimally important difference; POR: peto odds ratio; RoB: risk of bias; RR: risk ratio; SD: standard deviation
[1] Serious risk of bias in the evidence contributing to the outcomes as per RoB 2
[2] 95% CI crosses 2 MIDs
[3] 95% CI crosses 1 MID (±0.5x control group SD, for testosterone (nmol/l) in short term (severity of semen abnormalities not reported) = 2.9; testosterone (nmol/l) in med term (severity of semen abnormalities not reported) = 2.9; sperm concentration in short term (severity of semen abnormalities not reported) = 2.9; sperm concentration in med term (severity of semen abnormalities not reported) = 3.6; total sperm motility rate in med term (severity of semen abnormalities not reported) = 8.95)
[4] 95% CI crosses 2 MIDs (±0.5x control group SD, for sperm motility rate in short term (severity of semen abnormalities not reported) = 8.5)

Table 17: Evidence profile for comparison between androgen and placebo: participants' severity of semen abnormality not reported

Quality assessment							No of participants		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Androgen**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Pregnancy rate in short term (Pregnancy not defined) – Severity of semen abnormalities not reported												
1 (Aribarg 1989)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	15/82 (18.3%)	5/43 (11.6%)	RR 1.57 (0.61 to 4.04)	66 more per 1000 (from 45 less to 353 more)	VERY LOW	CRITICAL

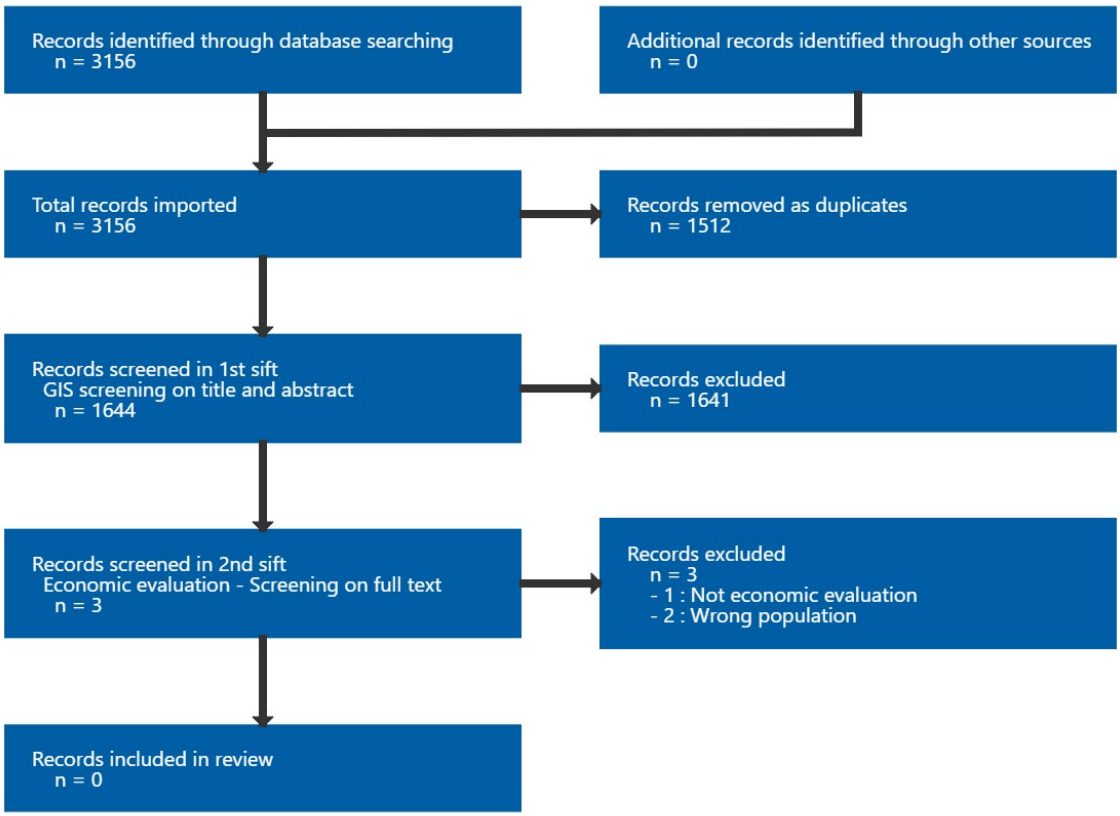
CI: confidence intervals; MID: minimally important difference; RoB: risk of bias; RR: risk ratio
[1] Serious risk of bias in the evidence contributing to the outcomes as per RoB 2
[2] 95% CI crosses 2 MIDs

Appendix G Economic evidence study selection

Study selection for review question: What is the effectiveness of hormone treatment in male factor fertility problems?

No economic evidence was identified which was applicable to this review question.

Figure 23: Study selection flow chart



Appendix H Economic evidence tables

Economic evidence tables for review question: What is the effectiveness of hormone treatment in male factor fertility problems?

No evidence was identified which was applicable to this review question.

Appendix I Economic model

Economic model for review question: What is the effectiveness of hormone treatment in male factor fertility problems?

No economic analysis was conducted for this review question.

Appendix J Excluded studies

Excluded studies for review question: What is the effectiveness of hormone treatment in male factor fertility problems?

Excluded effectiveness studies

Table 18: Excluded studies and reasons for their exclusion

Study	Code [Reason]
Adamopoulos, D A, Nicopoulou, S, Kapolla, N et al. (1995) Endocrine effects of testosterone undecanoate as a supplementary treatment to menopausal gonadotropins or tamoxifen citrate in idiopathic oligozoospermia. Fertility and sterility 64(4): 818-24	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Adamopoulos, D.A., Karamertzanis, M., Nicopoulou, S. et al. (1997) The combination of testosterone undecanoate with tamoxifen citrate enhances the effects of each agent given independently on seminal parameters in men with idiopathic oligozoospermia. Fertility and Sterility 67(4): 756-762	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Ahmadi-Asrbadr, Yadollah, Hemmati-Ghavshough, Mahdi, Khanzadeh, Navid et al. (2022) Comparison of the effect of combined therapy of HCG ampule and letrozole tablet with each method separately on the spermogram parameters in the obese men with idiopathic infertility: a clinical trial. American journal of clinical and experimental urology 10(4): 258-265	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
AinMelk, Y., Belisle, S., Carmel, M. et al. (1987) Tamoxifen citrate therapy in male infertility. Fertility and Sterility 48(1): 113-117	- Insufficient presentation of results *Cross-over study, pregnancy rates not reported prior to cross-over period*
AinMelk, Y.; Belisle, S.; Kandalaft, N. (1982) Bromocriptine therapy in oligozoospermic infertile men. Archives of Andrology 8(2): 135-141	- Insufficient presentation of results *Cross-over study, results prior to cross-over period not reported separately*
Akirov, Amit and Rudman, Yaron (2023) The Role of Aromatase Inhibitors in Male Prolactinoma. Journal of clinical medicine 12(4)	- Study design does not meet inclusion criteria *Systematic review of observational studies only*
Al-Inany, H, Aboulghar, MA, Mansour, RT et al. (2005) Ovulation induction in the new millennium: recombinant follicle-stimulating hormone versus human menopausal gonadotropin. Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology 20(3): 161-9	- Systematic review - included studies checked for relevance
Alexander, Emma C, Faruqi, Duaa, Farquhar, Robert et al. (2024) Gonadotropins for pubertal induction in males with hypogonadotropic hypogonadism: systematic review and meta-analysis. European journal of endocrinology 190(1): 1-s11	- Systematic review - included studies checked for relevance

Study	Code [Reason]
Aliaev, IuG; Vinarov, AZ; Akhvlediani, ND (2010) Choice of treatment of erectile dysfunction associated with hypogonadism. Urologiia (Moscow, Russia : 1999): 37-8, 40	- Study not available in English
Alkandari, Mohammad H and Zini, Armand (2021) Medical management of non-obstructive azoospermia: A systematic review. Arab journal of urology 19(3): 215-220	- Systematic review - included studies checked for relevance
Allegra, A, Volpes, A, Coffaro, F et al. (1990) Superovulation with buserelin and gonadotropins dramatically improves the success rate of intrauterine insemination with husband's washed semen. Acta Europaea fertilitatis 21(4): 191-195	- Study unavailable
Alleyassin, A., Ghasemi, M., Aghahosseini, M. et al. (2018) Final oocyte maturation with a dual trigger compared to human chorionic gonadotropin trigger in antagonist co-treated cycles: A randomized clinical trial. Middle East Fertility Society Journal 23(3): 199-204	- Intervention does not meet inclusion criteria *Combined treatment of human chorionic gonadotrophin (hCG) plus Triptoreline versus hCG only*
Amooee, S., Shomali, Z., Namazi, N. et al. (2022) Is There any Role for Granulocyte Colony Stimulating Factor in Improvement of Implantation in Intrauterine Insemination? A Prospective Double-Blind Randomized Control Trial. International Journal of Fertility and Sterility 16(4): 281-285	- Population does not meet inclusion criteria *Participants do not have male factor infertility (normal physical exam and laboratory studies including semen analysis with no medical diagnosis and a total motile count >10 million)*
Amory, J.K., Bush, M.A., Zhi, H. et al. (2011) Oral testosterone with and without concomitant inhibition of 5alpha-reductase by dutasteride in hypogonadal men for 28 days. Journal of Urology 185(2): 626-632	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Anapliotou, M.G.L., Evagellou, E., Kastanias, I. et al. (1996) Effect of growth hormone cotreatment with human chorionic gonadotropin in testicular steroidogenesis and seminal insulin-like growth factor-1 in oligozoospermia. Fertility and Sterility 66(2): 305-311	- Study design does not meet inclusion criteria *Non-comparative trial: each participant acted as their own control*
Anonymous (1999) Testosterone gel shows promise in Phase III trial. AIDS alert 14(6): 67	- Study design does not meet inclusion criteria *Commentary*
Anonymous (1989) Mesterolone and idiopathic male infertility: a double-blind study. World Health Organization Task Force on the Diagnosis and Treatment of Infertility. International journal of andrology 12(4): 254-64	- Duplicate
Ansari, A H; Wieland, R G; Klein, D E (1972) Ciscomiphene citrate in the management of oligospermia. The Journal of urology 108(1): 131-3	- Outcomes do not meet inclusion criteria *Study compares 2 different doses of cisclomiphene citrate*

