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Growth hormone for in vitro fertilisation (IVF) (Review)

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[Intervention Review]

Growth hormone for in vitro fertilisation (IVF)

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A B S T R A C T

Background

In an effort to improve outcomes of in vitro fertilisation (IVF) cycles, the use of growth hormone (GH) has been considered as adjuvant treatment in ovarian stimulation. Improving the outcomes of IVF is especially important for women with infertility who are considered 'poor responders'. We have compared the outcomes of IVF with adjuvant GH versus no adjuvant treatment in routine use, and specifically in poor responders.

Objectives

To assess the effectiveness and safety of growth hormone as an adjunct to IVF compared to standard IVF for women with infertility

Search methods

We searched the following databases (to November 2020): Cochrane Gynaecology and Fertility (CGF) Group specialised register, CENTRAL, MEDLINE, Embase, CINAHL, Epistemonikos database and trial registers together with reference checking and contact with study authors and experts in the field to identify additional trials.

Selection criteria

We included all randomised controlled trials (RCTs) of adjuvant GH treatment in IVF compared with no adjuvant treatment for women with infertility. We excluded trials where additional adjuvant treatments were used with GH. We also excluded trials comparing different IVF protocols.

Data collection and analysis

We used standard methodological procedures recommended by Cochrane. Two review authors independently performed assessment of trial risk of bias and extraction of relevant data. The primary review outcome was live birth rate. The secondary outcomes were clinical pregnancy rate, oocytes retrieved, embryo transfer, units of gonadotropin used and adverse events, i.e. ectopic pregnancy, multiple pregnancy, ovarian hyperstimulation syndrome (OHSS), congenital anomalies, oedema.

Main results

We included 16 RCTs (1352 women). Two RCTs (80 women) studied GH in routine use, and 14 RCTs (1272 women) studied GH in poor responders. The evidence was low to very low certainty, the main limitations being risk of bias, imprecision and heterogeneity.

Adjuvant growth hormone compared to no adjuvant: routine use for in vitro fertilisation (IVF)

The evidence is very uncertain about the effect of GH on live birth rate per woman randomised for routine use in IVF (odds ratio (OR) 1.32, 95% confidence interval (CI) 0.40 to 4.43; I^2 = 0%; 2 trials, 80 participants; very low-certainty evidence). If the chance of live birth without adjuvant GH is assumed to be 15%, the chance of live birth with GH would be between 6% and 43%.

There was insufficient evidence to reach a conclusion regarding clinical pregnancy rates per woman randomised, number of women with at least one oocyte retrieved per woman randomised and embryo transfer achieved per woman randomised; reported data were unsuitable for analysis.

The evidence is very uncertain about the effect of GH on mean number of oocytes retrieved in normal responders (mean difference (MD) -0.02, 95% CI -0.79 to 0.74; I^2 = 0%; 2 trials, 80 participants; very low-certainty evidence).

The evidence is very uncertain about the effect of GH on mean units of gonadotropin used in normal responders (MD 13.57, 95% CI -112.88 to 140.01; I^2 = 0%; 2 trials, 80 participants; very low-certainty evidence).

We are uncertain of the effect of GH on adverse events in normal responders.

Adjuvant growth hormone compared to no adjuvant: use in poor responders for in vitro fertilisation (IVF)

The evidence is very uncertain about the effect of GH on live birth rate per woman randomised for poor responders (OR 1.77, 95% CI 1.17 to 2.70; I^2 = 0%; 8 trials, 737 participants; very low-certainty evidence). If the chance of live birth without adjuvant GH is assumed to be 11%, the chance of live birth with GH would be between 13% and 25%. Adjuvant GH results in a slight increase in pregnancy rates in poor responders (OR 1.85, 95% CI 1.35 to 2.53; I^2 = 15%; 11 trials, 1033 participants; low-certainty evidence). The results suggest, if the pregnancy rate without adjuvant GH is assumed to be 15%, with GH the pregnancy rate in poor responders would be between 19% and 31%. The evidence suggests that GH results in little to no difference in number of women with at least one oocyte retrieved (OR 5.67, 95% CI 1.54 to 20.83; I^2 = 0%; 2 trials, 148 participants; low-certainty evidence). If the chance of retrieving at least one oocyte in poor responders was 81%, with GH the chance is between 87% and 99%. There is a slight increase in mean number of oocytes retrieved with the use of GH for poor responders (MD 1.40, 95% CI 1.16 to 1.64; I^2 = 87%; 12 trials, 1153 participants; low-certainty evidence). The evidence is very uncertain about the effect of GH on embryo transfer achieved (OR 2.32, 95% CI 1.08 to 4.96; I^2 = 25%; 4 trials, 214 participants; very low-certainty evidence). If the chance of achieving embryo transfer is assumed to be 77%, the chance with GH will be 78% to 94%. Use of GH results in reduction of mean units of gonadotropins used for stimulation in poor responders (MD -1088.19, 95% CI -1203.20 to -973.18; I^2 = 91%; 8 trials, 685 participants; low-certainty evidence).

High heterogeneity in the analyses for mean number of oocytes retrieved and units of GH used suggests quite different effects according to differences including in trial protocols (populations, GH dose and schedule), so these results should be interpreted with caution.

We are uncertain of the effect of GH on adverse events in poor responders as six of the 14 included trials failed to report this outcome.

Authors' conclusions

The use of adjuvant GH in IVF treatment protocols has uncertain effect on live birth rates and mean number of oocytes retrieved in normal responders. However, it slightly increases the number of oocytes retrieved and pregnancy rates in poor responders, while there is an uncertain effect on live birth rates in this group. The results however, need to be interpreted with caution, as the included trials were small and few in number, with significant bias and imprecision. Also, the dose and regimen of GH used in trials was variable. Therefore, further research is necessary to fully define the role of GH as adjuvant therapy in IVF.

P L A I N   L A N G U A G E   S U M M A R Y

Growth hormone for in vitro fertilisation (IVF)

Review question

Cochrane researchers reviewed the evidence about giving growth hormone as an additional treatment to women undergoing IVF compared to not giving this treatment to such women.

Background

During an IVF cycle, women need to be given gonadotrophin therapy to stimulate ovaries to produce eggs. Theoretically, the use of growth hormone as an added treatment may enhance the response of gonadotrophin therapy. We assessed the benefits and risks of using growth hormone compared with no growth hormone treatment in women undergoing IVF. 'Poor responders' in IVF treatment are usually older women with low ovarian reserve or women who had previous IVF treatment with less than five eggs collected despite a maximum dose of stimulation medication. Younger women with good ovarian reserve and good ovarian response (> 5 eggs collected) after ovarian stimulation are considered normal responders.

Study characteristics

We found 16 randomised controlled trials with 1352 women. This type of trial randomly assigns people into two groups. In this case, one group received IVF plus growth hormone and the other group received IVF only. The evidence is current to 11 November 2020.

Key results

In normal responders, with adjuvant GH use, the effect on live birth rate is very uncertain; if the chance of live birth without growth hormone is assumed to be 15%, the chance of live birth with growth hormone would be between 6% and 43%. There was not enough evidence to reach a conclusion regarding clinical pregnancy rates, number of women with at least one egg retrieved, embryo transfer achieved, and number of eggs retrieved in normal responders. The evidence is also very uncertain about the effect of growth hormone on mean units of gonadotropin used in normal responders.

The evidence is very uncertain about the effect of growth hormone on live birth rate for poor responders, based on eight trials. If the chance of live birth without growth hormone is assumed to be 11%, the chance of live birth with growth hormone would be between 13% and 25%. Growth hormone results in a slight increase in pregnancy rates in poor responders, based on 11 trials with low-certainty evidence. The results suggest, if the pregnancy rate without growth hormone is assumed to be 15%, with growth hormone use, the pregnancy rate in poor responders would be between 19% and 31%. The evidence suggests that growth hormone results in little to no difference in the number of women with at least one oocyte retrieved, based on two trials with low-certainty evidence. If the chance of retrieving at least 1 egg in poor responders was 81%, with growth hormone the chance is between 87% and 99%. There is a slight increase in the mean number of oocytes retrieved with the use of growth hormone for poor responders, based on 12 trials with low-certainty evidence. The evidence is very uncertain about the effect of growth hormone on embryo transfer achieved, based on four trials. If the chance of achieving embryo transfer is assumed to be 77%, the chance with use of growth hormone will be between 78% and 94%. Use of growth hormone results in reduction of mean units of gonadotropins used for stimulation in poor responders, based on eight trials with low-certainty evidence.

High heterogeneity in the analyses for the mean number of oocytes retrieved and the mean units of GH used suggests quite different effects according to differences including in trial protocols (populations, GH dose and schedule), so these results should be interpreted with caution.

We are uncertain of the effect of growth hormone on adverse events in normal or poor responders as 6 of the 16 included trials failed to report this outcome.

Quality of the evidence

The evidence was of low to very low certainty, with the main limitations being poor reporting of study methods, imprecise data and variability among the trials.

SUMMARY OF FINDINGS

Summary of findings 1.   Adjuvant growth hormone compared to no adjuvant: routine use for in vitro fertilisation (IVF)

Adjuvant growth hormone compared to no adjuvant: routine use for in vitro fertilisation (IVF)

Patient or population: women with infertility
Setting: IVF
Intervention: growth hormone
Comparison: no adjuvant

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants(trials)	Certainty of the evidence (GRADE)	Comments
	Risk with no adjuvant: routine use	**Risk with growth hormone**				
Live birth rate per woman randomised	Study population		OR 1.32 (0.40 to 4.43)	80 (2 RCTs)	⊕⊖⊖⊖ Very low[a,b]	The evidence is very uncertain about the effect of growth hormone on live birth rate per woman randomised in normal responders
	15 per 100	18 per 100 (6 to 43)				
Clinical pregnancy rate per woman randomised	Study population		OR 1.78 (0.49 to 6.50)	42 (1 RCT)	⊕⊖⊖⊖ Very low[b,c,d]	Only one study reported this outcome, hence conclusions cannot be drawn.
	27 per 100	40 per 100 (16 to 71)				
Number of women with at least one oocyte retrieved per woman randomised	Study population		OR 2.86 (0.11 to 74.31)	42 (1 RCT)	⊕⊖⊖⊖ Very low[b,c,d]	Only one study reported this outcome, hence conclusions cannot be drawn.
	95 per 100	98 per 100 (70 to 100)				
Mean number of oocytes retrieved	The mean number of oocytes retrieved ranged from 6 to 13	MD 0.02 lower (0.79 lower to 0.74 higher)	-	80 (2 RCTs)	⊕⊖⊖⊖ Very low[b,c]	The evidence is very uncertain about the effect of growth hormone on mean number of oocytes retrieved in normal responders.
Embryo transfer achieved per woman randomised	Study population		OR 7.36 (0.36 to 151.91)	42 (1 RCT)	⊕⊖⊖⊖ Very low[b,c,d]	Only one study reported this outcome, hence conclusions cannot be drawn.
	86 per 100	98 per 100 (70 to 100)				

Mean units of gonadotrophin used	The mean units of gonadotrophin used ranged from 1327 to 2820 units	MD 13.57 units higher (112.88 lower to 140.01 higher)	-	80 (2 RCTs)	⊕⊝⊝⊝ Very low[a,b]	The evidence is very uncertain about the effect of growth hormone on mean units of gonadotrophin used in normal responders.
Adverse events	Younis 1992 reported: - ectopic pregnancy 0/20 in GH group and 2/22 in control group - multiple pregnancy 5/20 in GH group and 2/22 in control group - OHSS 0/20 in GH group and 0/22 in control group Tapanainen 1992 reported: - multiple pregnancy 0/19 in GH group and 1/19 in control group. Other adverse events were not reported.		-	80 (2 RCTs)	⊕⊕⊝⊝ Low[e,f]	The evidence suggests that growth hormone does not increase or reduce adverse events in normal responders.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

__CI:__ confidence interval; __GH__: growth hormone; __IVF__: in vitro fertilisation; __MD__: mean difference; __OR:__ odds ratio; __RCT__: randomised controlled trial.

__GRADE Working Group grades of evidence__

__High certainty:__ we are very confident that the true effect lies close to that of the estimate of the effect.

__Moderate certainty:__ we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

__Low certainty:__ our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

__Very low certainty:__ we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded one level due to randomisation bias and selective reporting. There are only 2 trials in this analysis.
[b]Downgraded 2 levels due to imprecision, small study numbers and very wide confidence intervals.
[c]Downgraded one level due to randomisation bias and selective reporting.
[d]Only one study reported this outcome, hence downgraded.
[e]Not all outcomes reported uniformly.
[f]Small study numbers.