Study	Code [Reason]
Ashkenazi, J., Bar-Hava, I., Farhi, J. et al. (1999) The role of purified follicle stimulating hormone therapy in the male partner before intracytoplasmic sperm injection. Fertility and Sterility 72(4): 670-673	- Intervention does not meet inclusion criteria *The comparison is not described and so it is unclear what the control group received.* - Study design does not meet inclusion criteria *Quasi-randomised study*
Attia, A.M.; Abou-Setta, A.M.; Al-Inany, H.G. (2013) Gonadotrophins for idiopathic male factor subfertility. Cochrane Database of Systematic Reviews 2013(8): cd005071	- Systematic review - included studies checked for relevance
Attia, A.M.; Al-Inany, H.G.; Proctor, M.L. (2007) Gonadotrophins for idiopathic male factor subfertility: A Cochrane systematic review. Middle East Fertility Society Journal 12(2): 77-85	- Systematic review - included studies checked for relevance
Awouters, M.; Vanderschueren, D.; Antonio, L. (2020) Aromatase inhibitors and selective estrogen receptor modulators: Unconventional therapies for functional hypogonadism?. Andrology 8(6): 1590-1597	- Systematic review - included studies checked for relevance
Baccetti, B, Strehler, E, Capitani, S et al. (1997) The effect of follicle stimulating hormone therapy on human sperm structure (Notulae seminologicae 11). Human reproduction (Oxford, England) 12(9): 1955-68	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Badenoch, D.F., Waxman, J., Boorman, L. et al. (1988) Administration of a gonadotropin releasing hormone analogue in oligozoospermic infertile males. Acta Endocrinologica 117(2): 265-267	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Barwin, B N, Clarke, S D, Biggart, J D et al. (1973) Mesterolone in the treatment of male infertility. The Practitioner 211(265): 669-74	- Study design does not meet inclusion criteria *Non-comparative study*
Behre, H.M. and Nieschlag, E. (1992) Testosterone buciclate (20 Aet-1) in hypogonadal men: Pharmacokinetics and pharmacodynamics of the new long-acting androgen ester. Journal of Clinical Endocrinology and Metabolism 75(5): 1204-1210	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Behzad, AB, Behzad, BB, Niroomand, H et al. (2015) The effect of recombinant follicle-stimulating hormone on semen parameters after varicocelectomy in infertile men. Tehran university medical journal 73(9): 653-659	- Study not available in English
Bendre, Sachin V; Murray, Pamela J; Basaria, Shehzad (2015) Clomiphene Citrate Effectively Increases Testosterone in Obese, Young, Hypogonadal Men. Reproductive system & sexual disorders : current research 4(4)	- Study design does not meet inclusion criteria *Non-randomised study*
Bettella, A, Merico, M, Rossato, M et al. (2001) Treatment of idiopathic oligozoospermia with	- Study design does not meet inclusion criteria

Study	Code [Reason]
recombinant FSH. Human reproduction (Oxford, England) 16(suppl1): 81	*Conference abstract*
Bhasin, S., Travison, T.G., O'Brien, L. et al. (2018) Contributors to the substantial variation in on-treatment testosterone levels in men receiving transdermal testosterone gels in randomized trials. Andrology 6(1): 151-157	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Bhathena, R.K.; Jassawalla, M.J.; Patel, D.N. (1987) The effects of mesterolone on sperm count in idiopathic oligospermia. International Journal of Fertility 32(4): 306-308	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Bhathena, RK and Patel, DN (1985) The influenceof mesterolone on serum gonadotrophins and plasma testosterone in subfertile men with idiopathic oligospermia. Archives of gynecology 237suppl: 95-96	- Study design does not meet inclusion criteria *Conference abstract*
Bhattacharya, S., Harrild, K., Mollison, J. et al. (2008) Clomifene citrate or unstimulated intrauterine insemination compared with expectant management for unexplained infertility: Pragmatic randomised controlled trial. BMJ 337(7666): 387-390	- Population does not meet inclusion criteria *Participants did not have male factor infertility (normal semen variables according to WHO criteria)*
Black, A.M.; Day, A.G.; Morales, A. (2004) The reliability of clinical and biochemical assessment in symptomatic late-onset hypogonadism: Can a case be made for a 3-month therapeutic trial?. BJU International 94(7): 1066-1070	- Study design does not meet inclusion criteria *Non-comparative study*
Bolland, M.J., Grey, A., Horne, A.M. et al. (2013) Testosterone levels following decreases in serum osteocalcin. Calcified Tissue International 93(2): 133-136	- Intervention does not meet inclusion criteria *Study compares zoledronate and placebo*
Boonyarangkul, A., Vinayanuvattikhun, N., Chiamchanya, C. et al. (2015) Comparative study of the effects of tamoxifen citrate and folate on semen quality of the infertile male with semen abnormality. Journal of the Medical Association of Thailand 98(11): 1057-1063	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Borges, J.Y.V. (2024) Oral Testosterone Therapy in Hypogonadal Men: A Comprehensive Systematic Review and Meta-Analysis of Safety, Efficacy, and Secondary Health Outcomes. medRxiv	- Systematic review - included studies checked for relevance
Bosdou, J.K., Venetis, C.A., Dafopoulos, K. et al. (2016) Transdermal testosterone pretreatment in poor responders undergoing ICSI: A randomized clinical trial. Human Reproduction 31(5): 977-985	- Population does not meet inclusion criteria *Participants are people with female-factor fertility problems*
Bosdou, JK, Venetis, CA, Kolibianakis, EM et al. (2012) The use of androgens or androgen-modulating agents in poor responders undergoing in vitro fertilization: a systematic review and meta-analysis. Human reproduction update 18(2): 127-45	- Systematic review - included studies checked for relevance

Study	Code [Reason]
Botella, J (1968) Treatment of oligoasthenospermia with human gonadotropin in infertile and subfertile men. Anales de la Real Academia Nacional de Medicina 85: 39-44	- Study not available in English
Bouloux, P. (2005) Testim 1% testosterone gel for the treatment of male hypogonadism. Clinical Therapeutics 27(3): 286-298	- Study design does not meet inclusion criteria *Narrative review*
Bouloux, P.-M.G., Nieschlag, E., Burger, H.G. et al. (2003) Induction of Spermatogenesis by Recombinant Follicle-Stimulating Hormone (Puregon) in Hypogonadotropic Azoospermic Men Who Failed to Respond to Human Chorionic Gonadotropin Alone. Journal of Andrology 24(4): 604-611	- Intervention does not meet inclusion criteria *Study compared 2 different doses of subcutaneous-injected recombinant follicle stimulating hormone*
Bridges, N., Trofimenko, V., Fields, S. et al. (2015) Male Factor Infertility and Clomiphene Citrate: A Meta-Analysis-The Effect of Clomiphene Citrate on Oligospermia. Urology Practice 2(4): 199-205	- Systematic review - included studies checked for relevance
Brock, G., Heiselman, D., Knorr, J. et al. (2016) 9-Month Efficacy and Safety Study of Testosterone Solution 2% for Sex Drive and Energy in Hypogonadal Men. Journal of Urology 196(5): 1509-1515	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Brock, G., Heiselman, D., Maggi, M. et al. (2016) Effect of Testosterone Solution 2% on Testosterone Concentration, Sex Drive and Energy in Hypogonadal Men: Results of a Placebo Controlled Study. Journal of Urology 195(3): 699-705	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Burnett-Bowie, S.-A.M., Roupenian, K.C., Dere, M.E. et al. (2009) Effects of aromatase inhibition in hypogonadal older men: A randomized, double-blind, placebo-controlled trial. Clinical Endocrinology 70(1): 116-123	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Burris, A S; Ewing, L L; Sherins, R J (1988) Initial trial of slow-release testosterone microspheres in hypogonadal men. Fertility and sterility 50(3): 493-7	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Buvat, J., Montorsi, F., Maggi, M. et al. (2011) Hypogonadal Men Nonresponders to the PDE5 Inhibitor Tadalafil Benefit from Normalization of Testosterone Levels with a 1% Hydroalcoholic Testosterone Gel in the Treatment of Erectile Dysfunction (TADTEST Study). Journal of Sexual Medicine 8(1): 284-293	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Byrne, M.M., Rolf, C., Depenbusch, M. et al. (2003) Lack of effect of a single i.v. dose of oxytocin on sperm output in severely oligozoospermic men. Human Reproduction 18(10): 2098-2102	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Cannarella, R., La Vignera, S., Condorelli, R.A. et al. (2020) FSH dosage effect on conventional sperm parameters: A meta-analysis of randomized controlled studies. Asian Journal of Andrology 22(3): 309-316	- Systematic review - included studies checked for relevance

Study	Code [Reason]
Cannarella, Rossella, Condorelli, Rosita A, Mongioi, Laura M et al. (2019) Effects of the selective estrogen receptor modulators for the treatment of male infertility: a systematic review and meta-analysis. Expert opinion on pharmacotherapy 20(12): 1517-1525	- Systematic review - included studies checked for relevance
Caroppo, Ettore, Niederberger, Craig, Vizziello, Giovanni Michele et al. (2003) Recombinant human follicle-stimulating hormone as a pretreatment for idiopathic oligoasthenoteratozoospermic patients undergoing intracytoplasmic sperm injection. Fertility and sterility 80(6): 1398-403	- Study design does not meet inclusion criteria *Non-randomised study*
Carson III, C, Khera, M, Dobs, A et al. (2016) Hypogonadal men with sexual function disorder benefit from LPCN 1021 (oral testosterone)-SOAR (study of androgen replacement) trial. Journal of urology 195(4suppl): e1010-1	- Study design does not meet inclusion criteria *Conference abstract*
Cha, Yu-Jung, Kim, Kyoung-Ah, Oh, Tae Young et al. (2015) Pharmacokinetics and Safety Profile of DA-3803, a Proposed Biosimilar of Recombinant Human Chorionic Gonadotropin, in Healthy Subjects. BioDrugs : clinical immunotherapeutics, biopharmaceuticals and gene therapy 29(3): 199-205	- Population does not meet inclusion criteria *Participants do not have male factor infertility (healthy subjects)*
Chaffkin, L M, Nulsen, J C, Luciano, A A et al. (1991) A comparative analysis of the cycle fecundity rates associated with combined human menopausal gonadotropin (hMG) and intrauterine insemination (IUI) versus either hMG or IUI alone. Fertility and sterility 55(2): 252-7	- Insufficient presentation of results *Participants had variable reasons for infertility (male factor, cervical factor, endometriosis and unexplained) and the results for pregnancy are not reported separately for participants with male factor infertility*
Chen, Y-X, Xing, Q, Li, Z-Q et al. (2020) Effects of Low Dose Clomiphene Combined with Vitamin E on Sperm Quality and Sex Hormones in Patients with Idiopathic Oligospermia. Chinese journal of pharmaceutical biotechnology 27(1): 63-67	- Study not available in English
Chen, Y.-W., Niu, Y.-H., Wang, D.-Q. et al. (2018) Effect of adjuvant drug therapy after varicocelectomy on fertility outcome in males with varicocele-associated infertility: Systematic review and meta-analysis. Andrologia 50(8): e13070	- Systematic review - included studies checked for relevance
Chiang, H.S., Hwang, T.I.S., Hsui, Y.S. et al. (2007) Transdermal testosterone gel increases serum testosterone levels in hypogonadal men in Taiwan with improvements in sexual function. International Journal of Impotence Research 19(4): 411-417	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Chua, M.E., Escusa, K.G., Luna, S. et al. (2013) Revisiting oestrogen antagonists (clomiphene or tamoxifen) as medical empiric therapy for idiopathic male infertility: A meta-analysis. Andrology 1(5): 749-757	- Systematic review - included studies checked for relevance