Summary of findings 2. Adjuvant growth hormone compared to no adjuvant: poor responders for in vitro fertilisation (IVF)

Growth hormone compared to no adjuvant: poor responders for in vitro fertilisation (IVF)

Patient or population: women with infertility subclassified as poor responders
Setting: IVF
Intervention: growth hormone
Comparison: no adjuvant

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of partici-pants (trials)	Certainty of the evidence (GRADE)	Comments
	Risk with no adjuvant: poor responders	**Risk with growth hormone**				
Live birth rate per woman ran-domised	Study population		OR 1.77 (1.17 to 2.70)	737 (8 RCTs)	⊕⊖⊖⊖ Very low[a,b,c]	The evidence is very uncer-tain about the effect of growth hormone on live birth rate per woman randomised in poor re-sponders.
	11 per 100	18 per 100 (13 to 25)				
Clinical preg-nancy rate per woman ran-domised	Study population		OR 1.85 (1.35 to 2.53)	1033 (11 RCTs)	⊕⊕⊖⊖ Low[c,d,e]	Growth hormone may result in a slight increase in clinical pregnancy rate per woman ran-domised in poor responders.
	15 per 100	25 per 100 (19 to 31)				
Number of women with at least one oocyte re-trieved per woman ran-domised	Study population		OR 5.67 (1.54 to 20.83)	148 (2 RCTs)	⊕⊕⊖⊖ Low[c,d]	The evidence suggests that growth hormone results in lit-tle to no difference in num-ber of women with at least one oocyte retrieved per woman randomised.
	81 per 100	96 per 100 (87 to 99)				
Mean number of oocytes re-trieved	The mean number of oocytes retrieved ranged from 2 to 6	MD 1.40 higher (1.16 higher to 1.64 higher)	-	1153 (12 RCTs)	⊕⊕⊖⊖ Low[c,d,f]	Growth hormone may result in a slight increase in mean num-ber of oocytes retrieved in poor responders.
Embryo trans-fer achieved per woman ran-domised	Study population		OR 2.32 (1.08 to 4.96)	214 (4 RCTs)	⊕⊖⊖⊖ Very low[b,c,f]	The evidence is very uncer-tain about the effect of growth hormone on embryo trans-fer achieved per woman ran-domised in poor responders.
	77 per 100	89 per 100 (78 to 94)				

Mean units gonadotropin used	The mean units gonadotropin used ranged from 2548 to 5590 units	MD 1088.19 units lower (1203.2 lower to 973.18 lower)	-	685 (8 RCTs)	⊕⊕⊖⊖ Low[c,d]	The evidence suggests growth hormone results in a slight reduction in mean units of gonadotropin used in poor responders.
Adverse events	Six trials did not report adverse events (Choe 2017; Dakhly 2018; Dor 1995; Hazout 2003; Tesarik 2005; Zhuang 1994). The other 8 trials reported adverse events. Owen 1991 reported ectopic pregnancies: 0/13 in GH group and 1/12 in control; the other trials in poor responder group reported no cases of ectopic pregnancy in either group. Multiple pregnancy was reported in Owen 1991: 2/13 in GH group and 0/12 in control group; Mohammad 2019 reported 1/78 in GH group and 1/78 in control group; Suikkari 1996 reported 1/10 in 4 IU GH group and 0/6 in control group; and other trials reported no cases of multiple pregnancies in either group. Norman 2019 reported congenital anomalies: 1/65 in GH group and 1/65 in control group; other trials reported no cases of congenital anomalies in either group. Bergh 1994 reported that 2/29 cases in GH group had oedema, but this outcome was not reported by any other study. Kucuk 2008, Safdarian 2019 and Lee 2019 reported that no adverse events were seen in either group. This information has been presented in tabular form (Table 1).	-		512 (7 RCTs)	⊕⊖⊖⊖ Very low[e,g]	Results reported varied across the studies, from an increase to a decrease of AEs with use of GH, but the evidence is very uncertain.

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: confidence interval; IVF: in vitro fertilisation; MD: mean difference; OR: odds ratio; RCT: randomised controlled trial.

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded one level due to high risk of attrition bias.
[b]Downgraded one level due to imprecision, small numbers and wide confidence intervals.
[c]Downgraded one level due to publication bias as per funnel plot.
[d]Downgraded one level due to randomisation bias and selective reporting.

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eThe dose, form, timing of administration was inconsistent across various trials.

fDowngraded one level due to allocation bias and selective reporting.

gAdverse events have not been reported by all trials, and the ones reporting have not reported adverse events long term. In particular effects on developing foetus have only been reported by one study.

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BACKGROUND

Description of the condition

Infertility, usually defined as absence of conception after one year of regular intercourse, is a common problem affecting as many as one in six couples(NICE CG156). The main causes include sperm dysfunction, ovulation disorder and fallopian tube damage (Cahill 2002). Even after undergoing diagnostic tests, approximately 30% cases of infertility remain unexplained. One method of treating infertile couples is assisted conception via in vitro fertilisation (IVF). IVF involves using hormones to stimulate ovaries in order to increase follicular growth and thus develop more than one oocyte. Ovulation is then triggered with human chorionic gonadotropin and the oocytes are retrieved and fertilised with sperm in the laboratory setting outside the body (in vitro) (Bhandari 2018). The fertilised oocytes (embryos) are then transferred into the uterus, two to five days after egg retrieval. IVF protocols are constantly under review in an attempt to decrease hormone (gonadotrophin) requirement, improve follicular recruitment, and ultimately increase live birth rates (Bhandari 2018). A challenge for IVF practitioners is to optimise the outcome in 'poor responders'. As per the consensus from the European Society of Human Reproduction and Embryology (ESHRE), poor ovarian response has been defined if at least two of the following three features are present: i) increased maternal age (> 40 years); ii) any other risk factor for poor ovarian response (3 or fewer oocytes with ovulation induction); and iii) low scores on tests of ovarian reserve (i.e. antral follicle count < 5 to 7 follicles or anti-Müllerian hormone < 0.5 ng/mL to 1.1 ng/mL (Ferraratti 2011). A newer classification system has been proposed by the POSEIDON group (**P**atient-**O**riented **S**trategies **E**ncompassing **I**ndividualize**D** **O**ocyte **N**umber; POSEIDON Group 2016). In this classification, four subgroups have been suggested based on quantitative and qualitative parameters, namely, age and the expected aneuploidy rate; ovarian biomarkers (i.e. antral follicle count and anti-Müllerian hormone); and ovarian response - provided a previous stimulation cycle was performed (POSEIDON criteria 2016). The POSEIDON group also introduced a new measure for successful assisted reproductive technology treatment, namely, the ability to retrieve the number of oocytes needed for the patient to obtain at least one euploid embryo for transfer. This feature represents a pragmatic endpoint for clinicians and enables the development of prediction models aiming to reduce the time-to-pregnancy. This however, can only be applied to prospective RCTs, and has not been used by any of the trials included in this meta-analysis.

Description of the intervention

Over the last 25 years growth hormone (GH) has been used in IVF treatment (Jacobs 1995; Landolfi 1994). GH is a biological peptide hormone, synthesised, stored and secreted by somatotroph cells located in the anterior pituitary gland (Regan 2018). GH can be synthetically produced using recombinant DNA technology and is licensed to be used in the human population. There is currently no consensus as to the route, dose or timing of GH administration in IVF protocols (Ahmad 2009)

How the intervention might work

The administration of GH may potentiate the effect of exogenous gonadotrophins (Homburg 1988; Zhou 2013). GH is reported to modulate the action of follicular stimulating hormones on granulosa cells by up-regulating the local synthesis of insulin-like growth factor-1 (IGF-1) (Regan 2018). This interest has been stimulated by animal trials which suggest that GH may increase the intraovarian production of IGF-1 (Hsu 1987; Yoshimura 1996). IGF-1 displays GH dependence both in vivo and in vitro (Blumenfeld 1996). The interaction between GH and IGF-1 is of significance since IGF-1 has been shown to play an important part in ovarian function in both animal and human models (Adashi 1985; Erickson 1989; Zhou 2013). The addition of IGF-1 to gonadotrophins in granulosa cell cultures increased gonadotrophin action on the ovary by several mechanisms including augmentation of aromatase activity, 17 beta-oestradiol and progesterone production and luteinising hormone receptor formation (Erickson 1989; Mason 1990). In human ovarian cells, IGF-1, in synergy with FSH (follicle stimulating hormone), stimulates protein synthesis and steroidogenesis. Following the presence of luteinising hormone receptors, IGF-1 enhances luteinising hormone-induced progesterone synthesis and stimulates proliferation of granulosa-luteal cells. IGF-1, in synergy with FSH, is very influential in stimulating aromatase activity in preovulatory follicles. Thus, IGF-1 can be involved in both estradiol and progesterone synthesis (Zhou 2013). In other words, the existence of GH is essential in follicle development and ovarian steroidogenesis. IGF-1 has also been found to stimulate follicular development, oestrogen production and oocyte maturation (Regan 2018; Yoshimura 1996). Trials have shown that maturation and evolution of oocytes have been impaired or severely reduced by inhibiting the GH receptor in animal models (Lucy 2011). GH is an essential requirement in treatment of infertility for women with GH deficiency, with many such women presenting with ovulation disorder (Park 2007).

Why it is important to do this review

The aim of this review is to establish the role of GH in IVF. Improving the outcomes of IVF with the use of GH adjuvant therapy is important particularly in those women who are considered poor responders. Since GH treatment is expensive, it is important to examine the available evidence as to the effectiveness and safety of its use as an adjunct to IVF, as its routine use could render IVF treatment unaffordable for many more patients, than is the case now (Kucuk 2008).

OBJECTIVES

To assess the effectiveness and safety of growth hormone as an adjunct to IVF compared to standard IVF for women with infertility

METHODS

Criteria for considering studies for this review

Types of studies

Only randomised controlled trials (RCTs) were eligible for inclusion.

Types of participants

Women with infertility undergoing ovarian stimulation for IVF

Types of interventions

We included all RCTs comparing the use of adjuvant GH in IVF cycles with standard IVF cycles, with or without placebo control.

Types of outcome measures

Primary outcomes

- Live birth rate per woman randomised: number of women achieving a live birth divided by the number of women randomised

Secondary outcomes

- Cinical pregnancy rate per woman randomised: number of women achieving a clinical pregnancy (established with confirmation of ongoing intrauterine pregnancy at 6 weeks on ultrasound), divided by the number of women randomised
- Oocyte retrieval per woman randomised: number of women with at least one oocyte retrieved divided by the number of women randomised
- Mean number of oocytes retrieved
- Embryo transfer per woman randomised: number of women with at least one embryo transferred divided by the number of women randomised
- Mean units of gonadotrophin used
- Adverse events (ectopic pregnancy, multiple pregnancy, ovarian hyperstimulation syndrome (OHSS), congenital anomalies, oedema).

Search methods for identification of studies

Electronic searches

We searched the following electronic databases for relevant trials to 11 November 2020:

- The Cochrane Gynaecology and Fertility (CGF) Group Specialised Register of Controlled Trials, ProCite platform (searched 11 November 2020) (Appendix 1);
- CENTRAL, via the Cochrane Register of Studies Online (CRSO); Web platform (searched 11 November 2020) (Appendix 2);
- MEDLINE, Ovid platform (searched from 1946 to 11 November 2020) (Appendix 3);
- Embase, Ovid platform (searched from 1980 to 11 November 2020) (Appendix 4);
- PsycINFO, Ovid platform (searched from 1806 to 11 November 2020) (Appendix 5);
- CINAHL Plus, Ebsco platform (searched from 1961 to 20 January 2020 and any later CINAHL search output from the 11 November 2020 search is contained in the CENTRAL output) (Appendix 6).

The MEDLINE search was combined with the Cochrane highly sensitive search strategy for identifying randomised trials which appears in the *Cochrane Handbook for Systematic Reviews of Interventions* (Version 5.1.0 chapter 6, 6.4.11)(Higgins 2021). We combined the Embase searches with trial filters developed by the Scottish Intercollegiate Guidelines Network (SIGN) (www.sign.ac.uk/what-we-do/methodology/search-filters/)

Other electronic sources of trials include:

- LILACS (Latin American and Caribbean Health Science Information database (searched from 1982 to 11 November 2020), found in the Virtual Health Library Regional Portal (VHL) (pesquisa.bvsalud.org/portal);

- Google Scholar (for recent trials not yet indexed in the major databases).

Searching other resources

We handsearched the reference lists of articles retrieved by the search and made personal contact with experts in the field and with the manufacturers of GH to obtain any additional relevant trials. In liaison with the Information Specialist, we handsearched any relevant journals and conference abstracts that were not covered in the CGF register.

We also rescreened the trials included in the previous version of this review.

Data collection and analysis

Selection of studies

Two review authors (AS and GM) scanned retrieved searches for relevant titles and abstracts and retrieved the full text of all potentially eligible trials. The same review authors independently examined the full text articles for compliance with the inclusion criteria and elected trials eligible for inclusion in the review. We corresponded with study investigators to clarify study eligibility (for example, with respect to participant eligibility criteria and allocation method). Disagreements as to study eligibility were resolved by discussion with a third review author (LM). We used a PRISMA flow chart to explain this process (PRISMA 2021)

Data extraction and management

Two review authors (GM and AS) independently extracted data from eligible trials using a data extraction form designed and pilot tested by review authors. Any disagreements were resolved by a third review author (LM). Where trials have multiple publications, we used the main trial report as the reference and supplemented this with additional details from secondary papers. Review authors corresponded with study investigators in order to resolve data queries.

Assessment of risk of bias in included studies

Two review authors (GM and AS) assessed the included trials for risk of bias using the Cochrane RoB 1 tool (Higgins 2011); any disagreements were resolved by discussion with a third review author (LM). We assessed: sequence generation; allocation concealment; blinding of participants, providers and outcome assessors; completeness of outcome data; selective outcome reporting; and other potential sources of bias (Higgins 2011). The conclusions are presented in the risk of bias table and incorporated in the interpretation of review findings by means of sensitivity analyses (see below). Where identified trials failed to report the primary outcomes of live birth, but did report secondary outcomes such as clinical pregnancy, we undertook informal assessment as to whether those reporting the primary outcomes have typical values of the secondary outcomes.

Measures of treatment effect

For dichotomous data (e.g. live birth rates), we used the numbers of events in the control and intervention groups of each study to calculate Mantel-Haenszel odds ratios (ORs) or (where events are very rare) Peto ORs*. For continuous data (e.g. weight gain), if all trials report exactly the same outcomes, we calculated the mean difference (MD) between treatment groups. If similar outcomes are

reported on different scales (e.g. change in weight) we calculated the standardised mean difference (SMD). We reversed the direction of effect of individual trials, if required, to ensure consistency across trials. We treated ordinal data (e.g. quality of life scores) as continuous data. We presented 95% confidence intervals (CIs) for all outcomes. Where data to calculate ORs or MDs were not available, we utilised the most detailed numerical data available that facilitated similar analyses of included trials (e.g. test statistics, P values). We assessed whether the estimates calculated in the review for individual trials are compatible in each case with the estimates reported in the study publications. Three trials reported data as median and range (Bergh 1994; Dor 1995; Owen 1991). We converted the data to mean and standard deviation (SD) using Hozo's method (Hozo 2005).

Unit of analysis issues

The primary analysis was per woman randomised. Multiple live births (e.g. twins or triplets) were to be counted as one live birth event.

Dealing with missing data

We analysed the data on an intention-to-treat basis as far as possible and made attempts to obtain missing data from the original investigators. If trials reported sufficient detail to calculate MDs but no information on associated SD, we planned to assume that the outcome had a SD equal to the highest SD from other trials within the same analysis. We assumed live births and pregnancies not to have occurred in participants with unreported outcomes. Where these were unobtainable, imputation of individual values was undertaken for the primary outcomes only. For other outcomes, we only analysed the available data. Any imputation undertaken was subjected to sensitivity analysis (see below).