Study	Code [Reason]
Clark, R V and Sherins, R J (1989) Treatment of men with idiopathic oligozoospermic infertility using the aromatase inhibitor, testolactone. Results of a double-blinded, randomized, placebo-controlled trial with crossover. Journal of andrology 10(3): 240-7	- Insufficient presentation of results *Data cannot be extracted as number of participants in each group not reported*
Clopper, R.R., Voorhess, M.L., MacGillivray, M.H. et al. (1993) Psychosexual behavior in hypopituitary men: A controlled comparison of gonadotropin and testosterone replacement. Psychoneuroendocrinology 18(2): 149-161	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Colacurci, N., Monti, M.G., Fornaro, F. et al. (2012) Recombinant human FSH reduces sperm DNA fragmentation in men with idiopathic oligoasthenoteratozoospermia. Journal of Andrology 33(4): 588-593	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Colao, Annamaria, Vitale, Giovanni, Cappabianca, Paolo et al. (2004) Outcome of cabergoline treatment in men with prolactinoma: effects of a 24-month treatment on prolactin levels, tumor mass, recovery of pituitary function, and semen analysis. The Journal of clinical endocrinology and metabolism 89(4): 1704-11	- Study design does not meet inclusion criteria *Non-comparative study*
Colleluori, G., Chen, R., Turin, C.G. et al. (2020) Aromatase Inhibitors Plus Weight Loss Improves the Hormonal Profile of Obese Hypogonadal Men Without Causing Major Side Effects. Frontiers in Endocrinology 11: 277	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Comhaire, F (1990) Treatment of idiopathic testicular failure with high-dose testosterone undecanoate: a double-blind pilot study. Fertility and sterility 54(4): 689-93	- Insufficient presentation of results *Study does not report the number of participants in each group*
Conway, A.J., Boylan, L.M., Howe, C. et al. (1988) Randomized clinical trial of testosterone replacement therapy in hypogonadal men. International Journal of Andrology 11(4): 247-264	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Corona, G., Isidori, A.M., Buvat, J. et al. (2014) Testosterone Supplementation and Sexual Function: A Meta-Analysis Study. Journal of Sexual Medicine 11(6): 1577-1592	- Systematic review - included studies checked for relevance
Cruickshank, Moira, Hudson, Jemma, Hernandez, Rodolfo et al. (2024) The effects and safety of testosterone replacement therapy for men with hypogonadism: the TestES evidence synthesis and economic evaluation. Health technology assessment (Winchester, England) 28(43): 1-210	- Systematic review - included studies checked for relevance
Dadhich, P., Ramasamy, R., Scovell, J. et al. (2017) Testosterone versus clomiphene citrate in managing symptoms of hypogonadism in men. Indian Journal of Urology 33(3): 236-240	- Study design does not meet inclusion criteria *Observational study*

Study	Code [Reason]
Danhof, Noor A, van Wely, Madelon, Repping, Sjoerd et al. (2020) Gonadotrophins or clomiphene citrate in couples with unexplained infertility undergoing intrauterine insemination: a cost-effectiveness analysis. Reproductive biomedicine online 40(1): 99-104	- Population does not meet inclusion criteria *Participants do not have male factor infertility (couples with unexplained infertility)*
de Silva, Nipun Lakshitha, Dissanayake, Harsha, Suarez, Camila et al. (2023) Effect of oestrogen modulation on semen parameters in men with secondary hypogonadism: Systematic review and meta-analysis. Andrology	- Systematic review - included studies checked for relevance *Systematic review includes both non randomised and randomised studies. Relevant randomised controlled trials were checked for relevance against the inclusion criteria.*
Deaton, J L, Gibson, M, Blackmer, K M et al. (1990) A randomized, controlled trial of clomiphene citrate and intrauterine insemination in couples with unexplained infertility or surgically corrected endometriosis. Fertility and sterility 54(6): 1083-8	- Population does not meet inclusion criteria *Participants do not have male factor infertility (unexplained infertility or endometriosis)*
Del Fabbro, E., Garcia, J.M., Dev, R. et al. (2013) Testosterone replacement for fatigue in hypogonadal ambulatory males with advanced cancer: A preliminary double-blind placebo-controlled trial. Supportive Care in Cancer 21(9): 2599-2607	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Del Giudice, F., Busetto, G., De Berardinis, E. et al. (2020) A systematic review and meta-analysis of clinical trials implementing aromatase inhibitors to treat male infertility. Asian Journal of Andrology 22(4): 360-367	- Systematic review - included studies checked for relevance
Diaz, P., Reddy, R., Blachman-Braun, R. et al. (2022) Comparison of Intratesticular Testosterone between Men Receiving Nasal, Intramuscular, and Subcutaneous Pellet Testosterone Therapy: Evaluation of Data from Two Single-Center Randomized Clinical Trials. World Journal of Men's Health 40: 210261	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Diem, S.J., Greer, N.L., MacDonald, R. et al. (2020) Efficacy and safety of testosterone treatment in men: An evidence report for a clinical practice guideline by the American college of physicians. Annals of Internal Medicine 172(2): 105-118	- Systematic review - included studies checked for relevance
Ding, Y.-M., Zhang, X.-J., Li, J.-P. et al. (2015) Treatment of idiopathic oligozoospermia with recombinant human follicle-stimulating hormone: A prospective, randomized, double-blind, placebo-controlled clinical study in Chinese population. Clinical Endocrinology 83(6): 866-871	- Intervention does not meet inclusion criteria *Study compared different dosages of recombinant human follicle-stimulating hormone to each other*
Dobs, A.S., Meikle, A.W., Arver, S. et al. (1999) Pharmacokinetics, efficacy, and safety of a permeation-enhanced testosterone transdermal system in comparison with bi-weekly injections of testosterone enanthate for the treatment of hypogonadal men. Journal of Clinical Endocrinology and Metabolism 84(10): 3469-3478	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*

Study	Code [Reason]
Dougherty, R.H., Rohrer, J.L., Hayden, D. et al. (2005) Effect of aromatase inhibition on lipids and inflammatory markers of cardiovascular disease in elderly men with low testosterone levels. Clinical Endocrinology 62(2): 228-235	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Dutta, D., Mohindra, R., Kumar, M. et al. (2022) Role of aromatase inhibitors in managing hypogonadism in adult males related to obesity and aging: A systematic review and meta-analysis. Indian Journal of Endocrinology and Metabolism 26(6): 501-509	- Systematic review - included studies checked for relevance *The systematic review includes randomised controlled trials that do not report any of the primary outcomes specified in the protocol*
Dwyer, A.A., Sykiotis, G.P., Hayes, F.J. et al. (2013) Trial of recombinant follicle-stimulating hormone pretreatment for GnRH-induced fertility in patients with congenital hypogonadotropic hypogonadism. Journal of Clinical Endocrinology and Metabolism 98(11): e1790-e1795	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Ebrahimi, M Akbari Asbagh F Poormand GR Bagheri Behzad A (2015) The effect of recombinant human follicle stimulating hormone (RHFSH) on semen parameters after varicocele repair in subfertile men. International journal of gynaecology and obstetrics 131suppl5: e230	- Study design does not meet inclusion criteria *Conference abstract*
El Meliegy, Amr; Motawi, Ahmad; El Salam, Mohamed Ahmed Abd (2018) Systematic review of hormone replacement therapy in the infertile man. Arab journal of urology 16(1): 140-147	- Systematic review - included studies checked for relevance
Elanjian, S.I. (1996) Clomiphene for male infertility. Journal of Pharmacy Technology 12(3): 102-104	- Study design does not meet inclusion criteria *Correspondence*
Elliott, J., Kelly, S.E., Millar, A.C. et al. (2017) Testosterone therapy in hypogonadal men: A systematic review and network meta-analysis. BMJ Open 7(11): e015284	- Systematic review - included studies checked for relevance
Elsheikh, M.G., Hosny, M.B., Elshenoufy, A. et al. (2015) Combination of vitamin E and clomiphene citrate in treating patients with idiopathic oligoasthenozoospermia: A prospective, randomized trial. Andrology 3(5): 864-867	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Emperaire, J.C., Riviere, J., Ruffie, A. et al. (1979) Clomiphene test and clomiphene therapy in idiopathic male infertility. Archives of Andrology 2(3): 223-231	- Insufficient presentation of results *Results not presented for control group who received no treatment*
Ermolenko, V M, Kukhtevich, A V, Dedov, I I et al. (1986) Parlodel treatment of uremic hypogonadism in men. Nephron 42(1): 19-22	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Farrag, A; Manna, C; Grimaldi, G (2006) Efficacy of recombinant human FSH in the treatment of idiopathic	- Study design does not meet inclusion criteria

Study	Code [Reason]
male factor infertility before ICSI. Human reproduction (Oxford, England) 21(suppl): i27	*Conference abstract*
Fink, J., Schoenfeld, B.J., Hackney, A.C. et al. (2021) Human chorionic gonadotropin treatment: a viable option for management of secondary hypogonadism and male infertility. Expert Review of Endocrinology and Metabolism 16(1): 1-8	- Study design does not meet inclusion criteria *Literature review (summarized randomised controlled trials reporting human chorionic gonadotropin treatment on fertility parameters were checked for relevance)*
Fisch, P, Casper, R F, Brown, S E et al. (1989) Unexplained infertility: evaluation of treatment with clomiphene citrate and human chorionic gonadotropin. Fertility and sterility 51(5): 828-33	- Population does not meet inclusion criteria *Participants did not have male factor infertility (couples with unexplained infertility)*
Foresta, C., Bettella, A., Ferlin, A. et al. (1998) Evidence for a stimulatory role of follicle-stimulating hormone on the spermatogonial population in adult males. Fertility and Sterility 69(4): 636-642	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Foresta, C., Bettella, A., Merico, M. et al. (2002) Use of recombinant human follicle-stimulating hormone in the treatment of male factor infertility. Fertility and Sterility 77(2): 238-244	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Foss, G L; Tindall, V R; Birkett, J P (1973) The treatment of subfertile men with clomiphene citrate. Journal of reproduction and fertility 32(1): 167-70	- Insufficient presentation of results *Cross-sectional study, data from first phase not presented separately*
Francomano, D, Bruzziches, R, Barbaro, G et al. (2014) Effects of testosterone undecanoate replacement and withdrawal on cardio-metabolic, hormonal and body composition outcomes in severely obese hypogonadal men: a pilot study. Journal of endocrinological investigation 37(4): 401-411	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Fritz, Andrew A and Reinert, Justin P (2024) Efficacy and Safety of Testosterone Replacement in Testicular Cancer Survivors With Treatment-Influenced Hypogonadism: A Systematic Review. The Annals of pharmacotherapy: 10600280241278786	- Systematic review - included studies checked for relevance
Gerli, S. and Di Renzo, G.C. (2013) Establishing a combined stimulation protocol hFSH followed by rFSH might represent a breakthrough in the IVF practice. European Review for Medical and Pharmacological Sciences 17(15): 2091-2096	- Study unavailable *Study has been withdrawn from publication*
Gerris, J, Comhaire, F, Hellemans, P et al. (1991) Placebo-controlled trial of high-dose Mesterolone treatment of idiopathic male infertility. Fertility and sterility 55(3): 603-7	- Study design does not meet inclusion criteria *Non-randomised trial*
Ghanem, H.; Shaeer, O.; El-Segini, A. (2010) Combination clomiphene citrate and antioxidant therapy	- Intervention does not meet inclusion criteria

Study	Code [Reason]
for idiopathic male infertility: A randomized controlled trial. Fertility and Sterility 93(7): 2232-2235	*Study compared clomiphene citrate plus vitamin E to placebo*
Glander, H.-J. and Albrecht, M. (1999) Conception rate after treatment of male idiopathic infertility with pure human follicle stimulating hormone. Andrologia 31(1): 55-56	- Study design does not meet inclusion criteria *Non-randomised study*
Gooren, LJ, Bouloux, PM, Giltay, EJ et al. (2011) The effect of 6 months' treatment with testosterone gel versus placebo on body composition and health-related quality of life in hypogonadal men. Journal of diabetes 3: 147	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Grinspoon, S., Corcoran, C., Askari, H. et al. (1998) Effects of androgen administration in men with the AIDS wasting syndrome. A randomized, double-blind, placebo-controlled trial. Annals of Internal Medicine 129(1): 18-26	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Groti Antonic, K., Antonic, B., Zuran, I. et al. (2021) Testosterone treatment longer than 1 year shows more effects on functional hypogonadism and related metabolic, vascular, diabetic and obesity parameters (results of the 2-year clinical trial). Aging Male 23(5): 1442-1454	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Guay, A.T.; Bansal, S.; Heatley, G.J. (1995) Effect of raising endogenous testosterone levels in impotent men with secondary hypogonadism: Double blind placebo-controlled trial with clomiphene citrate. Journal of Clinical Endocrinology and Metabolism 80(12): 3546-3552	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Gul, U and Turunc, T (2016) The effect of human chorionic gonadotropin treatment before testicular sperm extraction in non-obstructive azoospermia. Journal of clinical and analytical medicine 7(1): 55-59	- Study design does not meet inclusion criteria *Non-randomised study*
Gundewar, Tejas; Kuchakulla, Manish; Ramasamy, Ranjith (2021) A paradoxical decline in semen parameters in men treated with clomiphene citrate: A systematic review. Andrologia 53(1): e13848	- Systematic review - included studies checked for relevance
Gunn, Deidre D and Bates, G Wright (2016) Evidence-based approach to unexplained infertility: a systematic review. Fertility and sterility 105(6): 1566-1574e1	- Systematic review - included studies checked for relevance
Guo, B., Li, J.-J., Ma, Y.-L. et al. (2022) Efficacy and safety of letrozole or anastrozole in the treatment of male infertility with low testosterone-estradiol ratio: A meta-analysis and systematic review. Andrology 10(5): 894-909	- Systematic review - included studies checked for relevance
Guo, C., Gu, W., Liu, M. et al. (2016) Efficacy and safety of testosterone replacement therapy in men with hypogonadism: A meta-analysis study of placebo-	- Systematic review - included studies checked for relevance

Study	Code [Reason]
controlled trials. Experimental and Therapeutic Medicine 11(3): 853-863	
Habous, M., Giona, S., Tealab, A. et al. (2018) Clomiphene citrate and human chorionic gonadotropin are both effective in restoring testosterone in hypogonadism: a short-course randomized study. BJU International 122(5): 889-897	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Hackett, G., Cole, N., Bhartia, M. et al. (2013) Testosterone Replacement Therapy with Long-Acting Testosterone Undecanoate Improves Sexual Function and Quality-of-Life Parameters vs. Placebo in a Population of Men with Type 2 Diabetes. Journal of Sexual Medicine 10(6): 1612-1627	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Hamilton, C R, Henkin, R I, Weir, G et al. (1973) Olfactory status and response to clomiphene in male gonadotrophin deficiency. Annals of internal medicine 78(1): 47-55	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Hansen, Karl R, Eisenberg, Esther, Baker, Valerie et al. (2018) Midluteal Progesterone: A Marker of Treatment Outcomes in Couples With Unexplained Infertility. The Journal of clinical endocrinology and metabolism 103(7): 2743-2751	- Population does not meet inclusion criteria *Participants do not have male factor infertility (couples with unexplained infertility and a male partner with at least 5 million motile sperm in the ejaculate)*
He, X, Song, T, Li, G et al. (2006) Clinical study of small doses androgen on the treatment of oligo-asthenospermatism. Chinese journal of andrology 20(7): 28-32	- Study not available in English
Helo, S Mechlin C Alkaram A Feustel P Ditkoff E Grossman M McCullough A (2014) Clomiphene citrate is superior to anastrazole in raising testosterone in hypogonadal infertile men: a prospective randomized double blind comparison trial. Fertility and sterility 102suppl(3): e46-e47	- Study design does not meet inclusion criteria *Conference abstract*
Helo, S., Ellen, J., Mechlin, C. et al. (2015) A Randomized Prospective Double-Blind Comparison Trial of Clomiphene Citrate and Anastrozole in Raising Testosterone in Hypogonadal Infertile Men. Journal of Sexual Medicine 12(8): 1761-1769	- Study design does not meet inclusion criteria *Editorial commentary*
Herzog, A.G., Farina, E.L., Drislane, F.W. et al. (2010) A comparison of anastrozole and testosterone versus placebo and testosterone for treatment of sexual dysfunction in men with epilepsy and hypogonadism. Epilepsy and Behavior 17(2): 264-271	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Ho, C.C.K., Tong, S.F., Low, W.Y. et al. (2012) A randomized, double-blind, placebo-controlled trial on the effect of long-acting testosterone treatment as assessed by the Aging Male Symptoms scale. BJU International 110(2): 260-265	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*

Study	Code [Reason]
Ho, Christopher Chee Kong and Tan, Hui Meng (2013) Treatment of the Hypogonadal Infertile Male-A Review. Sexual medicine reviews 1(1): 42-49	- Study design does not meet inclusion criteria *Narrative (non-systematic) review*
Hohl, A., Marques, M.O., Coral, M.H. et al. (2009) Evaluation of late-onset hypogonadism (andropause) treatment using three different formulations of injectable testosterone. Arquivos brasileiros de endocrinologia e metabologia 53(8): 989-995	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Hojer, E.G., Kreiberg, M., Dehlendorff, C. et al. (2022) Effect of Testosterone Replacement Therapy on Quality of Life and Sexual Function in Testicular Cancer Survivors With Mild Leydig Cell Insufficiency: Results From a Randomized Double-blind Trial. Clinical Genitourinary Cancer 20(4): 334-343	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Honig, S., Gittelman, M., Kaminetsky, J. et al. (2022) Two-Year Analysis of a New Oral Testosterone Undecanoate (TU) Formulation in Hypogonadal Men: Efficacy, Impact on Psychosexual Function, and Safety. Journal of Sexual Medicine 19(12): 1750-1758	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Hovatta, O, Koskimies, A I, Ranta, T et al. (1979) Bromocriptine treatment of oligospermia: a double blind study. Clinical endocrinology 11(4): 377-82	- Study design does not meet inclusion criteria *Non-randomised study*
Howell, S.J., Radford, J.A., Adams, J.E. et al. (2001) Randomized placebo-controlled trial of testosterone replacement in men with mild Leydig cell insufficiency following cytotoxic chemotherapy. Clinical Endocrinology 55(3): 315-324	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Huijben, M., Lock, M.T.W.T., de Kemp, V.F. et al. (2022) Clomiphene citrate for men with hypogonadism: a systematic review and meta-analysis. Andrology 10(3): 451-469	- Systematic review - included studies checked for relevance
Huijben, Manou, Huijsmans, Roel L N, Lock, M Tycho W T et al. (2023) Clomiphene citrate for male infertility: A systematic review and meta-analysis. Andrology	- Systematic review - included studies checked for relevance *Systematic review of both non randomised and randomised controlled trials. Randomised controlled trials were checked for relevance against the inclusion criteria.*
Iacono, F Ruffo A Prezioso D Illiano E Romeo G Romis L Capasso F Di Lauro G (2014) Combination therapy with antiestrogen and a natural composite containing tribulus terrestris, alga ecklonia bicyclis, biovis and myo-inositol in the treatment of male idiopathic infertility. Journal of sexual medicine 11: 92	- Study not available in English
Iacono, F, Barra, S, Montano, L et al. (1996) Value of high-dose pure FSH in the treatment of idiopathic male infertility. Journal d'urologie 102(2): 81-84	- Study design does not meet inclusion criteria *Conference Abstract*