Assessment of heterogeneity

We considered whether the clinical and methodological characteristics of the included trials were sufficiently similar for meta-analysis to provide a meaningful summary. We assessed statistical heterogeneity using the I^2 statistic. An I^2 measurement greater than 50% indicated substantial heterogeneity (Higgins 2011), and if present, we addressed this through sensitivity analysis, subgroup analysis, or both.

Assessment of reporting biases

In view of the difficulty in detecting and correcting for publication bias and other reporting biases, we aimed to minimise their potential impact by ensuring a comprehensive search for eligible trials, by being alert for duplication of data, and by constructing a funnel plot if there were sufficient trials (10 or more) in one analysis.

Data synthesis

We combined the data from primary trials using fixed-effect models in the following comparisons.

- GH versus no adjuvant treatment: routine use of adjuvant GH in IVF protocols
- GH versus no adjuvant treatment: use of GH in poor responders
- GH versus no adjuvant treatment: subgroup analysis based on age

Subgroup analysis and investigation of heterogeneity

We subgrouped the poor responders as follows.

- Women identified as poor responders by definition or based on test results showing low ovarian reserve who did not have IVF cycle before
- Women identified as poor responders based on previous poor response in IVF stimulation cycle

If we identified substantial heterogeneity, we planned to explore methodological and clinical differences between the trials

Sensitivity analysis

We conducted sensitivity analyses for the primary outcomes to determine whether the conclusions are robust to arbitrary decisions made regarding eligibility and analysis. These analyses considered whether conclusions would have differed under the following circumstances.

- If eligibility was restricted to trials without high risk of bias. Risk of bias assessment conducted as per Cochrane RoB 1 tool (Higgins 2011). Serial exclusion of each study from the meta-analysis did not produce significant changes in any outcome.
- If trials with outlying results had been excluded. Serial exclusion of each study from the meta-analysis did not produce significant changes in any outcome.
- If a random-effects model had been adopted. Changing from fixed-effect to random-effects model did not change the conclusions, but the results showed wider CIs.
- If a sensitivity analysis was performed to detect whether the inclusion of RCTs with high numbers of participants affected the results. Serial exclusion of each study from the meta-analysis did not produce significant changes in any outcome.

Summary of findings and assessment of the certainty of the evidence

We prepared a summary of findings table using GRADEpro GDT and Cochrane methods (GRADEpro GDT 2015; Higgins 2021; Schünemann 2013). We prepared two summary of findings tables for GH compared to no adjuvant in: i) normal responders; and ii) poor responders. Each table evaluated the overall certainty of the body of evidence for live birth rate, clinical pregnancy rate, number of women with at least one oocyte retrieved, mean number of oocytes retrieved, embryo transfer rate, mean units of gonadotrophin used, and adverse events for adjuvant GH treatment versus no adjuvant in normal responders. We assessed the certainty of the evidence using GRADE criteria (Schünemann 2013): risk of bias, consistency of effect, imprecision, indirectness and publication bias). Two review authors (AS and LM) working independently made judgements about evidence quality (high, moderate, low or very low), with disagreements resolved by discussion. We justified, documented, and incorporated judgements into reporting of results for each outcome.

We extracted the study data, formatting our comparisons in data tables and prepared the summary of findings tables before writing the results and conclusions of our review.

R E S U L T S

Description of studies

We only included randomised controlled trials (RCTs) with growth hormone (GH) used as an adjuvant treatment for ovarian stimulation with the control group using placebo or no placebo.

Results of the search

We included 16 RCTs in the meta-analysis. The search retrieved 436 articles. After removing duplicates, 304 abstracts were screened. Fifty five studies were potentially eligible and were retrieved in full text. Sixteen studies met our inclusion criteria. We excluded 35 studies, 4 are awaiting classification and 7 are ongoing. See study tables: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification; Characteristics of ongoing studies; Table 2. For details of the screening and selection process see Figure 1.

Figure 1.

Figure 1.

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┌─────────────────────┐   ┌─────────────────────┐
│ 430 records         │   │ 6 records identified│
│ identified through  │   │ through other       │
│ database searching  │   │ sources             │
└─────────────────────┘   └─────────────────────┘
           │                        │
           └──────────┬─────────────┘
                      ▼
          ┌─────────────────────┐
          │ 304 records after   │
          │ duplicates removed  │
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                      ▼
          ┌─────────────────────┐      ┌─────────────────────┐
          │ 304 records         │─────▶│ 249 records         │
          │ screened            │      │ excluded            │
          └─────────────────────┘      └─────────────────────┘
                      │
                      │                ┌─────────────────────────┐
                      │                │ 35 full-text articles   │
                      │                │ excluded, with          │
                      │                │ reasons:                │
                      │                │                         │
                      │                │ ineligible study        │
                      │                │ design (n = 17)         │
                      │                │                         │
                      │                │ ineligible              │
                      │                │ population (n = 12 )    │
                      │                │                         │
                      │                │ more than 1             │
                      │                │ adjuvant (n = 4)        │
                      │                │                         │
                      │                │ insufficient data (n    │
                      ▼                │ = 1)                    │
          ┌─────────────────────┐     │                         │
          │ 55 full-text        │────▶│ ineligible drug (n =    │
          │ articles assessed   │     │ 1)                      │
          │ for eligibility     │     │                         │
          └─────────────────────┘     │ Awaiting                │
                      │               │ classification (n = 4)  │
                      │               │                         │
                      │               │ Ongoing (n = 7)         │
                      │               └─────────────────────────┘
                      ▼
          ┌─────────────────────┐
          │ 16 trials included in│
          │ qualitative synthesis│
          └─────────────────────┘
                      │
                      ▼
          ┌─────────────────────┐
          │ 16 trials included in│
          │ quantitative        │
          │ synthesis           │
          │ (meta-analysis); 10 │
          │ of these studies    │
          │ were in the 2010    │
          │ review and 6        │
          │ studies have been   │
          └─────────────────────┘
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Figure 1. (Continued)

> review and 6
> studies have been
> added to this
> update

Included studies

Design

We included 16 parallel-group RCTs in this review (Bergh 1994; Choe 2017; Dakhly 2018; Dor 1995; Hazout 2003; Kucuk 2008; Lee 2019; Mohammad 2019; Norman 2019; Owen 1991; Safdarian 2019; Suikkari 1996; Tapanainen 1992; Tesarik 2005; Younis 1992; Zhuang 1994). Further descriptive details about the included trials are provided in Characteristics of included studies. All included trials were published reports either as full papers or as conference abstracts (Hazout 2003).

There are 4 studies on which we are awaiting further information (Bassiouny 2016; Bayoumi 2015; Eftekhar 2012; Gong 2020). Further details for these are available under Characteristics of studies awaiting classification.

In addition, there are 7 ongoing trials for which the results are awaited: (ChiCTR1800016106; CTRI/2019/03/018047; NCT01715324; NCT02179255; NCT03027843; NCT03373149; NCT03759301). The details for these trials are provided in Characteristics of ongoing studies.

Participants

We included 16 trials with a total of 1352 subfertile couples in the review. The number of couples included in each trial ranged from 14 in Dor 1995 to 240 in Dakhly 2018.

Two trials included women who were not identified as poor responders (Tapanainen 1992; Younis 1992). The other 14 trials were conducted in poor responders. The subgroups were as follows.

- Poor responder by definition/test results showing low ovarian reserve
  - Over 40 years old (Tesarik 2005)
  - ESHRE criteria
    - age > 40 years
    - previous treatment that resulted with < 3 oocytes
    - anti-Müllerian hormone level < 0.5 ng/mL to 1.1 ng/mL
    - antral follicle count < 5 to 7 follicles (Lee 2019)
  - Bologna criteria
    - age ≥ 40 years or other factor for poor ovarian response
    - previous poor ovarian response (≤ 3 oocytes on ovulation induction)
    - low ovarian reserve test (anti-Müllerian hormone level < 0.5 ng/mL to 1.1 ng/mL
    - antral follicle count < 5 to 7 follicles (Choe 2017; Dakhly 2018; Safdarian 2019)
- Poor responder based on previous low response to ovarian stimulation

- < 3 oocytes retrieved in previous cycle or at least 48 ampoules of human menopausal gonadotrophin (hMG) used (Suikkari 1996)
- < 5 oocytes retrieved and > 250 IU follicle stimulating hormone (FSH) in previous cycle (Norman 2019)
- ≥ 2 previous cycles with < 5 oocytes retrieved (Bergh 1994)
- < 6 oocytes retrieved and < 3 embryos developed in previous cycle (Owen 1991)
- Previous poor response (not further defined) (Zhuang 1994)
- History of oocyte dysmorphia (Hazout 2003)
- Previous low response to high-dose gonadotrophin treatment (Kucuk 2008)
- Oestradiol < 500 pg/mL, < 3 oocytes retrieved in two previous IVF cycles (Dor 1995)
- IVF in previous poor responders with ≥ 2 failed cycles with < 5 oocytes (Mohammad 2019)

Exclusion criteria were not stated in Hazout 2003, Lee 2019, Owen 1991, Safdarian 2019, Suikkari 1996 and Tapanainen 1992. The remaining trials based their exclusion criteria on serum FSH concentrations (Kucuk 2008; Tesarik 2005), obesity (Bergh 1994), ovarian pathology (Bergh 1994), endometriosis (Bergh 1994), severe intercurrent illness (Bergh 1994), and unsatisfactory sperm quality (Tesarik 2005). Women with high FSH levels (> 20 IU/L), a history of infertility due to other causes such as azoospermia and diabetes (type 1 or 2) were excluded in Safdarian 2019.

Interventions

There was no consistency as to the dose or timing of GH administration (see Characteristics of included studies tables). The dose of GH ranged from 4 IU in Mohammad 2019 and Suikkari 1996 to 24 IU in Owen 1991 and Tapanainen 1992. Both Hazout 2003 and Suikkari 1996 conducted a multiple-arm study comparing two different doses of GH to a placebo arm, and their data have been reported separately in the analyses, with explanatory footnotes. The timing of GH administration varied between trials from daily administration prestimulation to alternate doses after the start of stimulation. Sustained-release GH preparation was used by Choe 2017; all other trials used recombinant GH.

Placebo was not used in five trials (Choe 2017; Dakhly 2018; Kucuk 2008; Lee 2019; Zhuang 1994). The remaining 11 trials used placebo in the control group: five used saline (Bergh 1994; Mohammad 2019; Safdarian 2019; Suikkari 1996; Tapanainen 1992), two used mannitol (Dor 1995; Younis 1992), one used metacresol in water (Norman 2019), and in three trials the nature of placebo used was not stated (Hazout 2003; Owen 1991; Tesarik 2005).

Outcomes

Primary outcome measure

Live birth rates were reported in 10 of the included trials (Dakhly 2018; Mohammad 2019; Norman 2019; Owen 1991; Safdarian 2019; Suikkari 1996; Tapanainen 1992; Tesarik 2005; Younis 1992; Zhuang 1994).

Secondary outcome measures

Pregnancy rates were reported in 13 of the included trials (Bergh 1994; Choe 2017; Dakhly 2018; Hazout 2003; Kucuk 2008; Lee 2019; Mohammad 2019; Owen 1991; Safdarian 2019; Suikkari 1996; Tesarik 2005; Younis 1992; Zhuang 1994). The number of oocytes retrieved per women was reported in 15 trials, except Hazout 2003, where SD was not mentioned, hence data could not be used. Adverse events were reported in 10 trials (Bergh 1994; Kucuk 2008;

Lee 2019; Mohammad 2019; Norman 2019; Owen 1991; Safdarian 2019; Suikkari 1996; Tapanainen 1992; Younis 1992).

Excluded studies

Thirty five studies were excluded from the review, for the following reasons:

- 17/35 were not RCTs
- 12/35 were not done in women undergoing IVF (ineligible population)
- 4/35 had used more than 1 adjuvant treatment
- 1/35 had insufficient data
- 1/35 had used ineligible drug

Risk of bias in included studies

Please refer to Characteristics of included studies table, Figure 2 and Figure 3.

Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included trials.
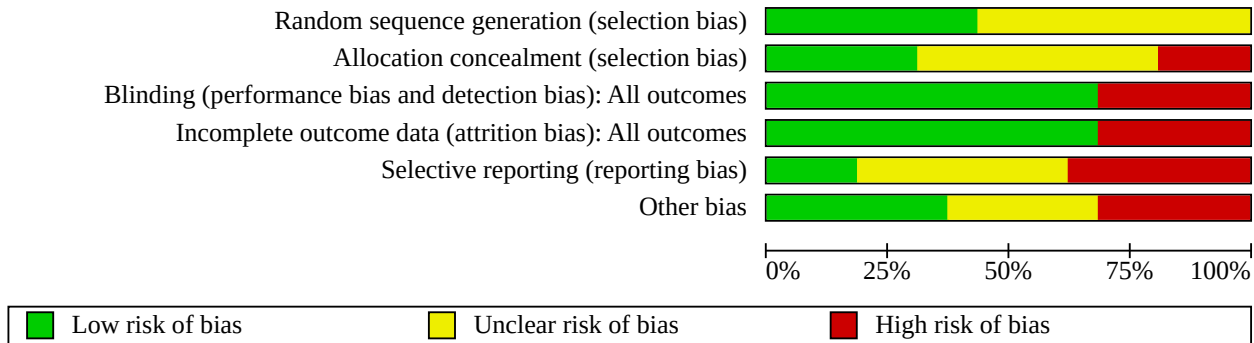
Figure 3.   Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

Allocation

Random sequence generation

The method of randomisation was clearly stated in seven trials and we assessed them at low risk of selection bias (Bergh 1994; Dakhly 2018; Kucuk 2008; Norman 2019; Tesarik 2005; Mohammad 2019; Safdarian 2019). The method of randomisation was unclear in the remaining trials.

Allocation concealment

Five studies were rated as at low risk of selection bias related to allocation concealment as they used sequentially labelled, sealed, opaque envelopes (Mohammad 2019; Tesarik 2005; Younis 1992; Norman 2019; Dakhly 2018). No allocation concealment was described in 3 studies, which we rated as high risk of bias for this domain (Dor 1995; Lee 2019; Safdarian 2019). The other eight studies failed to describe methods of allocation concealment or opaque envelopes were not used and we rated these as at unclear risk of bias for this domain.