Study	Code [Reason]
Ingerslev, H.J., Hojgaard, A., Hindkjaer, J. et al. (2001) A randomized study comparing IVF in the unstimulated cycle with IVF following clomiphene citrate. Human Reproduction 16(4): 696-702	- Population does not meet inclusion criteria *Participants did not have male factor infertility (infertility caused by tubal factor or unexplained infertility)*
Ionescu, C. and Pacu, I. (2011) Ovarian stiulation with clomiphen citrat versus low dose of FSHrec follow bz IUI in unexplained infertility. Obstetrica si Ginecologie 59(3): 201-204	- Study unavailable
Izumi, K., Iwamoto, H., Yaegashi, H. et al. (2021) Androgen replacement therapy for cancer-related symptoms in male: result of prospective randomized trial (ARTFORM study). Journal of Cachexia, Sarcopenia and Muscle 12(4): 831-842	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Jee, B.C., Ku, S.Y., Suh, C.S. et al. (2006) Use of letrozole versus clomiphene citrate combined with gonadotropins in intrauterine insemination cycles: a pilot study. Fertility and Sterility 85(6): 1774-1777	- Study design does not meet inclusion criteria *Observational study*
Jockenhovel, F., Blum, W.F., Vogel, E. et al. (1997) Testosterone substitution normalizes elevated serum leptin levels in hypogonadal men. Journal of Clinical Endocrinology and Metabolism 82(8): 2510-2513	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Jockenhovel, F., Bullmann, C., Schubert, M. et al. (1999) Influence of various modes of androgen substitution on serum lipids and lipoproteins in hypogonadal men. Metabolism: Clinical and Experimental 48(5): 590-596	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Jones, T Hugh, Dobs, Adrian S, Randeva, Harpal et al. (2023) Leflutrozole in male obesity-associated hypogonadotropic hypogonadism: Ph 2b double-blind randomised controlled trial. European journal of endocrinology 189(3): 297-308	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Kalinchenko, S, Vishnevskiy, EL, Koval, AN et al. (2008) Beneficial effects of testosterone administration on symptoms of the lower urinary tract in men with late-onset hypogonadism: a pilot study. Aging male 11(2): 57-61	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Kalkanli, Arif, Akdere, Hakan, Cevik, Gokhan et al. (2021) Hypergonadotropic Hypogonadism: Management of Infertility. Current pharmaceutical design 27(24): 2790-2795	- Systematic review - included studies checked for relevance
Kaminetsky, J.; Jaffe, J.S.; Swerdloff, R.S. (2015) Pharmacokinetic Profile of Subcutaneous Testosterone Enanthate Delivered via a Novel, Prefilled Single-Use Autoinjector: A Phase II Study. Sexual Medicine 3(4): 269-279	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Kaminetsky, J., Werner, M., Fontenot, G. et al. (2013) Oral enclomiphene citrate stimulates the endogenous	- Outcomes do not meet inclusion criteria

Study	Code [Reason]
production of testosterone and sperm counts in men with low testosterone: Comparison with testosterone gel. Journal of Sexual Medicine 10(6): 1628-1635	*Study does not report a primary outcome*
Kaminetsky, Jed C, Moclair, Betsy, Hemani, Micah et al. (2011) A phase IV prospective evaluation of the safety and efficacy of extended release testosterone pellets for the treatment of male hypogonadism. The journal of sexual medicine 8(4): 1186-96	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Kapoor, D., Clarke, S., Stanworth, R. et al. (2007) The effect of testosterone replacement theraphy on adipocytokines and C-reactive protein in hypogonadal men with type 2 diabetes. European Journal of Endocrinology 156(5): 595-602	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Karlstrom, P O; Bergh, T; Lundkvist, O (1993) A prospective randomized trial of artificial insemination versus intercourse in cycles stimulated with human menopausal gonadotropin or clomiphene citrate. Fertility and sterility 59(3): 554-9	- Population does not meet inclusion criteria *Participants do not have male factor infertility (couples with unexplained fertility and males had a normal sperm sample according to the WHO criteria)*
Kaufman, J.M., Miller, M.G., Fitzpatrick, S. et al. (2012) One-Year Efficacy and Safety Study of a 1.62% Testosterone Gel in Hypogonadal Men: Results of a 182-Day Open-Label Extension of a 6-Month Double-Blind Study. Journal of Sexual Medicine 9(4): 1149-1161	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Kaufman, J.M., Miller, M.G., Garwin, J.L. et al. (2011) Efficacy and Safety Study of 1.62% Testosterone Gel for the Treatment of Hypogonadal Men. Journal of Sexual Medicine 8(7): 2079-2089	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Khashaba, S., Krishan, A., Bruce, A. et al. (2024) Efficacy of clomiphene citrate and tamoxifen on pregnancy rates in idiopathic male subfertility: A systematic review and meta-analysis. Asian Journal of Urology	- Systematic review - included studies checked for relevance
Kim, E.D.; McCullough, A.; Kaminetsky, J. (2016) Oral enclomiphene citrate raises testosterone and preserves sperm counts in obese hypogonadal men, unlike topical testosterone: Restoration instead of replacement. BJU International 117(4): 677-685	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Kim, Edward D, Crosnoe, Lindsey, Bar-Chama, Natan et al. (2013) The treatment of hypogonadism in men of reproductive age. Fertility and sterility 99(3): 718-24	- Systematic review - included studies checked for relevance
Korani, M. (2023) Aromatase inhibitors in male: A literature review. Medicina Clinica Practica 6(1): 100356	- Study design does not meet inclusion criteria *Literature review of aromatase inhibitors for different usages, not specific to male infertility*
Korbonits, M., Slawik, M., Cullen, D. et al. (2004) A Comparison of a Novel Testosterone Bioadhesive	- Outcomes do not meet inclusion criteria

Study	Code [Reason]
Buccal System, Striant, with a Testosterone Adhesive Patch in Hypogonadal Males. Journal of Clinical Endocrinology and Metabolism 89(5): 2039-2043	*Study does not report a primary outcome*
Kotoulas, I.-G., Cardamakis, E., Michopoulos, J. et al. (1994) Tamoxifen treatment in male infertility. I. Effect on spermatozoa. Fertility and Sterility 61(5): 911-914	- Outcomes do not meet inclusion criteria *Study did not report a primary outcome*
Kuhnert, B., Byrne, M., Simoni, M. et al. (2005) Testosterone substitution with a new transdermal, hydroalcoholic gel applied to scrotal or non-scrotal skin: A multicentre trial. European Journal of Endocrinology 153(2): 317-326	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Kumar, S., Khatri, M., Memon, R.A. et al. (2022) Effects of testosterone therapy in adult males with hypogonadism and T2DM: A meta-analysis and systematic review. Diabetes and Metabolic Syndrome: Clinical Research and Reviews 16(8): 102588	- Systematic review - included studies checked for relevance
La Vignera, Sandro, Condorelli, Rosita Angela, Cimino, Laura et al. (2016) Late-onset hypogonadism: the advantages of treatment with human chorionic gonadotropin rather than testosterone. The aging male : the official journal of the International Society for the Study of the Aging Male 19(1): 34-9	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Leder, B.Z., Rohrer, J.L., Rubin, S.D. et al. (2004) Effects of aromatase inhibition in elderly men with low or borderline-low serum testosterone levels. Journal of Clinical Endocrinology and Metabolism 89(3): 1174-1180	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Li, CD, Weng, ZL, Zhang, YR et al. (1988) A Comparative study of guilu sizi mixture and clomiphene and prednisone in the treatment of idiopathic oligospermia. Chinese journal of urology 9(2): 109-111	- Study not available in English
Li, GY, Liang, JH, Meng, ZB et al. (2013) Low-dose testosterone undecanoate capsules combined with tadalafil for late-onset hypogonadism accompanied with ED. Zhonghua nan ke xue [National journal of andrology] 19(7): 630-633	- Study not available in English
Li, X, Lin, J, Zhang, L et al. (2022) Effects of gonadotropin-releasing hormone agonist pretreatment on frozen embryo transfer outcomes in artificial cycles: a meta-analysis. Archives of gynecology and obstetrics	- Systematic review - included studies checked for relevance
Lin, Jianli, Mao, Jiangfeng, Wang, Xi et al. (2019) Optimal treatment for spermatogenesis in male patients with hypogonadotropic hypogonadism. Medicine 98(31): e16616	- Insufficient presentation of results *Study reports number of pregnancies but only for participants who were married and had reached an adequate level of spermatogenesis to be fertile. The number of these participants is not reported and therefore cannot be extracted*

Study	Code [Reason]
Lunglmayr, G; Maier, U; Spona, J (1983) Effect of bromocriptine on semen quality and endocrine profiles in idiopathic oligozoospermia, results of a double blind prospective clinical trial. Andrologia 15(speciss): 548-553	- Study not available in English
Lunglmayr, G; Maier, U; Spona, J (1983) Bromocriptine vs placebo for oligospermia: prospective controlled study. Andrologia 15: 548-553	- Study design does not meet inclusion criteria *Non-randomised study*
Malkin, C.J., Pugh, P.J., Morris, P.D. et al. (2004) Testosterone replacement in hypogonadal men with angina improves ischaemic threshold and quality of life. Heart 90(8): 871-876	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Mangolim, A.S.; Brito, L.A.R.; Nunes-Nogueira, V.D.S. (2021) Effectiveness of testosterone replacement in men with obesity: a systematic review and meta-analysis. European journal of endocrinology 186(1): 123-135	- Systematic review - included studies checked for relevance
Mannaerts, B., Fauser, B., Lahlou, N. et al. (1996) Serum hormone concentrations during treatment with multiple rising doses of recombinant follicle stimulating hormone (Puregon) in men with hypogonadotropic hypogonadism. Fertility and Sterility 65(2): 406-410	- Study design does not meet inclusion criteria *Non-comparative study*
Mansour, Ragga, Aboulghar, Mohammed, Serour, Gamal I et al. (2003) The use of clomiphene citrate/human menopausal gonadotrophins in conjunction with GnRH antagonist in an IVF/ICSI program is not a cost effective protocol. Acta obstetricia et gynecologica Scandinavica 82(1): 48-52	- Study design does not meet inclusion criteria *Non-randomised study*
Mao, J.-F., Liu, Z.-X., Nie, M. et al. (2017) Pulsatile gonadotropin-releasing hormone therapy is associated with earlier spermatogenesis compared to combined gonadotropin therapy in patients with congenital hypogonadotropic hypogonadism. Asian Journal of Andrology 19(6): 680-685	- Study design does not meet inclusion criteria *Non-randomised study*
Marbury, T., Hamill, E., Bachand, R. et al. (2003) Evaluation of the pharmacokinetic profiles of the new testosterone topical gel formulation, TestinTM, compared to AndroGel. Biopharmaceutics and Drug Disposition 24(3): 115-120	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Marks, L.S., Mazer, N.A., Mostaghel, E. et al. (2006) Effect of testosterone replacement therapy on prostate tissue in men with late-onset hypogonadism: A randomized controlled trial. JAMA 296(19): 2351-2361	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Masterson, T.A., Turner, D., Vo, D. et al. (2021) The Effect of Longer-Acting vs Shorter-Acting Testosterone Therapy on Follicle Stimulating Hormone and Luteinizing Hormone. Sexual Medicine Reviews 9(1): 143-148	- Systematic review - included studies checked for relevance