Blinding

We did not consider that blinding of participants and personnel was likely to influence findings for the primary review outcome (live birth rate). Eleven trials were rated as low risk for selection bias related to blinding; among which two trials reported single-blinding (Safdarian 2019; Zhuang 1994), seven trials were double-blinded (Bergh 1994; Hazout 2003; Norman 2019; Owen 1991; Suikkari 1996; Tapanainen 1992; Tesarik 2005), and two trials reported triple-blinding (Kucuk 2008; Younis 1992). The remaining 5 trials were not blinded.

Incomplete outcome data

Two women were lost to follow-up in the Bergh 1994 study and four women were lost to follow-up in the Suikkari 1996 study, and both these were rated as high risk of attrition bias. Also, 3 studies with > 10% cycle cancellation rate were rated as high risk of attrition bias (Dakhly 2018; Lee 2019; Safdarian 2019). The remaining trials reported no losses and had a cycle cancellation rate < 10%.

Selective reporting

Six trials were rated as high risk of selective reporting as these did not report adverse events (Choe 2017; Dakhly 2018; Dor 1995;

Hazout 2003; Tesarik 2005, Zhuang 1994). A registered protocol was available for four trials (Dakhly 2018; Norman 2019, Safdarian 2019, Mohammad 2019), 3 of these were rated as low risk of selection bias; adverse effects were not reported by Dakhly 2018. We rated the remaining 7 studies as at unclear risk of bias although they reported our review's primary outcomes; we could not obtain a study protocol and the study was not prospectively registered so there was no information we could use to verify study details.

Other potential sources of bias

Five trials have been rated as high risk: three trials received a free supply of GH from the manufacture (Owen 1991; Tapanainen 1992; Younis 1992), one trial received a grant (Choe 2017) and one trial had very low numbers (Dor 1995). Five trials have been rated as unclear risk of this bias: placebo was not used in four (Dakhly 2018; Kucuk 2008; Lee 2019; Zhuang 1994) and one was a conference abstract (Hazout 2003). Placebo was not used in Choe 2017 as well but this has been rated as high risk. No other bias was noted in the remaining six trials.

Effects of interventions

See: **Summary of findings 1** Adjuvant growth hormone compared to no adjuvant: routine use for in vitro fertilisation (IVF); **Summary of findings 2** Adjuvant growth hormone compared to no adjuvant: poor responders for in vitro fertilisation (IVF)

1 Adjuvant growth hormone compared to no adjuvant or placebo: routine use for IVF

Primary outcomes

1.1 Live birth rate per woman randomised

Only two of the RCTs were conducted in women who were not identified as poor responders (Tapanainen 1992; Younis 1992). The evidence is very uncertain about the effect of GH on live birth rate per woman randomised for routine use in IVF (odds ratio (OR) 1.32, 95% confidence interval (CI) 0.40 to 4.43; I^2 = 0%; 2 trials, 80 participants; very low-certainty evidence) Analysis 1.1, Figure 4). If the chance of live birth without use of GH as adjuvant is assumed to be 15%, the chance of live birth with use of GH would be between 6% and 43%.

Figure 4. Forest plot of comparison: 1 Adjuvant GH compared to no adjuvant: routine use for IVF, outcome: 1.1 Live birth rate per woman randomised.
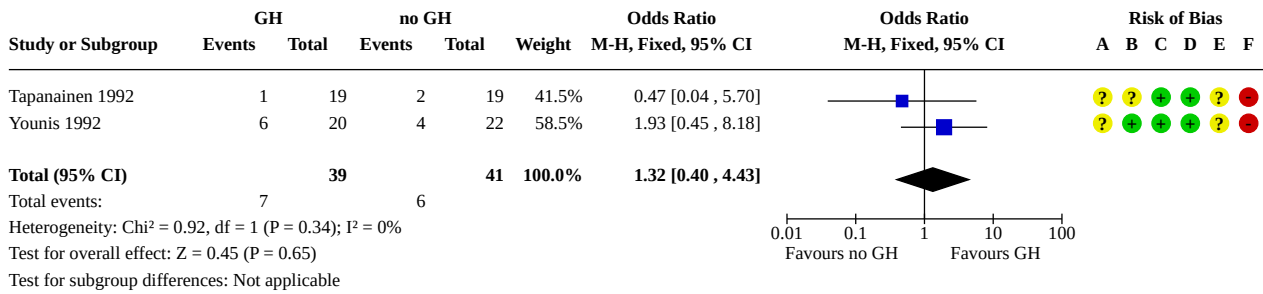
Study or Subgroup	GH Events	Total	no GH Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
Tapanainen 1992	1	19	2	19	41.5%	0.47 [0.04 , 5.70]		? ? + + ? −
Younis 1992	6	20	4	22	58.5%	1.93 [0.45 , 8.18]		? + + + ? −
Total (95% CI)		**39**		**41**	**100.0%**	**1.32 [0.40 , 4.43]**		
Total events:	7		6					

Heterogeneity: Chi² = 0.92, df = 1 (P = 0.34); I² = 0%
Test for overall effect: Z = 0.45 (P = 0.65)
Test for subgroup differences: Not applicable

0.01 0.1 1 10 100
Favours no GH   Favours GH

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding (performance bias and detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

Secondary outcomes

1.2 Clinical pregnancy rate per woman randomised

Only one RCT was conducted in women who were not identified as poor responders (Younis 1992), hence we could not perform meta-analysis (Analysis 1.2).

1.3 Number of women with at least one oocyte retrieved per woman randomised

One trial reported number of women with at least one oocyte retrieved (Younis 1992), hence we could not perform meta-analysis (Analysis 1.3).

1.4 Mean number of oocytes retrieved

Two trials reported the mean number of oocytes retrieved per woman randomised (Tapanainen 1992; Younis 1992). The evidence is very uncertain about the effect of GH on mean number of oocytes retrieved in normal responders (mean difference (MD) -0.02, 95% CI -0.79 to 0.74; I² = 0%; 2 trials, 80 participants; very low-certainty evidence) (Analysis 1.4). The mean number of oocytes retrieved were 6 to 13.

1.5 Embryo transfer per woman randomised

One trial reported the number of embryos transferred per woman randomised (Younis 1992), hence we could not perform meta-analysis (Analysis 1.5).

1.6 Mean units of gonadotrophin used

Two trials reported the mean number of ampoules of gonadotrophin used per woman randomised (Tapanainen 1992; Younis 1992). We converted the ampoules into units for standardisation throughout the review. We are uncertain if the mean number of ampoules of gonadotropin used changed with GH in IVF protocols when compared to standard IVF protocols (MD 13.57, 95% CI -112.88 to 140.01; I² = 0%; 2 trials, 80 participants; very low-certainty evidence; Analysis 1.6).

1.7 Adverse events

Low-certainty evidence suggests that GH does not increase or reduce adverse events in normal responders. Adverse events were reported by Younis 1992 and Tapanainen 1992. Younis 1992 reported ectopic pregnancy 0/20 in GH group and 2/22 in control group, multiple pregnancy 5/20 in GH group and 2/22 in control group, ovarian hyperstimulation syndrome (OHSS) 0/20 in GH group and 0/22 in control group. Tapanainen 1992 reported multiple pregnancy 0/19 in GH group and 1/19 in control group. Other adverse events were not reported (Table 1).

2 Adjuvant GH compared to no adjuvant or placebo: poor responders for IVF

Primary outcome

2.1 Live birth rate per woman randomised

Eight trials reported the live birth rate per woman randomised (Dakhly 2018; Mohammad 2019; Norman 2019; Owen 1991; Safdarian 2019; Suikkari 1996; Tesarik 2005; Zhuang 1994). The evidence is very uncertain about the effect of GH on live birth rate per woman randomised for poor responders (OR 1.77, 95% CI 1.17 to 2.70; I² = 0%; 8 trials, 737 participants; very low-certainty evidence; Analysis 2.1, Figure 5). If the chance of live birth without use of GH as adjuvant is assumed to be 11%, the chance of live birth with use of GH would be between 13% and 25%.

Figure 5. Forest plot of comparison: 2 Growth hormone versus no adjuvant: poor responders, outcome: 2.1 Live birth rate per woman randomised.
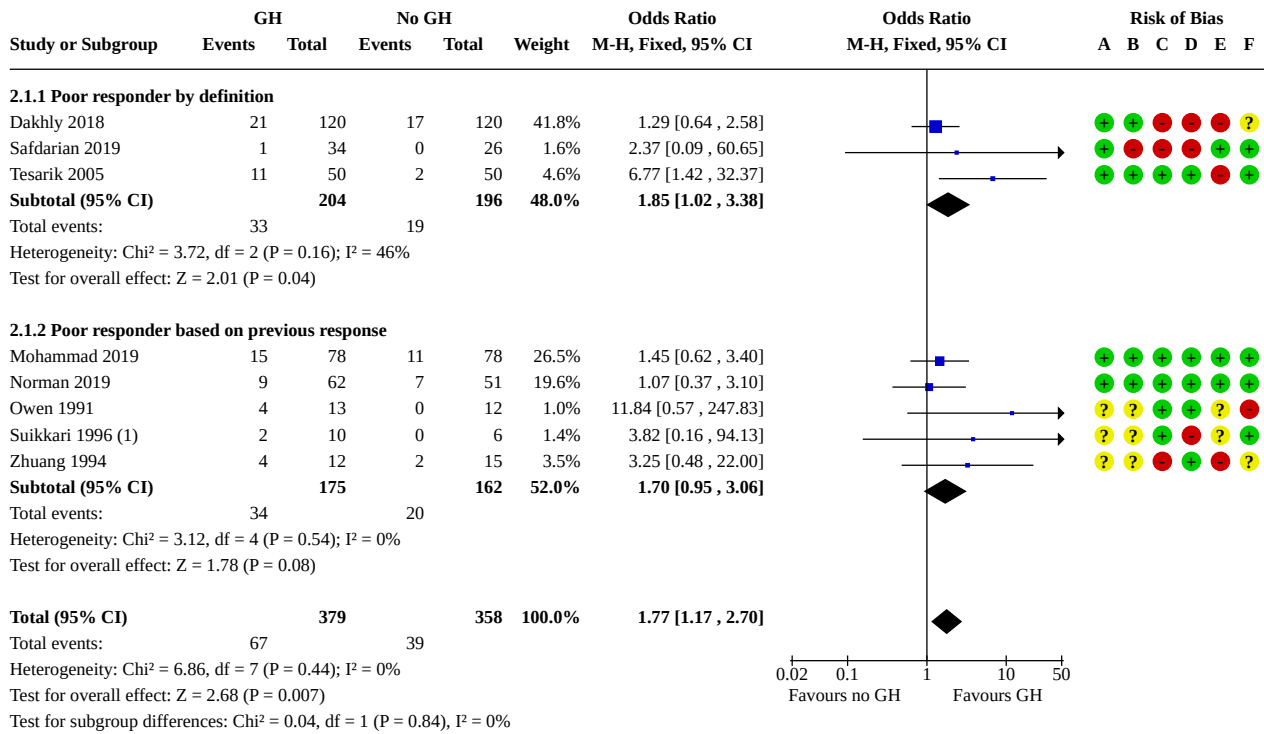
Footnotes

(1) This is data from 4 IU arm of Suikkari 1996

Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding (performance bias and detection bias)

(D) Incomplete outcome data (attrition bias)

(E) Selective reporting (reporting bias)

(F) Other bias

Subgroup analysis

Live birth rates in the poor responder by definition subgroup (Dakhly 2018; Safdarian 2019; Tesarik 2005), evidence is uncertain if adjuvant GH increases live birth rates (OR 1.85, 95% CI 1.02 to 3.38; I² = 46%; 3 trials, 400 participants); and in the poor responder based on previous response subgroup (Mohammad 2019; Norman 2019; Owen 1991; Suikkari 1996; Zhuang 1994), evidence is uncertain if adjuvant GH increases live birth rates (OR 1.70, 95% CI 0.95 to 3.06; I² = 0%; 5 trials, 337 participants).

We did not find evidence that the treatment effect differed between the groups of studies (test for subgroup differences: Chi² = 0.04, df = 1 (P = 0.84), I² = 0%).

Secondary outcomes

2.2 Clinical pregnancy rate per woman randomised

Eleven trials reported the pregnancy birth rate per woman randomised (Bergh 1994; Choe 2017; Dakhly 2018; Hazout 2003; Kucuk 2008; Lee 2019; Mohammad 2019; Owen 1991; Safdarian 2019; Tesarik 2005; Zhuang 1994). GH used as adjuvant results in a slight increase in pregnancy rates per woman randomised in poor responders (OR 1.85, 95% CI 1.35 to 2.53; I² = 15%; 11 trials, 1033 participants; low-certainty evidence; Analysis 2.2; Figure 6). The results suggest, if the pregnancy rate without adjuvant GH is assumed to be 15%, with GH use, the pregnancy rate in poor responders would be between 19% and 31%.

Figure 6. Forest plot of comparison: 2 Growth hormone versus no adjuvant: poor responders, outcome: 2.2 Pregnancy rate per woman randomised.