Study	Code [Reason]
Matsumiya, K (2004) New method of endocrine therapy for male infertility. Hinyokika kiyo. Acta urologica Japonica 50(8): 541-543	- Study not available in English
Meikle, A.W.; Matthias, D.; Huffman, A.R. (2004) Transdermal testosterone gel: Pharmacokinetics, efficacy of dosing and application site in hypogonadal men. BJU International 93(6): 789-795	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Menkveld, R, Smith, JW, Kruger, TF et al. (1995) Treatment of severe teratozoospermic males with pure follicle-stimulating hormone of human chorioic gonadotrophin. Human reproduction (Oxford, England) 10: 99	- Study design does not meet inclusion criteria *Conference abstract*
Meuleman, E.J.H., Legros, J.-J., Bouloux, P.M.G. et al. (2015) Effects of long-term oral testosterone undecanoate therapy on urinary symptoms: Data from a 1-year, placebo-controlled, dose-ranging trial in aging men with symptomatic hypogonadism. Aging Male 18(3): 157-163	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Milardi, D., Luca, G., Grande, G. et al. (2017) Prednisone treatment in infertile patients with oligozoospermia and accessory gland inflammatory alterations. Andrology 5(2): 268-273	- Intervention does not meet inclusion criteria *Study compares different doses of prednisone*
Miller, Jake A, Nguyen, Tuan T, Loeb, Charles et al. (2023) Oral testosterone therapy: past, present, and future. Sexual medicine reviews 11(2): 124-138	- Outcomes do not meet inclusion criteria
Muir, Christopher A, Zhang, Ting, Jayadev, Veena et al. (2025) Efficacy of Gonadotropin Treatment for Induction of Spermatogenesis in Men With Pathologic Gonadotropin Deficiency: A Meta-Analysis. Clinical endocrinology 102(2): 167-177	- Systematic review - included studies checked for relevance
Murphy, J.C.; Srinivas, S.; Terris, M.K. (2004) Flutamide administration at 500 mg dialy has similar effects on serum testosterone to 750 mg daily. Journal of Andrology 25(4): 630-634	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Nakhai Pour, H.R., Emmelot-Vonk, M.H., Sukel-Helleman, M. et al. (2006) Double blind randomized placebo-controlled trial on the effects of testosterone supplementation in elderly men with moderate to low testosterone levels: Design and baseline characteristics [ISRCTN23688581]. Trials 7: 24	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Nazari, A, Mokhtaree, M, Rouhafza, R et al. (2020) Pregnancy and live birth rate in idiopathic male infertility treated with Human Menopausal Gonadotropin: a pilot clinical trial. Journal of midwifery & reproductive health 8(1): 2016-2021	- Intervention does not meet inclusion criteria *Study compares different doses of the same drug (human menopausal gonadotrophin)*
Neveu, S, Hedon, B, Mares, P et al. (1987) Experience of a GnRH agonist: the Buserelin for in vitro fertilization. Contraception fertilite sexualite 15(78): 774-777	- Study not available in English

Study	Code [Reason]
Nian, Y., Ding, M., Hu, S. et al. (2017) Testosterone replacement therapy improves health-related quality of life for patients with late-onset hypogonadism: a meta-analysis of randomized controlled trials. Andrologia 49(4): e12630	- Systematic review - included studies checked for relevance
Niederberger, C. (2011) Combination clomiphene citrate and antioxidant therapy for idiopathic male infertility: A randomized controlled trial. Journal of Urology 185(1): 252	- Intervention does not meet inclusion criteria *Study compares clomiphene citrate plus vitamin E to placebo*
Nuojua-Huttunen, S, Tuomivaara, L, Juntunen, K et al. (1997) Long gonadotrophin releasing hormone agonist/human menopausal gonadotrophin protocol for ovarian stimulation in intrauterine insemination treatment. European journal of obstetrics, gynecology, and reproductive biology 74(1): 83-7	- Study design does not meet inclusion criteria *Not a randomised controlled trial*
O'Dea, L, Banks, K, Currie, K et al. (1998) Fertinex (urofollitropin for injection, puriefied) with hCG for the treatment of male hypogonadotropic hyogonadism. Fertility and sterility 70(3): 11	- Study design does not meet inclusion criteria *Conference abstract*
O'Donovan, P.A., Vandekerckhove, P., Lilford, R.J. et al. (1993) Treatment of male infertility: Is it effective? Review and meta-analyses of published randomized controlled trials. Human Reproduction 8(8): 1209-1222	- Systematic review - included studies checked for relevance
Ovesen, P, Jorgensen, J O, Ingerslev, J et al. (1996) Growth hormone treatment of subfertile males. Fertility and sterility 66(2): 292-8	- Study design does not meet inclusion criteria *Study compares the same intervention in 3 different populations*
Pandian, Z., Bhattacharya, S., Nikolaou, D. et al. (2003) The effectiveness of IVF in unexplained infertility: A systematic Cochrane review. Human Reproduction 18(10): 2001-2007	- Study design does not meet inclusion criteria *Abstract only*
Papadimas, J., Bili, E., Papadopoulou, F. et al. (1996) Testosterone undecanoate versus mesterolone in hypogonadal male patients. Review of Clinical Pharmacology and Pharmacokinetics, International Edition 10(1): 3-8	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Park, N.C., Yan, B.Q., Chung, J.M. et al. (2003) Oral testosterone undecanoate (Andriol) supplement therapy improves the quality of life for men with testosterone deficiency. Aging Male 6(2): 86-93	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Peeraer, Karen, Luyten, Jeroen, Tomassetti, Carla et al. (2018) Cost-effectiveness of ovarian stimulation with gonadotrophin and clomiphene citrate in an intrauterine insemination programme for subfertile couples. Reproductive biomedicine online 36(3): 302-310	- Intervention does not meet inclusion criteria *Intrauterine insemination following ovarian stimulation with subcutaneously administered low-dose human menopausal gonadotrophin or with orally administered clomiphene citrate in women*

Study	Code [Reason]
	- Outcomes do not meet inclusion criteria *No relevant primary outcomes are reported (cost effectiveness outcomes only)*
Pelusi, C., Fanelli, F., Baccini, M. et al. (2021) Impact of Clomiphene Citrate on the Steroid Profile in Dysmetabolic Men with Low Testosterone Levels. Hormone and Metabolic Research 53(8): 520-528	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Petreski, T, Organdziski, V, Mirkovska, G et al. (2001) Our results from the use of urinary gonadotropins and the recombined FSH Gonal F in the therapy of male infertility. 17th world congress on fertility and sterility: 184	- Study design does not meet inclusion criteria *Conference abstract*
Pozzi, Edoardo, Ila, Vishal, Petrella, Francis et al. (2024) Evaluating Sperm Recovery Time and Efficacy of Monotherapy vs. Combination Therapies in Men with Congenital Hypogonadotropic Hypogonadism: A Systematic Review and Meta-Analysis. The world journal of men's health	- Systematic review - included studies checked for relevance
Prizao, V.M., Souza, M.M., Morais, B.A.A.H. et al. (2024) TESTOSTERONE REPLACEMENT THERAPY IN HYPOGONADAL AND ANEMIC ELDERLY MEN: A META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS. Hematology, Transfusion and Cell Therapy 46: S5-S6	- Study design does not meet inclusion criteria *Conference abstract*
Pryor, J and Chaput De Saint Tonge, M (1981) Controlled clinical trial of bromocriptine for oligozoospermic men. Israel journal of medical sciences 17(8): 773-773	- Study design does not meet inclusion criteria *Conference abstract*
Puia, Dragos and Pricop, Catalin (2022) Effectiveness of Clomiphene Citrate for Improving Sperm Concentration: A Literature Review and Meta-Analysis. Cureus 14(5): e25093	- Systematic review - included studies checked for relevance
Qin, F., Zhou, Y., Huan, L. et al. (2020) Comparison of clomiphene and letrozole for superovulation in patients with unexplained infertility undergoing intrauterine insemination: A systematic review and meta-analysis. Medicine (United States) 99(31): e21006	- Systematic review - included studies checked for relevance *The systematic review included non randomised and randomised studies. Randomised studies were checked for inclusion according to the protocol*
Raheem, O.A., Chen, T.T., Akula, K.P. et al. (2021) Efficacy of Non-Testosterone-Based Treatment in Hypogonadal Men: A Review. Sexual Medicine Reviews 9(3): 381-392	- Systematic review - included studies checked for relevance
Raman, Jay D and Schlegel, Peter N (2002) Aromatase inhibitors for male infertility. The Journal of urology 167(2pt1): 624-9	- Study design does not meet inclusion criteria *Literature review*

Study	Code [Reason]
Ramasamy, Ranjith, Masterson, Thomas A, Best, Jordan C et al. (2020) Effect of Natesto on Reproductive Hormones, Semen Parameters and Hypogonadal Symptoms: A Single Center, Open Label, Single Arm Trial. The Journal of urology 204(3): 557-563	- Population does not meet inclusion criteria *12/60 (20%) of participants were actively trying to conceive; study notes that 'several' of the included participants were not in relationships*
Rastrelli, G, Corona, G, Mannucci, E et al. (2014) Factors affecting spermatogenesis upon gonadotropin-replacement therapy: a meta-analytic study. Andrology 2(6): 794-808	- Systematic review - included studies checked for relevance
Raynaud, J.-P., Colle, M., Pujos-Gautraud, M. et al. (2010) Comparison of oral versus transdermal testosterone supplementation in hypogonadal men. Hormone Molecular Biology and Clinical Investigation 2(3): 301-309	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Raynaud, J.-P., Legros, J.-J., Rollet, J. et al. (2008) Efficacy and safety of a new testosterone-in-adhesive matrix patch applied every 2 days for 1 year to hypogonadal men. Journal of Steroid Biochemistry and Molecular Biology 109(12): 168-176	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Reich, P; Knopf, B; Meyer, J (1975) Efficacy of pharmacotherapy in male subfertility. UNTERSUCHUNGEN ZUR EFFEKTIVITAT DER PHARMAKOTHERAPIE BEI SUBFERTILITAT DES MANNES. DERMMSCHR 161(1): 38-42	- Study not available in English
Ribeiro, M.A., Gameiro, L.F.O., Scarano, W.R. et al. (2016) Aromatase inhibitors in the treatment of oligozoospermic or azoospermic men: A systematic review of randomized controlled trials. Jornal Brasileiro de Reproducao Assistida 20(2): 82-88	- Systematic review - included studies checked for relevance
Roelfsema, F., Yang, R.J., Takahashi, P.Y. et al. (2018) Aromatized Estrogens Amplify Nocturnal Growth Hormone Secretion in Testosterone-Replaced Older Hypogonadal Men. Journal of Clinical Endocrinology and Metabolism 103(12): 4419-4427	- Population does not meet inclusion criteria *Study participants are healthy, gonadotropin-downregulated older men*
Rogol, A.D.; Tkachenko, N.; Bryson, N. (2016) NatestoTM, a novel testosterone nasal gel, normalizes androgen levels in hypogonadal men. Andrology 4(1): 46-54	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Ronnberg, L (1980) The effect of clomiphene citrate on different sperm parameters and serum hormone levels in preselected infertile men: a controlled double-blind cross-over study. International journal of andrology 3(5): 479-86	- Insufficient presentation of results *Cross-over trial, results from before cross-over period not presented separately for each group*
Sahib, Bahaa O, Hussein, Ibrahim H, Alibrahim, Nassar T et al. (2023) Management Outcomes in Males With Hypogonadotropic Hypogonadism Treated With Gonadotropins. Cureus 15(2): e35601	- Intervention does not meet inclusion criteria *Participants received combination treatments of either human chorionic gonadotrophin (hCG) and human*

Study	Code [Reason]
	menopausal gonadotrophin (HMG) or hCG alone for six months and then a combination of hCG and HMG, compared to hCG alone
Santi, D.; Granata, A.R.M.; Simoni, M. (2015) FSH treatment of male idiopathic infertility improves pregnancy rate: A meta-analysis. Endocrine Connections 4(3): r46-r58	- Systematic review - included studies checked for relevance
Santi, D.; Granata, A.R.M.; Simoni, M. (2015) Efficacy of follicle-stimulating hormone treatment in male idiopathic infertility: A meta-analysis. Human Reproduction: i136	- Systematic review - included studies checked for relevance
Schubert, M., Minnemann, T., Hubler, D. et al. (2004) Intramuscular testosterone undecanoate: Pharmacokinetic aspects of a novel testosterone formulation during long-term treatment of men with hypogonadism. Journal of Clinical Endocrinology and Metabolism 89(11): 5429-5434	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Seidman, S.N. and Rabkin, J.G. (1998) Testosterone replacement therapy for hypogonadal men with SSRI-refractory depression. Journal of Affective Disorders 48(23): 157-161	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Seidman, S.N. and Roose, S.P. (2006) The sexual effects of testosterone replacement in depressed men: Randomized, placebo-controlled clinical trial. Journal of Sex and Marital Therapy 32(3): 267-273	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Shabsigh, R., Kaufman, J.M., Steidle, C. et al. (2004) Randomized study of testosterone gel as adjunctive therapy to sildenafil in hypogonadal men with erectile dysfunction who do not respond to sildenafil alone. Journal of Urology 172(2): 658-663	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Shahid, M.N., Khan, T.M., Neoh, C.F. et al. (2021) Effectiveness of Pharmacological Intervention Among Men with Infertility: A Systematic Review and Network Meta-Analysis. Frontiers in Pharmacology 12: 638628	- Systematic review - included studies checked for relevance
Shahin, Ahmed Y, Ismail, Alaa M, Zahran, Kamal M et al. (2008) Adding phytoestrogens to clomiphene induction in unexplained infertility patients--a randomized trial. Reproductive biomedicine online 16(4): 580-8	- Population does not meet inclusion criteria *Participants did not have male factor infertility (unexplained fertility)* - Intervention does not meet inclusion criteria *Intervention was a combination of clomiphene plus phytoestrogens compared to clomiphene only*
Sharma, DS (2021) Pregnancy rate in male factor infertility with oligoastheneteratozoospermia - evaluation of Letrozole and Coenzyme Q10 supplementation on sperm parameter. Human reproduction. 37th virtual	- Study design does not meet inclusion criteria *Conference abstract*

Study	Code [Reason]
annual meeting of the european society of human reproduction and embryology 36suppl1: i169	
Shirai, M., Tsujimura, A., Mizushima, K. et al. (2022) Novel testosterone gel improves serum testosterone concentrations and aging males' symptoms in patients with late-onset hypogonadism: an active control equivalence, randomized, double-blind, crossover study. Endocrine journal	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Singhania, N, Devi, KB, Kaur, J et al. (2024) Effect of Combined Low Dose hCG, FSH and Testosterone therapy (LFT Regimen) versus Conventional High Dose hCG and FSH on Spermatogenesis and Biomarkers in Men with Hypogonadotropic Hypogonadism. Endocrine practice	- Duplicate
Singhania, Nikhil, Devi, Konsam Biona, Kaur, Japleen et al. (2024) Effect of Combined Low Dose Human Gonadotropic Hormone, Follicle Stimulating Hormone, and Testosterone Therapy (LFT Regimen) Versus Conventional High Dose Human Gonadotropic Hormone and Follicle Stimulating Hormone on Spermatogenesis and Biomarkers in Men With Hypogonadotropic Hypogonadism. Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists 30(10): 978-986	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Skakkebaek, N.E., Bancroft, J., Davidson, D.W. et al. (1981) Androgen replacement with oral testosterone undecanoate in hypogonadal men: A double blind controlled study. Clinical Endocrinology 14(1): 49-61	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Soares, A.H., Horie, N.C., Chiang, L.A.P. et al. (2018) Effects of clomiphene citrate on male obesity-associated hypogonadism: A randomized, double-blind, placebo-controlled study. International Journal of Obesity 42(5): 953-963	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Song, B and Cai, Z-M (2012) Effectiveness of testosterone undecanoate treatment in men with asthenospermia. Journal of reproduction and contraception 23(2): 119-126	- Study design does not meet inclusion criteria *Non-randomised study*
Strawford, A., Barbieri, T., Neese, R. et al. (1999) Effects of nandrolone decanoate therapy in borderline hypogonadal men with HIV-associated weight loss. Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology 20(2): 137-146	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Swerdloff, R.S. and Dudley, R.E. (2020) A new oral testosterone undecanoate therapy comes of age for the treatment of hypogonadal men. Therapeutic Advances in Urology 12	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Swerdloff, R.S., Wang, C., White, W.B. et al. (2020) A New Oral Testosterone Undecanoate Formulation	- Outcomes do not meet inclusion criteria

Study	Code [Reason]
Restores Testosterone to Normal Concentrations in Hypogonadal Men. Journal of Clinical Endocrinology and Metabolism 105(8): dgaa238	*Study does not report a primary outcome*
Tan, R.S. and Pu, S.J. (2003) A pilot study on the effects of testosterone in hypogonadal aging male patients with Alzheimer's disease. Aging Male 6(1): 13-17	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Tang, KF, Xing, Y, Wu, CY et al. (2011) Tamoxifen combined with coenzyme Q10 for idiopathic oligoasthenospermia. Zhonghua nan ke xue [National journal of andrology] 17(7): 615-618	- Study not available in English
Tesarik, J, Greco, E, Rienzi, L et al. (1998) Differentiation of spermatogenic cells during in-vitro culture of testicular biopsy samples from patients with obstructive azoospermia: effect of recombinant follicle stimulating hormone. Human reproduction (Oxford, England) 13(10): 2772-2781	- Study design does not meet inclusion criteria *Non-randomised study*
Tharakan, T., Corona, G., Foran, D. et al. (2022) Does hormonal therapy improve sperm retrieval rates in men with non-obstructive azoospermia: a systematic review and meta-analysis. Human reproduction update 28(5): 609-628	- Systematic review - included studies checked for relevance
Tokgoz, V.Y., Sukur, Y.E., Ozmen, B. et al. (2021) Clomiphene citrate versus recombinant FSH in intrauterine insemination cycles with mono-or bi-follicular development. Jornal Brasileiro de Reproducao Assistida 25(3): 383-389	- Study design does not meet inclusion criteria *Study is not a randomised controlled trial (retrospective cohort study)*
Torok, L (1985) Treatment of oligozoospermia with tamoxifen (open and controlled studies). Andrologia 17(5): 497-501	- Study design does not meet inclusion criteria *Non-randomised study*
Traish, Abdulmaged M (2018) Benefits and Health Implications of Testosterone Therapy in Men With Testosterone Deficiency. Sexual medicine reviews 6(1): 86-105	- Systematic review - included studies checked for relevance
Tripathy, S.K., Singh, R., Dalal, S. et al. (2024) EVALUATING MALE FERTILITY OUTCOMES (CAPACITATION, ACROSOME REACTION, PENETRATION TO ZONA PELLUCIDA, MOTILITY, COUNT, MORPHOLOGY AND SEMEN QUALITY) WITH A PATENTED PROPRIETARY FORMULATION CONTAINING D-ASPARTATE, BETAINE, AND UBIQUINOL COMPARED TO COMPARATIVE THERAPY: CAPTURE TRIAL. International Journal of Medicine and Public Health 14(2): 611	- Intervention does not meet inclusion criteria
Turner, L., Ly, L.P., Desai, R. et al. (2019) Pharmacokinetics and Acceptability of Subcutaneous Injection of Testosterone Undecanoate. Journal of the Endocrine Society 3(8): 1531-1540	- Systematic review - included studies checked for relevance