Study or Subgroup	GH Events	GH Total	No GH Events	No GH Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
2.2.1 Poor responder by definition								
Choe 2017	6	62	11	65	16.7%	0.53 [0.18 , 1.52]		? ? ● + ● ●
Dakhly 2018	29	120	23	120	30.0%	1.34 [0.72 , 2.49]		+ + ● ● ● ?
Lee 2019	30	94	15	90	18.0%	2.34 [1.16 , 4.74]		? ● ● ● ? ?
Safdarian 2019	5	34	1	26	1.7%	4.31 [0.47 , 39.40]		+ ● ● ● + +
Tesarik 2005	13	50	3	50	3.8%	5.50 [1.46 , 20.76]		+ + + + ● +
Subtotal (95% CI)		**360**		**351**	**70.2%**	**1.70 [1.16 , 2.50]**		
Total events:	83		53					

Heterogeneity: Chi² = 9.73, df = 4 (P = 0.05); I² = 59%
Test for overall effect: Z = 2.72 (P = 0.006)

Study or Subgroup	GH Events	GH Total	No GH Events	No GH Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
2.2.2 Poor responder based on previous response								
Bergh 1994	3	9	2	9	2.3%	1.75 [0.22 , 14.22]		+ ? + ● ? +
Hazout 2003 (1)	6	12	2	6	2.3%	2.00 [0.26 , 15.38]		? ? + ● ● ?
Hazout 2003 (2)	6	11	1	6	1.0%	6.00 [0.52 , 69.75]		? ? + ● ● ?
Kucuk 2008	10	31	5	30	5.9%	2.38 [0.70 , 8.07]		+ ? + ● ? ?
Mohammad 2019	15	78	11	78	15.3%	1.45 [0.62 , 3.40]		+ + + + + +
Owen 1991	4	13	1	12	1.2%	4.89 [0.46 , 51.87]		? ? + + ? ●
Zhuang 1994	5	12	2	15	1.8%	4.64 [0.71 , 30.42]		? ? ● + ● ?
Subtotal (95% CI)		**166**		**156**	**29.8%**	**2.19 [1.26 , 3.81]**		
Total events:	49		24					

Heterogeneity: Chi² = 2.68, df = 6 (P = 0.85); I² = 0%
Test for overall effect: Z = 2.77 (P = 0.006)

Total (95% CI)		**526**		**507**	**100.0%**	**1.85 [1.35 , 2.53]**		
Total events:	132		77					

Heterogeneity: Chi² = 12.94, df = 11 (P = 0.30); I² = 15%
Test for overall effect: Z = 3.82 (P = 0.0001)
Test for subgroup differences: Chi² = 0.53, df = 1 (P = 0.46), I² = 0%

0.01 0.1 1 10 100
Favours no GH   Favours GH

Footnotes
(1) This is data from 4 IU study arm of Hazout 2003
(2) This data is from 8 IU study arm of Hazout 2003

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding (performance bias and detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

Subgroup analysis

In both subgroups, pregnancy rates probably increased in women who received adjuvant GH. Poor responder by definition group: OR 1.70, 95% CI 1.16 to 2.50; I² = 59%; 5 trials, 711 participants; and the poor responder based on previous response group: OR 2.19, 95% CI 1.26 to 3.81; I² = 0%; 6 trials, 322 participants; Analysis 2.2).

We did not find evidence that the treatment effect differed between the groups of studies (test for subgroup differences: Chi² = 0.53, df = 1 (P = 0.46), I² = 0%).

2.3 Number of women with at least one oocyte retrieved per woman randomised

Two trials reported number of women with at least 1 oocyte retrieved per woman randomised (Bergh 1994; Norman 2019). The evidence suggests that GH results in little to no difference in the number of women with at least one oocyte retrieved per woman randomised (OR 5.67, 95% CI 1.54 to 20.83; I² = 0; 2 trials, 148 participants; low-certainty evidence; Analysis 2.3). If the chance of retrieving at least one oocyte in poor responders was 81%, with GH the chance is between 87% and 99%.

2.4 Mean number of oocytes retrieved

Twelve trials reported number of oocytes retrieved (Bergh 1994; Choe 2017; Dakhly 2018; Dor 1995; Kucuk 2008; Lee 2019; Mohammad 2019; Norman 2019; Owen 1991; Safdarian 2019; Suikkari 1996; Tesarik 2005). Hazout 2003 reported the mean numbers but standard deviation (SD) was not mentioned, hence data could not be used in the analysis. There is a slight increase in the mean number of oocytes retrieved with the use of GH for poor responders (MD 1.40, 95% CI 1.16 to 1.64; I² = 87%; 12 trials, 1153 participants; low-certainty evidence; Analysis 2.4). The mean

number of oocytes retrieved were 2 to 6. However heterogeneity of over 85% suggests quite different effects according to differences including in trial protocols (populations, GH dose and schedule), so the result should be interpreted with caution.

We did not find evidence that the treatment effect differed between the groups of studies (test for subgroup differences: Chi² = 0.08, df = 1 (P = 0.77), I² = 0%).

2.5 Embryo transfer achieved per woman randomised

Four trials reported embryo transfer per woman randomised (Bergh 1994; Kucuk 2008; Norman 2019; Suikkari 1996). The evidence is very uncertain about the effect of GH on embryo transfer achieved per woman randomised (OR 2.32, 95% CI 1.08 to 4.96; I² = 25%; 4 trials, 214 participants; very low-certainty evidence; Analysis 2.5). If the chance of achieving embryo transfer per woman randomised is assumed to be 77%, the chance with use of GH will be 78% to 94%.

2.6 Mean units of gonadotrophin used

Eight trials reported mean units of gonadotropin used (Bergh 1994; Choe 2017; Dakhly 2018; Dor 1995; Kucuk 2008; Norman 2019; Owen 1991; Safdarian 2019). Use of GH results in reduction of mean units of gonadotropins used for stimulation in poor responders (MD -1088.19, 95% CI -1203.20 to -973.18; I² = 91%; 8 trials, 685 participants; low-certainty evidence; Analysis 2.6). However amongst studies including poor responders based on a definition there was considerable heterogeneity, such that the pooled estimate may not represent a useful summary.

The test for subgroup differences showed that treatment effect differed between the groups of trials (Chi² = 14.41, df = 1 (P = 0.0001), I² = 93.1%).

2.7 Adverse events

Six trials did not report adverse events (Choe 2017; Dakhly 2018; Dor 1995; Hazout 2003; Tesarik 2005, Zhuang 1994). Owen 1991 reported ectopic pregnancies: 0/13 in GH group and 1/12 in control; the other trials in poor responder group reported no cases of ectopic pregnancy in either group. Multiple pregnancy was reported in Owen 1991: 2/13 in GH group and 0/12 in control group; Mohammad 2019 reported 1/78 in GH group and 1/78 in control group; Suikkari 1996 reported 1/10 in 4 IU GH group and 0/6 in control group; and other trials reported no cases of multiple pregnancies in either group. Norman 2019 reported congenital anomalies: 1/65 in GH group and 1/65 in control group; other

trials reported no cases of congenital anomalies in either group. Bergh 1994 reported that 2/29 cases in GH group had oedema, but this outcome was not reported by any other study. Kucuk 2008, Safdarian 2019 and Lee 2019 reported that no adverse events were seen in either group. This information has been presented in tabular form in Table 1.

2.8 Other analyses

We conducted sensitivity analyses for the primary outcome, live birth rate, to determine whether the conclusions are robust to arbitrary decisions made regarding eligibility and analysis. These analyses considered whether conclusions would have differed under the following circumstances.

- If eligibility was restricted to trials without high risk of bias. Risk of bias assessment conducted as per Cochrane RoB 1 tool (Higgins 2011). Serial exclusion of each study from the meta-analysis did not produce significant changes in this outcome.
- If trials with outlying results had been excluded. Serial exclusion of each study from the meta-analysis did not produce significant changes in this outcome.
- If a random-effects model had been adopted. Changing from fixed-effect to random-effects model did not change the conclusions, but the results showed wider CIs.
- If a sensitivity analysis was performed to detect whether the inclusion of RCTs with high numbers of participants affected the results. Serial exclusion of each study from the meta-analysis did not produce significant changes in this outcome.

3 Adjuvant GH compared to no adjuvant or placebo: subgroup analysis based on age

3.1 Live birth rate per woman randomised

Ten trials reported the live birth rate per woman randomised (Dakhly 2018; Mohammad 2019; Norman 2019; Owen 1991; Safdarian 2019; Suikkari 1996; Tesarik 2005; Zhuang 1994; Tapanainen 1992; Younis 1992).

Subgroup analysis based on age showed that it is uncertain if adjuvant GH increases live birth rates both in < 40 years group (OR 1.45, 95% CI 0.82 to 2.56; I² = 0%; 6 trials, 390 participants) and > 40 years group (OR 1.69, 95% CI 0.90 to 3.20; I² = 72%; 2 trials, 340 participants; Analysis 3.1, Figure 7). High heterogeneity was noted in the subgroup > 40 years, suggesting different effects according to differences including in trial protocols (populations, GH dose and schedule).

Figure 7.

Study or Subgroup	GH Events	GH Total	no GH Events	no GH Total	Weight	Odds Ratio IV, Fixed, 95% CI
3.1.1 Age < 40 years						
Mohammad 2019	15	78	11	78	23.2%	1.45 [0.62 , 3.40]
Norman 2019	9	62	7	51	14.8%	1.07 [0.37 , 3.10]
Owen 1991	4	13	0	12	1.8%	11.84 [0.57 , 247.83]
Suikkari 1996 (1)	2	10	0	6	1.6%	3.82 [0.16 , 94.13]
Tapanainen 1992	1	19	2	19	2.7%	0.47 [0.04 , 5.70]
Younis 1992	6	20	4	22	8.1%	1.93 [0.45 , 8.18]
Subtotal (95% CI)		202		188	52.3%	1.45 [0.82 , 2.56]
Total events:	37		24			

Heterogeneity: Chi² = 3.43, df = 5 (P = 0.63); I² = 0%
Test for overall effect: Z = 1.29 (P = 0.20)

3.1.2 Age > 40 years						
Dakhly 2018	21	120	17	120	34.7%	1.29 [0.64 , 2.58]
Tesarik 2005	11	50	2	50	6.9%	6.77 [1.42 , 32.37]
Subtotal (95% CI)		170		170	41.5%	1.69 [0.90 , 3.20]
Total events:	32		19			

Heterogeneity: Chi² = 3.61, df = 1 (P = 0.06); I² = 72%
Test for overall effect: Z = 1.62 (P = 0.11)

3.1.3 Age criteria not defined						
Safdarian 2019	1	34	0	26	1.6%	2.37 [0.09 , 60.65]
Zhuang 1994	4	12	2	15	4.6%	3.25 [0.48 , 22.00]
Subtotal (95% CI)		46		41	6.2%	3.00 [0.58 , 15.56]
Total events:	5		2			

Heterogeneity: Chi² = 0.03, df = 1 (P = 0.87); I² = 0%
Test for overall effect: Z = 1.31 (P = 0.19)

Total (95% CI)		418		399	100.0%	1.62 [1.07 , 2.44]
Total events:	74		45			

Heterogeneity: Chi² = 7.77, df = 9 (P = 0.56); I² = 0%
Test for overall effect: Z = 2.30 (P = 0.02)
Test for subgroup differences: Chi² = 0.69, df = 2 (P = 0.71), I² = 0%

Footnotes
(1) This is data from 4 IU study arm of Suikkari 1996

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding (performance bias and detection bias)
(D) Incomplete outcome data (attrition bias)
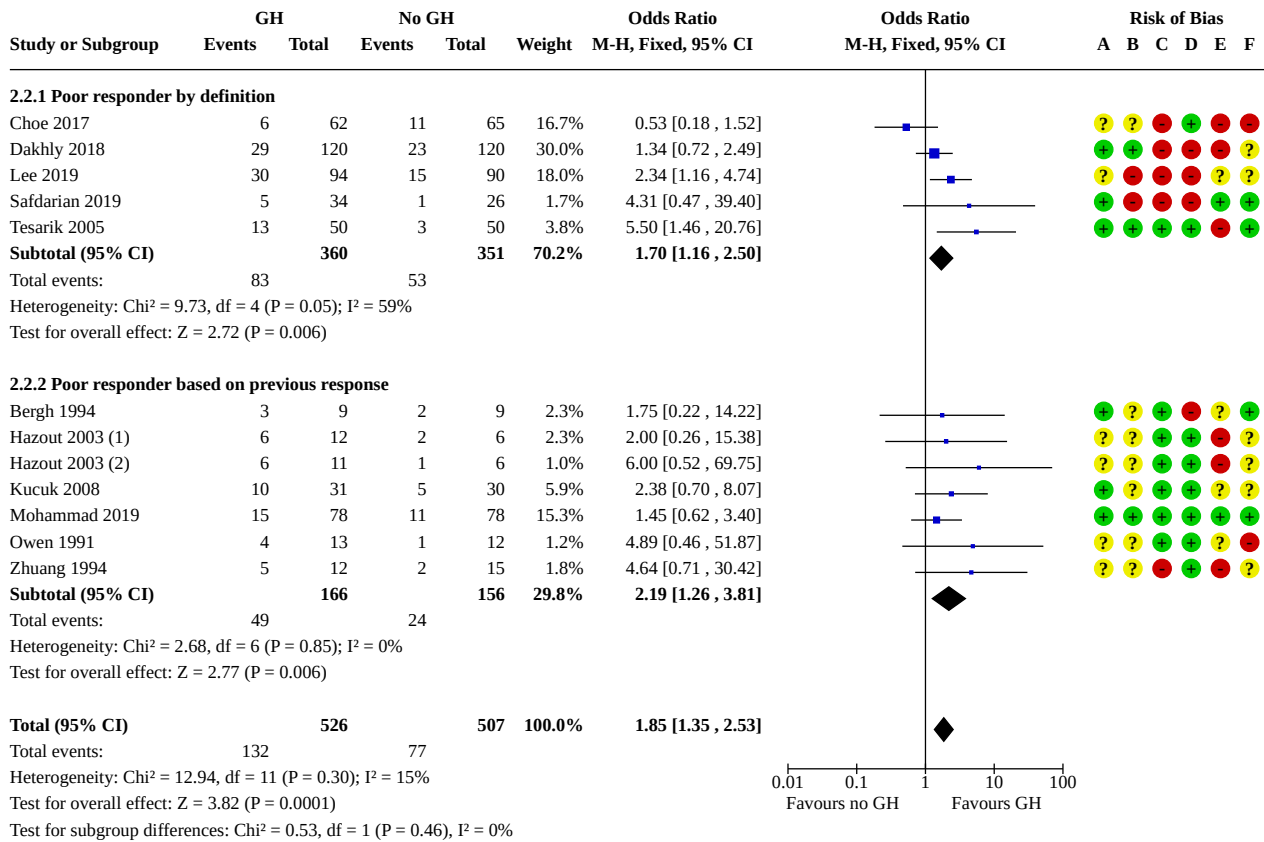(E) Selective reporting (reporting bias)
(F) Other bias

We did not find evidence that the treatment effect differed between the groups of studies (test for subgroup differences: Chi² = 1.71, df = 2 (P = 0.43), I² = 0%).

Secondary outcomes

3.2 Clinical pregnancy rate per woman randomised

Twelve trials reported the pregnancy birth rate per woman randomised (Bergh 1994; Choe 2017; Dakhly 2018; Hazout 2003; Kucuk 2008; Lee 2019; Mohammad 2019; Owen 1991; Safdarian 2019; Tesarik 2005; Zhuang 1994; Younis 1992).

On conducting further subgroup analysis based on age, pregnancy rates were slightly improved in < 40 years of age (OR 1.98, 95% CI 1.12 to 3.50; I² = 0%; 5 trials, 288 participants) be it in poor responder or normal responder, but this was not seen in the age group > 40 years (OR 1.64, 95% CI 1.11 to 2.42; I² = 67%; 4 trials, 651 participants; Analysis 3.2, Figure 8). There is high heterogeneity noted in clinical pregnancy rates in the > 40 years subgroup, suggesting different effects according to differences including in trial protocols, study population and also difference in GH dose and schedule.

Figure 8.

Study or Subgroup	Experimental		Control		Weight	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
	Events	Total	Events	Total				
3.2.1 Age < 40 years								
Bergh 1994	3	9	2	9	2.1%	1.75 [0.22 , 14.22]		+ ? + - ? +
Hazout 2003 (1)	6	11	3	12	2.1%	3.60 [0.62 , 21.03]		? ? + + - ?
Hazout 2003 (2)	6	12	3	12	2.4%	3.00 [0.53 , 16.90]		? ? + + - ?
Mohammad 2019	15	78	11	78	14.2%	1.45 [0.62 , 3.40]		+ + + + + +
Owen 1991	4	13	1	12	1.2%	4.89 [0.46 , 51.87]		? ? + + ? -
Younis 1992	8	20	6	22	5.5%	1.78 [0.49 , 6.50]		? + + + ? -
Subtotal (95% CI)		**143**		**145**	**27.5%**	**1.98 [1.12 , 3.50]**		
Total events:	42		26					
Heterogeneity: Chi² = 1.78, df = 5 (P = 0.88); I² = 0%								
Test for overall effect: Z = 2.36 (P = 0.02)								
3.2.2 Age > 40 years								
Choe 2017	6	62	11	65	15.5%	0.53 [0.18 , 1.52]		? ? - + - -
Dakhly 2018	29	120	23	120	27.9%	1.34 [0.72 , 2.49]		+ + - - - ?
Lee 2019	30	94	15	90	16.7%	2.34 [1.16 , 4.74]		? - - - ? ?
Tesarik 2005	13	50	3	50	3.6%	5.50 [1.46 , 20.76]		+ + + + - +
Subtotal (95% CI)		**326**		**325**	**63.8%**	**1.64 [1.11 , 2.42]**		
Total events:	78		52					
Heterogeneity: Chi² = 8.98, df = 3 (P = 0.03); I² = 67%								
Test for overall effect: Z = 2.48 (P = 0.01)								
3.2.3 Age criteria not defined								
Kucuk 2008	10	31	5	30	5.5%	2.38 [0.70 , 8.07]		+ ? + + ? ?
Safdarian 2019	5	34	1	26	1.5%	4.31 [0.47 , 39.40]		+ - - - + +
Zhuang 1994	5	12	2	15	1.7%	4.64 [0.71 , 30.42]		? ? - + - ?
Subtotal (95% CI)		**77**		**71**	**8.7%**	**3.15 [1.25 , 7.94]**		
Total events:	20		8					
Heterogeneity: Chi² = 0.44, df = 2 (P = 0.80); I² = 0%								
Test for overall effect: Z = 2.44 (P = 0.01)								
Total (95% CI)		**546**		**541**	**100.0%**	**1.87 [1.38 , 2.52]**		
Total events:	140		86					
Heterogeneity: Chi² = 12.91, df = 12 (P = 0.38); I² = 7%								
Test for overall effect: Z = 4.04 (P < 0.0001)								
Test for subgroup differences: Chi² = 1.71, df = 2 (P = 0.43), I² = 0%								

0.01 0.1 1 10 100
Favours no GH   Favours GH

Footnotes
(1) This data is from 8 IU study arm of Hazout 2003
(2) This data is from 4 IU study arm of Hazout 2003

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding (performance bias and detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

We did not find evidence that the treatment effect differed between the groups of studies (test for subgroup differences: Chi² = 0.69, df = 2 (P = 0.71), I² = 0%).

3.3 Number of women with at least one oocyte retrieved per woman randomised

Three trials reported number of women with at least 1 oocyte retrieved per woman randomised (Bergh 1994; Norman 2019; Younis 1992).

On conducting further subgroup analysis based on age, the number of women with at least one oocyte retrieved was higher in those <

40 years of age (OR 5.19, 95% CI 1.56 to 17.32; I² = 0; 3 trials, 190 participants; (Analysis 3.3)

3.4 Mean number of oocytes retrieved

Fifteen trials reported number of oocytes retrieved (Bergh 1994; Choe 2017; Dakhly 2018; Dor 1995; Kucuk 2008; Lee 2019; Mohammad 2019; Norman 2019; Owen 1991; Safdarian 2019; Suikkari 1996; Tesarik 2005; Tapanainen 1992; Younis 1992). Hazout 2003 reported the mean numbers but standard deviation (SD) was not mentioned, hence data could not be used in the analysis.

On further subgroup analysis based on age, there was uncertain effect on mean number of oocytes retrieved in women < 40 years (MD 0.73, 95% CI 0.34 to 1.13; I² = 67%; 7 trials, 437 participants; Analysis 3.4), whereas trials with participants > 40 years showed a slight increase in oocytes retrieved (MD 1.35, 95% CI 1.03 to 1.68; I² = 94%; 4 trials, 651 participants; Analysis 3.4), and similarly trials in which age criteria were not defined showed a slight increase in

oocytes retrieved (MD 2.12, 95% CI 1.55 to 2.69; I² = 83%; 4 trials, 172 participants) and the pooled result for all trials showed a slight increase in oocytes retrieved (MD 1.27, 95% CI 1.04 to 1.49; I² = 86%; 15 trials, 1260 participants; Analysis 3.4, Figure 9). There is high heterogeneity noted in the number of oocytes retrieved for all subgroups, suggesting different effects according to differences including in trial protocols, study population and also difference in GH dose and schedule.

Figure 9.
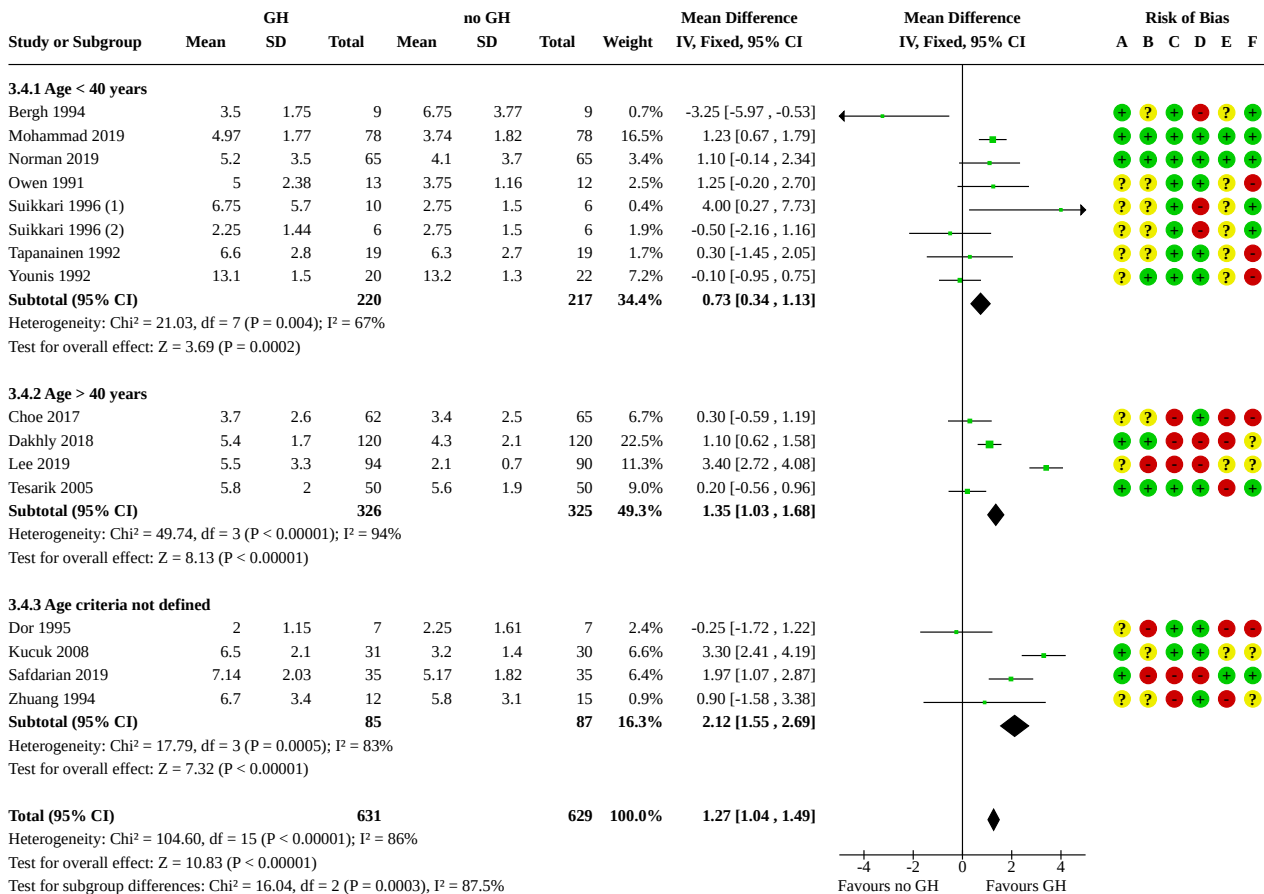
Footnotes
(1) This data is from 12 IU study arm of Suikkari 1996
(2) This data is from 4 IU study arm of Suikkari 1996

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding (performance bias and detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

The test for subgroup differences showed that the treatment effect differed between the groups of trials (Chi² = 16.04, df = 2 (P = 0.0003), I² = 87.5%).

3.5 Embryo transfer achieved per woman randomised

Five trials reported embryo transfer per woman randomised (Bergh 1994; Kucuk 2008; Norman 2019; Suikkari 1996; Younis 1992). On sub-group analysis, the evidence is very uncertain about the effect

of GH on embryo transfer achieved per woman randomised < 40 years (OR 1.73, 95% CI 0.80 to 3.74; participants = 201; studies = 5; I² = 0%); Analysis 3.5.

We found evidence that the treatment effect differed between the groups of trials (test for subgroup differences: Chi² = 2.92, df = 2 (P < 0.09), I² = 65.8%).
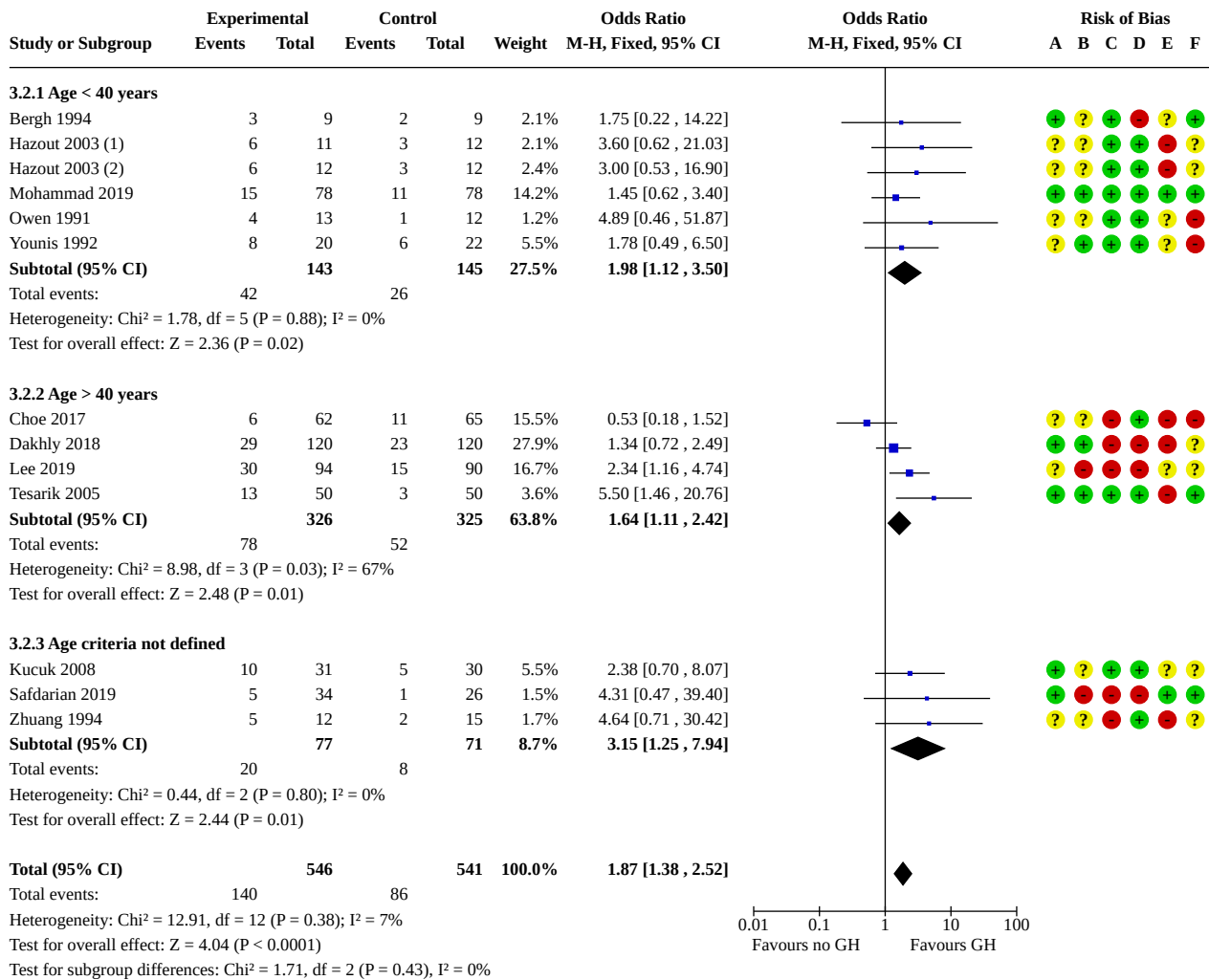
3.6 Mean units of gonadotrophin used

Ten trials reported mean units of gonadotropin used (Bergh 1994; Choe 2017; Dakhly 2018; Dor 1995; Kucuk 2008; Norman 2019; Owen 1991; Safdarian 2019; Younis 1992; Tapanainen 1992).