Study	Code [Reason]
Utigalieva, E., Morozov, A., Shoshany, O. et al. (2024) A systematic review and meta-analysis of the placebo effect on both semen quality and male infertility. Minerva Urology and Nephrology 76(4): 423	- Systematic review - included studies checked for relevance
Vandekerckhove, P., Lilford, R., Vail, A. et al. (2000) Clomiphene or tamoxifen for idiopathic oligo/asthenospermia. Cochrane database of systematic reviews (Online): cd000151	- Systematic review - included studies checked for relevance
Vandekerckhove, P., Lilford, R., Vail, A. et al. (2000) Androgens versus placebo or no treatment for idiopathic oligo/asthenospermia. Cochrane database of systematic reviews (Online): cd000150	- Systematic review - included studies checked for relevance
Verdi, A., Nasr-Esfahani, M.H., Forouzanfar, M. et al. (2021) The effect of recombinant human follicle-stimulating hormone on sperm quality, chromatin status and clinical outcomes of infertile oligozoospermic men candidate for intracytoplasmic sperm injection: A randomized clinical trial. International Journal of Fertility and Sterility 15(1): 1-7	- Study design does not meet inclusion criteria *Paper states that this is a randomised controlled trial. However, assignment is not random. People agreeing to receive the study drug formed the intervention group and those agreeing to provide blood and semen samples but refusing to take the study drug formed the control group*
von Eckardstein, Sigrid and Nieschlag, Eberhard (2002) Treatment of male hypogonadism with testosterone undecanoate injected at extended intervals of 12 weeks: a phase II study. Journal of andrology 23(3): 419-25	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Wang, C., Chan, C.W., Wong, K.K. et al. (1983) Comparison of the effectiveness of placebo, clomiphene citrate, mesterolone, pentoxifylline, and testosterone rebound therapy for the treatment of idiopathic oligospermia. Fertility and Sterility 40(3): 358-365	- Insufficient presentation of results *If there was no clinical response at the end of treatment participants were reassigned to an alternative treatment and data reported for all participants (cross-over with no first-phase data)*
Wang, Y, Yang, S, Cai, W et al. (2010) Clinical efficacy of L-carnitine combined with tamoxifen in treatment of oligoasthenozoospermia. Chinese journal of andrology 24(5): 55-57	- Study not available in English *Published in Chinese*
Wei, C., Long, G., Zhang, Y. et al. (2020) Spermatogenesis of male patients with congenital hypogonadotropic hypogonadism receiving pulsatile gonadotropin-releasing hormone therapy versus gonadotropin therapy: A systematic review and meta-analysis. World Journal of Men's Health 38	- Systematic review - included studies checked for relevance
Wheeler, Karen M, Sharma, Devang, Kavoussi, Parviz K et al. (2019) Clomiphene Citrate for the Treatment of Hypogonadism. Sexual medicine reviews 7(2): 272-276	- Systematic review - included studies checked for relevance
Wiehle, R., Cunningham, G.R., Pitteloud, N. et al. (2013) Testosterone restoration using enclomiphene citrate in men with secondary hypogonadism: A	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*

Study	Code [Reason]
pharmacodynamic and pharmacokinetic study. BJU International 112(8): 1188-1200	
Wiehle, R.D., Fontenot, G.K., Wike, J. et al. (2014) Enclomiphene citrate stimulates testosterone production while preventing oligospermia: A randomized phase II clinical trial comparing topical testosterone. Fertility and Sterility 102(3): 720-727	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Wiehle, R.D., Fontenot, G.K., Willett, M.S. et al. (2014) Enclomiphene citrate stimulates serum testosterone in men with low testosterone within 14 days. Journal of Men's Health 11(4): 1-10	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Wiehle, Ronald, Cunningham, Glenn R, Pitteloud, Nelly et al. (2013) Testosterone Restoration by Enclomiphene Citrate in Men with Secondary Hypogonadism: Pharmacodynamics and Pharmacokinetics. BJU international	- Duplicate *Duplicate of Wiehle 2013*
Wilson, D.E., Meikle, A.W., Boike, S.C. et al. (1998) Bioequivalence assessment of a single 5 mg/day testosterone transdermal system versus two 2.5 mg/day systems in hypogonadal men. Journal of Clinical Pharmacology 38(1): 54-59	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Wittert, G.A., Harrison, R.W., Buckley, M.J. et al. (2016) An open-label, phase 2, single centre, randomized, crossover design bioequivalence study of AndroForte 5 testosterone cream and Testogel 1% testosterone gel in hypogonadal men: Study LP101. Andrology 4(1): 41-45	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Yannas, D., Vignozzi, L., Maggi, M. et al. (2024) EFFICACY AND PREDICTORS OF SPERMATOGENESIS INDUCTION UPON GONADOTROPIN AND GNRH THERAPY IN CONGENITAL HYPOGONADOTROPIC HYPOGONADISM: A META-ANALYSIS. J. Sex. Med. 21: iv25-None	- Study design does not meet inclusion criteria *Conference abstract*
Young, J., Couzinet, B., Chanson, P. et al. (2000) Effects of human recombinant luteinizing hormone and follicle-stimulating hormone in patients with acquired hypogonadotropic hypogonadism: Study of Sertoli and Leydig cell secretions and interactions. Journal of Clinical Endocrinology and Metabolism 85(9): 3239-3244	- Insufficient presentation of results *Cross-over study, results prior to cross-over period not reported separately for each group*
Yun, B.H., Chon, S.J., Park, J.H. et al. (2015) Minimal stimulation using gonadotropin combined with clomiphene citrate or letrozole for intrauterine insemination. Yonsei Medical Journal 56(2): 490-496	- Study design does not meet inclusion criteria *Study is not a randomised controlled trial*
Zarrilli, S., Paesano, L., Colao, A. et al. (2000) FSH treatment improves sperm function in patients after varicocelectomy. Journal of Endocrinological Investigation 23(2): 68-73	- Population does not meet inclusion criteria *Participants are men with varicocele. Study does not mention whether all participants have fertility problems or*

Study	Code [Reason]
	whether they are trying to conceive. The number of participants actively trying to conceive is not reported and therefore pregnancy rates outcomes cannot be extracted
Zhang, M., Tong, G., Liu, Y. et al. (2015) Sequential versus continual purified urinary FSH/hCG in men with idiopathic hypogonadotropic hypogonadism. Journal of Clinical Endocrinology and Metabolism 100(6): 2449-2455	- Outcomes do not meet inclusion criteria *Study does not report a primary outcome*
Zhang, X., Chen, J., Cui, Y. et al. (2022) FSH can improve semen parameters in patients with idiopathic oligoasthenoteratozoospermia: A systematic review and meta-analysis. Andrologia 54(11): e14596	- Systematic review - included studies checked for relevance
Zheng, Y, Shen, XB, Zhou, YZ et al. (2015) [Effect and safety of testosterone undecanoate in the treatment of late-onset hypogonadism: a meta-analysis]. Zhonghua nan ke xue = National journal of andrology 21(3): 263-71	- Systematic review - included studies checked for relevance

Excluded economic studies

Table 19: Excluded studies and reasons for their exclusion

Study	Code
Cruickshank, Moira; Hudson, Jemma; Hernandez, Rodolfo et al. (2024) The effects and safety of testosterone replacement therapy for men with hypogonadism: the TestES evidence synthesis and economic evaluation. Health technology assessment (Winchester, England); 2024; vol. 28 (no. 43); 1-210	- Wrong population
Hernandez, Rodolfo; de Silva, Nipun Lakshitha; Hudson, Jemma et al. (2024) Cost-effectiveness of testosterone treatment utilising individual patient data from randomised controlled trials in men with low testosterone levels. Andrology; 2024; vol. 12 (no. 3); 477-486	- Wrong population
Cift, Ali; Benlioglu, Can; Yucel, Mehmet Ozgur et al. (2024) A New Sperm Concentration Threshold for Y Chromosome Microdeletion Analysis in Infertile Men: Could It Be Azoopermia?. Urology research & practice; 2024; vol. 50 (no. 3); 181-186	- Not an economic evaluation

Appendix K Research recommendations – full details

Research recommendations for review question: What is the effectiveness of hormone treatment in male factor fertility problems?

K.1.1 Research recommendation

K.1.2 What is the clinical and cost effectiveness of gonadotrophins or anti-oestrogens in men with impaired semen parameters, normal or high FSH, low or normal testosterone, and no hypogonadotropic hypogonadism or evidence of obstruction?

K.1.3 Why this is important

Men with hypogonadotropic hypogonadism are known to respond to treatment with gonadotrophins but for other men with impaired semen parameters (with low or normal testosterone levels and normal or high levels of FSH), the effectiveness of treatment is less certain, and it is not known whether gonadotrophins or anti-oestrogens will improve semen parameters or fertility.

K.1.4 Rationale for research recommendation

Table 20: Research recommendation rationale

Importance to 'patients' or the population	In men with normal or high FSH levels and low or normal testosterone who have semen abnormalities, medical management options are unclear and currently no medical treatment is recommended outside a clinical trial. Evidence in this specific group would increase the treatment options available to these men.
Relevance to NICE guidance	Due to a lack of clear evidence there are no recommendations for routine medical management for this group of men.
Relevance to the NHS	Effective medical treatment for this group of men may reduce the need for more expensive and invasive treatments such as surgical sperm retrieval and assisted reproduction technologies.
National priorities	High
Current evidence base	• No evidence for people with low testosterone and normal or high FSH • Contradictory evidence for people with normal testosterone and normal or high FSH
Equality considerations	None known

FSH: follicle-stimulating hormone

K.1.5 Modified PICO table

Table 21: Research recommendation modified PICO table

Population	Men with impaired semen parameters who have normal or high FSH levels, low or normal testosterone, and no hypogonadotropic hypogonadism or evidence of obstruction

Intervention	• Gonadotrophin therapy • Anti-oestrogens (for example, clomifene and tamoxifen)
Comparator	• Head-to-head comparisons between different interventions within each category • Head-to-head comparisons between different interventions between each category • Placebo • No intervention

Outcome	Critical:
	• Live birth following assisted reproduction
	• Clinical pregnancy rate (an ultrasound scan that has shown at least one fetal heart beat) following assisted reproduction
	
	Important:
	• Generic health-related or disease-specific quality of life measured using a validated instrument in the person with male factor fertility problems, for example:
	  ○ EQ-5D
	  ○ Health Utilities Index Mark 3 (HUI3) questionnaire
	  ○ FertiQoL
	• Increased testosterone production/ improved hormonal parameters
	• Improved semen parameters (sperm concentration, motile sperm count/concentration)
	• Miscarriage (loss of a baby before 24 weeks gestational age)
	• Number of participants requiring surgical sperm retrieval
	• Rate of successful surgical sperm retrieval
	• Cost-effectiveness.

Study design	Randomised controlled trial with cost-effectiveness analysis
Timeframe	6-12 months follow-up

Additional information	Evidence should be sub-grouped according to the following:
	• FSH levels:
	  ○ Normal FSH levels
	  ○ High FSH levels
	• Testosterone levels
	  ○ Normal testosterone levels
	  ○ Low testosterone levels
	• Severity of semen abnormalities
	  ○ Azoospermia
	  ○ Non-azoospermia

EQ-5D: European Quality of Life Five Dimension; FSH: follicle stimulating hormone