On further subgroup analysis based on age, there was uncertain effect in < 40 years (MD -24.30, 95% CI -145.14 to 96.55; participants = 253; studies = 5; I^2 = 34%; Analysis 3.6), whereas trials with participants > 40 years showed a slight reduction in mean units of gonadotropin used (MD -782.66, 95% CI -1004.35 to -560.97; participants = 367; studies = 2; I^2 = 97%; Analysis 3.6), and similarly trials in which age criteria were not defined showed there was a reduction in mean units of gonadotropins used (MD -1294.15, 95% CI -1436.54 to -1151.77; participants = 145; studies = 3; I^2 = 91%; Analysis 3.6) and the pooled result for all trials showed a slight reduction in mean units of gonadotropin used (MD -589.38, 95% CI -674.47 to -504.30; participants = 765; studies = 10; I^2 = 96%);Analysis 3.6. There is high heterogeneity noted in the number of oocytes retrieved for the subgroups of women > 40 years and where the age criteria were not defined, such that the pooled estimates may not represent useful summaries.

The test for subgroup differences showed that the treatment effect differed between the groups of trials (Chi² = 181.03, df = 2 (P < 0.00001), I^2 = 98.9%).

DISCUSSION

Summary of main results

This review was undertaken to establish the role of adjuvant GH therapy for IVF in improving IVF outcomes, particularly in those women who are considered poor responders. We included 16 RCTs (1352 women analysed). Two RCTs (80 women analysed) studied GH in routine use, and 14 RCTs (1272 women analysed) studied GH in poor responders. The evidence was low to very low certainty, with the main limitations being risk of bias, imprecision and heterogeneity.

Adjuvant growth hormone compared to no adjuvant: routine use for in vitro fertilisation (IVF)

The evidence is very uncertain about the effect of GH on live birth rate per woman randomised for routine use in IVF (low-certainty evidence). There was insufficient evidence to reach a conclusion regarding clinical pregnancy rates per woman randomised, number of women with at least one oocyte retrieved per woman randomised and embryo transfer achieved per woman randomised; reported data were unsuitable for analysis. The evidence is very uncertain about the effect of GH on mean number of oocytes retrieved in normal responders (very low-certainty evidence). The evidence suggests that GH does not increase or

reduce adverse events in normal responders. This information has been presented in tabular form in Table 1.

Adjuvant growth hormone compared to no adjuvant: use in poor responders for in vitro fertilisation (IVF)

The evidence is very uncertain about the effect of GH on live birth rate per woman randomised for poor responders (very low-certainty evidence). GH used as adjuvant results in a slight increase in pregnancy rates per woman randomised in poor responders compared to no use of GH (low-certainty evidence). The evidence suggests that GH results in little to no difference in the number of women with at least one oocyte retrieved per woman randomised (low-certainty evidence). There is a slight increase in the mean number of oocytes retrieved with the use of GH for poor responders (low-certainty evidence). The evidence is very uncertain about the effect of GH on embryo transfers achieved per woman randomised (very low-certainty evidence). Use of GH results in reduction of mean units of gonadotropins used for stimulation in poor responders (low-certainty evidence). Eight of 14 included trials reported adverse events. These included ectopic pregnancy, multiple pregnancy and congenital abnormality. This information has been presented in tabular form in Table 1.

High heterogeneity in the analyses for mean number of oocytes retrieved and units of GH used suggests quite different effects according to differences including in trial protocols (populations, GH dose and schedule), so these results should be interpreted with caution.

Overall completeness and applicability of evidence

The included trials did not answer the review question satisfactorily. Mainly, the primary outcome, live birth rate, was not reported in all trials. Also, since the dose, preparation and timing of administration of GH varied across the trials, robust conclusions cannot be derived.

The causative factors for poor response to controlled ovarian stimulation are not well described in the literature. Consequently, the definitions of a 'poor responder' are varied, ranging from age to poor responders to gonadotrophin stimulation on previous IVF cycles. Therefore the inclusion criteria of the included trials varied greatly. The evidence is low to very low certainty.

There was no uniformity of dose, preparation or timing of the intervention, and this can introduce bias (see Table 2). Also, the funnel plot could indicate publication bias (Figure 10), and this can skew the results of the review. Furthermore, some of the included trials had relatively small sample sizes, and this may have influenced the validity and reliability of the conclusions. Finally, not all the included trials had strict methods of randomisation, blinding and allocation concealment, which may affect conclusions.

Figure 10.   Funnel plot - Preganacy rate per woman randomised in poor responder group.
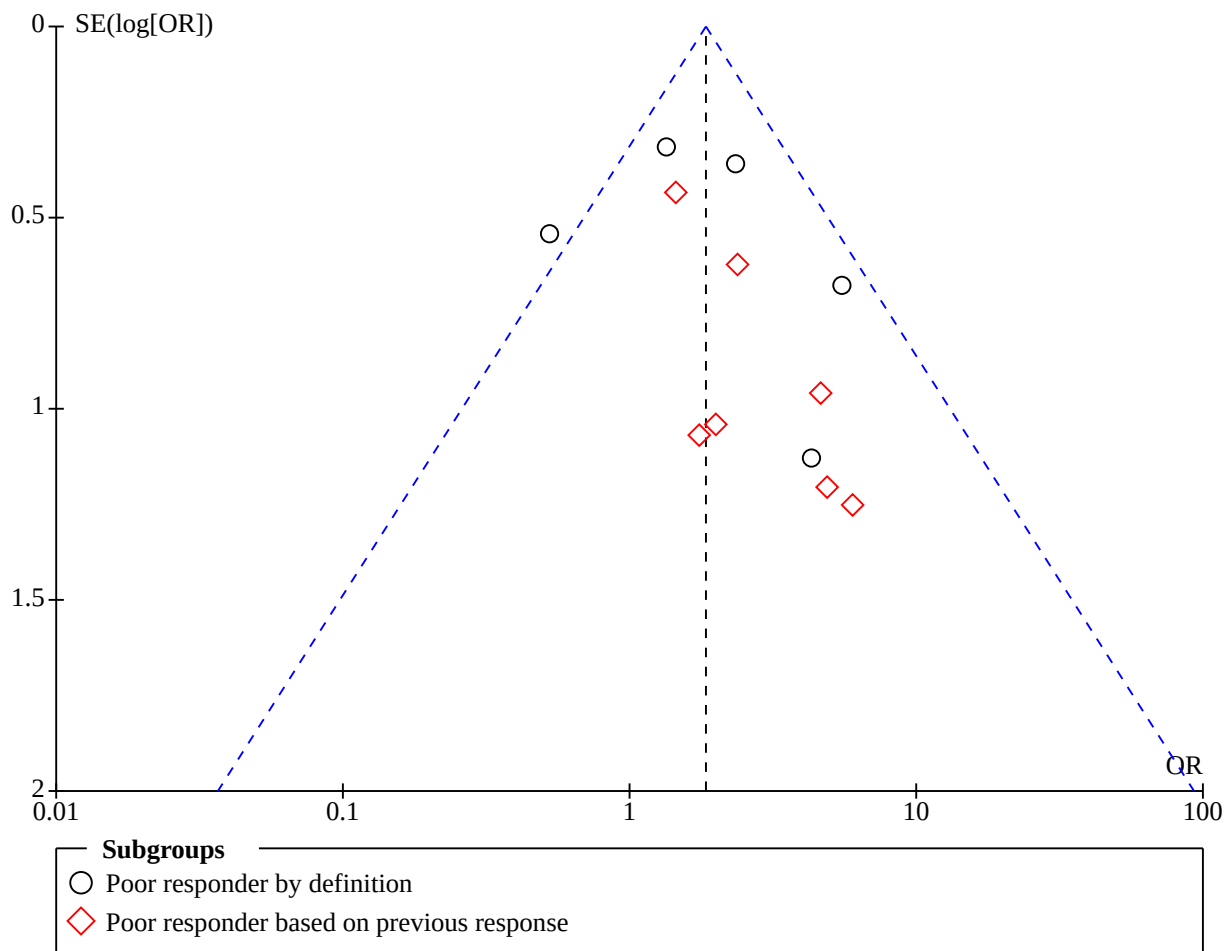
Quality of the evidence

Of the 16 RCTs included in the review, there were significant differences in the number of participants, variations in the cause of subfertility and variations in the IVF treatment protocol. The dose of GH also varied in the trials and the outcomes measured all varied considerably between the trials. As such, the certainty of evidence is very low due to imprecision, small sample size and heterogeneity. Also, there was asymmetry in the funnel plot (Figure 10), which could indicate publication bias, or small study effects or use of an inappropriate effect measure.

Potential biases in the review process

The methods established to conduct the current review were agreed by all review authors and any potential bias that could have been introduced was bypassed through independent screening, assessment, selection and data extraction with discrepancies resolved through team consensus. The search was supported by the CGFG Information Specialist.

We made every effort to identify all potentially eligible trials, and sought additional data from study authors as necessary. However, it is possible that there are unpublished trials that were not retrieved.

Also, there was asymmetry in the funnel plot (Figure 10), which could indicate publication bias, or small study effects or use of an inappropriate effect measure.

Agreements and disagreements with other studies or reviews

Currently, no national or international guidelines recommend the routine use of GH augmentation in IVF protocols. Unfortunately, due to the problems inherent with recruiting women who have undergone unsuccessful IVF treatment cycles and their inevitable low live birth rate per initiated cycle, many trials performed to date have been underpowered. However, a previous systematic review and meta-analysis concerning the evaluation of strategies to improve pregnancy rates in poor responders undergoing IVF concluded there was some evidence to suggest the addition of GH could improve live birth rates, but further research was required (Kyrou 2009). Another meta-analysis demonstrated a benefit for the use of adjunct GH, with a reduction in the duration of ovarian stimulation required for oocyte retrieval, the collection of a greater number of oocytes than placebo, and an improvement in many of the early clinical parameters; however, there was no evidence of an increased chance of a live birth with the use of GH (Hart 2017). Similar conclusions suggesting an increase in clinical pregnancy

rate but no increase in live birth rate was also seen in a meta-analysis in Cozzolino 2020. However, another recent meta-analysis concluded that GH supplementation might improve live birth rates, clinical pregnancy rates and oocytes retrieved (Yang 2020). The difference in results could possibly be explained by the further information we are awaiting from trials included in this review.

A retrospective analysis based on real-world data suggests a role for GH in POSEIDON (**P**atient-**O**riented **S**trategies **E**ncompassing **I**ndividualize**DO**ocyte **N**umber) group 4 patients (Cai 2019). This is the first publication to detect specific subgroups of poor ovarian responders that would benefit from GH supplementation. The authors explored the effects of GH in the POSEIDON groups 3 and 4, but they were capable of detecting an improvement in live birth rates together with a decrease in miscarriage rates only in POSEIDON group 4. A future prospective trial based on POSEIDON groups with a standardised protocol of GH supplementation may provide further answers.

New avenues are being explored for the use of GH in IVF. In a recent study of recurrent implantation failure patients undergoing IVF. The clinical pregnancy and live birth rates in the treatment group were significantly higher than those in the control group (Chen 2018). The mechanism was postulated to be increased GH receptors in granulosa cells. Another study reported improved implantation, pregnancy, and live birth rates among infertile patients with recurrent implantation failure; treatment with GH suggested that GH improves uterine receptivity (Altmae 2018). We await further investigation and clarification from a recently conducted meta-analysis that questioned whether the role of GH resides in the treatment of poor oocyte quality, the treatment of the 'suboptimal' responder, the treatment of the 'thin endometrium' or 'recurrent implantation failure' (Cui 2019; Hart 2019).

AUTHORS' CONCLUSIONS

Implications for practice

Use of adjuvant GH in IVF treatment protocols slightly increases the number of oocytes retrieved and pregnancy rates in 'poor responders' but has uncertain effects on live birth rates. The results however, need to be interpreted with caution, as the included trials were small and few in number, with significant bias and imprecision. Also, the dose and regimen of GH used in trials was variable. Therefore, further research is necessary to fully define the role of GH as adjuvant therapy in IVF. Furthermore, the cost of the intervention has been reported by only one study (Kucuk 2008), which was nearly double the cost without adjuvant GH use. This could affect the applicability of GH in practice, as the cost of IVF treatment with GH will be significantly higher than without, making treatment with GH unaffordable for some women.

Implications for research

With regards to women who are known poor responders to IVF, a multiple-centre randomised double-blinded trial is warranted to investigate the effect of GH augmentation. Key elements of design should include a power calculation to ensure the minimum number of participants needed for a significant result are included, the standardisation of controlled ovarian hyperstimulation protocols, and dose of GH and subgroups based on POSEIDON criteria (POSEIDON criteria 2016). The primary outcome of live birth rate should be measured. Only by considering such outcomes can this therapy be truly tested. Also, adverse events should be routinely reported. Given the high cost of GH treatment, one component of new trials should also be an economic evaluation. Newer avenues of research include the potential role of GH in improving uterine receptivity and improved outcomes in women with recurrent implantation failure.

ACKNOWLEDGEMENTS

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Bergh 1994

Study characteristics	
Methods	Randomisation: using a computerised list women were randomised to one of four arms
	Allocation concealment: unclear

Bergh 1994 *(Continued)*

Blinding: double-blind

Trial design: parallel

Analysis: power calculation was performed, no intention-to-treat analysis performed

Study setting: multicentre study - three IVF programmes in Sweden

Withdrawals: two women (< 10%)

Cancelled cycles: one woman in placebo group (< 10%)

Participants	• Number of women: 18 (9 GH, 9 placebo) • IVF previous poor responders: at least two failed cycles with < 5 oocytes • Regular menstrual cycle • Normal FSH, LH, PRL and ovarian ultrasound • BMI ≤ 28, age 25 to 38 years. Normal semen quality, (WHO criteria)
Interventions	Intervention • GH 0.1 IU/kg daily subcutaneous. Recombinant GH used Treatment protocol • 7 days pretreatment with placebo; pretreatment was started after ovarian down regulation was established (achieved with buserelin beginning on day one or two of cycle, administered intranasally 6/day or in a few cases by subcutaneous injection, 2 per day for a total dose of 1.2 mg/day. Treatment with buserelin continued during the pretreatment and stimulation periods. Ovarian stimulation was performed by hMG 225 IU/day to 300 IU/day and/or FSH in a dose of 75 IU/day to 300 IU/day for 10 to 25 days. • Protocol, n = 10 women and cycles • Dose of HCG: 10,000 IU when at least one follicle was >18 mm diameter and there had been 7 to 8 days of continued rise of serum estradiol
Outcomes	• Pregnancy rate • Oocyte retrieval • Embryo transfer
Notes	This trial involved four treatment arms (and 40 women) but only data comparing GH use in conjunction with GnRHa/hMG versus standard treatment (groups I, II) were included. Groups III and IV involved GH pretreatment and were excluded. The placebo used was NaCl.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation: using a computerised list women were randomised to one of four arms
Allocation concealment (selection bias)	Unclear risk	Not stated within the text
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	2 women lost to follow up

Bergh 1994 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	No registered protocol found
Other bias	Low risk	No other source of bias identified

Choe 2017

Study characteristics		
Methods	Trial design: open-label parallel randomised control trial Analysis: power calculation performed Study setting: single study centre (Seoul, South Korea) Cancelled cycles: 30 (12.5%) failed egg collection = 18, failed fertilisation = 12	
Participants	• Number of women: 127 (62 sustained release GH, 65 control) • IVF previous poor responders as defined by study design (Bologna criteria): ○ age ≥ 40 years or other factor for poor ovarian response ○ previous poor ovarian response (≤ 3 oocytes on ovulation induction) ○ low ovarian reserve test (AMH level < 0.5 ng/mL to 1.1 ng/mL, AFC < 5 to 7 follicles)	
Interventions	• Women in treatment group received sustained-release HGH (Eutropin Plus 20 mg, LG life sciences, Seoul, Korea) three times before and during COS (mid-luteal, late luteal, and menstrual cycle day 2). All participants received GnRH antagonist protocol starting with recombinant FSH from menstrual day 3 after confirming downregulation. Dose of FSH ranged from 225 IU to 375 IU. Dose was adjusted according to follicular development. GnRH antagonist was added when dominant follicle reached 15 mm until the day of trigger. • Recombinant HCG was administered when there was at least one follicle measuring 18 mm or more.	
Outcomes	Primary outcomes • Number of mature oocytes • Serum estradiol levels on day of trigger Secondary outcomes • Serum IGF-1 and IGFBP 3 levels • Number of follicles with diameter > 14 mm • Progesterone levels on day of trigger • Fertlization/implantation rate • Proportion of MII oocytes • Proportion of good quality embryos • Clinical/ongoing pregnancy rate • Spontaneous abortion rate	
Notes	Initially 164 patients screened for the study. 28 were excluded due to loss to follow-up, 8 were excluded due to abnormal findings at screening. No patients discontinued due to adverse events. Improved number of mature oocytes noted in GH group. Authors contacted regarding more information on adverse effects and allocation concealment - no reply received	

Risk of bias		

Choe 2017 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcomes were reported for all 127 women randomised to GH versus standard treatment
Selective reporting (reporting bias)	High risk	The study did not report adverse events
Other bias	High risk	This study was supported by a research grant from LG Life Sciences, Seoul, Korea (manufacturer of sustained release GH preparation used)

Dakhly 2018

Study characteristics	
Methods	Randomisation: using specific computer programmes
	Allocation concealment: results placed in opaque sealed envelopes with patients' number written outside (and after opening the envelope, it would reveal which group patient belonged to)
	Blinding: non-blinded
	Trial design: open-label randomised control trial
	Analysis: power calculation performed
	Study setting: single study centre (Egypt)
	Withdrawals: none
	Cancelled cycles: 30 (12.5%) failed egg collection = 18, failed fertilisation = 12
Participants	• Number of women: 240 (120 GH + long protocol, 120 long protocol)
	• IVF previous poor responders as defined by study design (Bologna criteria):
	○ age ≥ 40 years or other factor for poor ovarian response
	○ previous poor ovarian response (≤ 3 oocytes on ovulation induction)
	○ low ovarian reserve test (AMH level < 0.5 ng/mL to 1.1 ng/mL, AFC < 5 to 7 follicles)
Interventions	Both groups
	• Downregulation with triptorelin 0.1 mg/day from day 21 of previous cycle, reducing it to 0.05 mg/day from the start of following cycle and continued till HCG administration
	• Recombinant human FSH (Gonal F) 300 IU started on day 2 to 3 of menses. FSH dose adjusted from day 6 of stimulation according to ovarian response. 10,000 IU HCG given IM when at least 2 follicles had reached 18 mm or more. GH/ long (group A) patients received adjuvant GH 2.5 mg (7.5 IU) GH SC from day 21 of previous cycle along with GnRHa, until the day of HCG. Recombinant GH used.

Dakhly 2018 *(Continued)*

Outcomes	**Primary outcome** • LBR (fresh, frozen and cumulative) **Secondary outcomes** • Duration of gonadotropin stimulation (days) • Total units of gonadotropin • Number of oocytes retrieved • Number of MII oocytes • Number of fertilised oocytes • Number of embryos transferred and frozen • Fertilisation rate • Implantation rate • Chemical, clinical and ongoing pregnancy rates
Notes	Registered protocol NCT02338206 Improved number of MII oocytes noted Authors contacted regarding further information on adverse events data - no reply received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Opaque sealed envelopes used
Blinding (performance bias and detection bias) All outcomes	High risk	Unblinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Outcomes reported for per cycle started, 12.5% cancellation
Selective reporting (reporting bias)	High risk	Registered protocol NCT02338206 The study did not report adverse events
Other bias	Unclear risk	No placebo was used in control group

Dor 1995

Study characteristics

Methods	Randomisation: method not described Allocation concealment: none Blinding: double-blind Trial design: prospective, randomised, placebo-controlled, double-blind study

Dor 1995 *(Continued)*

Analysis: power calculation not performed

Study setting: Department of Obstetrics and Gynecblogy, The Chaim Sheba Medical Center, Tel Hashomer and Sackler School of Medicine, Tel Aviv University, Israel

Withdrawals: none

Participants	• A total of 14 poor responder participants (oestradiol < 500 pg/mL, < 3 oocytes retrieved in two previous IVF cycles)
Interventions	• GnRHa/HMG/GH (18 IU on alternate days, total dose 72 IU). Recombinant GH used • GnRHa/HMG placebo
Outcomes	• Number of HMG ampoules required to achieve an adequate ovarian response • number of follicles (> 14 mm) on the day of HCG administration • Number of oocytes • Fertilisation rate • Number of embryos achieved
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not described
Allocation concealment (selection bias)	High risk	No allocation concealment
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcomes reported per cycle started
Selective reporting (reporting bias)	High risk	The study did not report adverse events
Other bias	High risk	Very low number of participants - no power calculation

Hazout 2003

Study characteristics

Methods	Randomisation: stated as randomised
	Allocation concealment: unclear
	Blinding: double-blind
	Intention-to-treat analysis: not performed
	Power calculation: not performed

Hazout 2003 *(Continued)*

Study setting: single centre (Paris, France)

Withdrawals: none

Cancelled cycles: < 10%

Participants	• Number of women n = 35 (12 GH 4 IU, 11 GH 8 IU, 12 placebo) Inclusion criteria: • women were < 39 years old with normal hormonal status and history of oocyte dysmorphia defined by < 50% of abnormal oocyte at previous attempts Exclusion criteria: • not stated
Interventions	Intervention • 4 IU or 8 IU subcutaneous. Recombinant GH used Induction protocol • Unclear. Dose of HCG 1000 IU IM when at least two follicles were >16 mm in diameter
Outcomes	• Pregnancy rate
Notes	Thirty-five women in total were included in Hazout 2003 and they were divided into three groups: placebo, GH 4 IU and GH 8 IU. Since only two groups could be compared for the table of comparisons the two GH groups were separated and compared with half the placebo data for the meta-analysis but throughout the text the trial is referred to singly as Hazout 2003. Received a response from author regarding clarification of queries in the study.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated as randomised; no other details
Allocation concealment (selection bias)	Unclear risk	Not stated within the text
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawals: none. Cancelled cycles < 10%
Selective reporting (reporting bias)	High risk	The study did not report adverse events
Other bias	Unclear risk	Conference abstract only available as data not published as article, author contacted for additional information - response received by email

Kucuk 2008

Study characteristics

Methods	Randomisation: computer generated randomisation
	Allocation concealment: sealed envelopes
	Blinding: triple
	Intention-to-treat analysis: not performed
	Power calculation: not performed
	Study setting: single centre - Bursa, Turkey
	Withdrawals: none
	Cancelled cycles: < 10%
Participants	• Number of women n = 61 (31 GH, 30 placebo)
	• Inclusion criteria: women who responded poorly to high-dose gonadotrophin treatment in their first cycles in the same centre. Cause of subfertility: not stated
Interventions	• GH 12 IU subcutaneous from day 21 of preceding cycle along with GnRHa, until the day of HCG. Recombinant GH used
	• Treatment protocol: long GnRHa/FSH/hMG protocol used. Dose of HCG 10,000 IU when at least 1 follicle was > 17 mm in diameter
Outcomes	• Clinical pregnancy
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Unclear risk	Sealed envelopes; no details as to whether opaque
Blinding (performance bias and detection bias) All outcomes	Low risk	Triple-blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawals: none. Cancelled cycles < 10%
Selective reporting (reporting bias)	Unclear risk	There is no indication the study has reported outcomes selectively
Other bias	Unclear risk	No placebo used in control group

Lee 2019 *(Continued)*

Study characteristics

Methods	Randomisation: simple randomisation using a coin toss method
	Allocation concealment: none
	Blinding: not blinded
	Trial design: parallel
	Analysis: no power calculation or intention-to-treat analysis performed
	Study setting: single centre, location Taipei Medical University Hospital from January 2010 to October 2012
	Withdrawals: none
	Cancelled cycles: 40%
Participants	Inclusion criteria
	• Poor responders who had fulfilled at least two of the following criteria:
	◦ advanced maternal age (40 years old) or any other risk factors for poor ovarian response.
	◦ previous episode of poor ovarian response (3 mature oocytes retrieved with a conventional stimulation protocol)
	◦ an abnormal ovarian reserve test (AFC < 5 to 7 follicles or AMH < 0.5 ng/mL to 1.1 ng/mL)
	Exclusion criteria
	• Not stated
Interventions	• Patients in the GH (+) group (n = 94) received co-treatment with GH adjuvant therapy (Recombinant GH- Saizen; Merck Serono) at a dosage of 4 IU, 4 IU, and 2 IU for three successive days, along with the ovulation induction. The total GH dosage was 10 IU for each patient in the GH (+) group. Patients in the GH (–) group (n = 90) received the same IVF protocol without GH adjuvant therapy.
Outcomes	• Number of oocytes retrieved
	• Number of embryos transferred
	• Clinical pregnancy
	• Miscarriage
Notes	The second part of the study was a retrospective comparison of poor responders treated with adjuvant GH with normal responders - these data were not included in the review.
	The data presented for number of oocytes and number of embryos transferred was an average and number of women who had the procedure not mentioned.
	Authors contacted regarding further data on adverse events if available - reply received to confirm that no adverse events were reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Tossing a coin used for randomisation
Allocation concealment (selection bias)	High risk	No allocation concealment

Lee 2019 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	High risk	No blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	No mention of cycle cancellation or withdrawals
Selective reporting (reporting bias)	Unclear risk	No registered protocol
Other bias	Unclear risk	Live birth rates were not reported. Second half of the study was retrospective in nature, hence only data from the prospective part was analysed No placebo used in control group

Mohammad 2019

Study characteristics

Methods	Randomisation: using computer generated tables
	Allocation concealment: closed envelope technique
	Blinding: double-blind
	Trial design: parallel randomised controlled trial
	Analysis: power calculation performed
	Study setting: single study centre (Egypt)
	Withdrawals: 8 (< 10%)
	Cancelled cycles: 16
Participants	• Total enrolled to study: 156, GH group = 78 (7 cancelled), control group = 78 (9 cancelled)
	Inclusion criteria: age 25 to 38 years, IVF previous poor responders with at least two failed cycles with < 5 oocytes, abnormal ovarian reserve tests e.g. AMH < 1 ng/mL, patients with unexplained infertility, normal hormonal profile (FSH, LH, PRL), normal ovarian ultrasound, normal pelvic ultrasound, women that were willing to do ICSE-ET.
	Poor responders were identified according to the Bologna Criteria but without advanced maternal age.
	Exclusion criteria: women with known medical disease (e.g. severe hypertension or hepatic disease), history of altered karyotype in one or both partners, history of chronic, autoimmune or metabolic diseases, presence of endocrinopathies, male factor infertility, participation in any other clinical trial during enrolment, women who in the investigator's judgment cannot be expected to comply with the protocol or study procedures, and refusal to participate in the study.
Interventions	Stimulation protocol
	• Ultrashort protocol - GnRH antagonist 450 IU + GnRH daily for 3 days (0.1 mg sc of triptorelin acetate or leuprolide)
	• GH group - received GH 4 IU per day from day 2 of cycle until 1 day before egg collection. Recombinant GH used

Mohammad 2019 *(Continued)*

	• Control group - placebo instead of GH - saline

Outcomes	Primary outcome
	• Clinical pregnancy per allocated woman, defined as the presence of at least one foetus with heartbeat
	Secondary outcomes
	• E2 levels of hCG day, number of oocytes collected
	• M II oocyte number
	• Number of G1 embryos
	• Number of G1 embryos transferred
	• Implantation rate
	• Chemical pregnancy rate
	• Multiple pregnancy
	• Endometrial thickness when at least one follicle ≥ 17 mm is observed

Notes	Clinical Trial Registration: ClinicalTrials.gov Identifier: NCT03759301
	Authors contacted regarding further data on adverse effects if available- reply received to confirm that only multiple pregnancy was noted. No other adverse events noted

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence genera-tion (selection bias)	Low risk	Computer-generated tables used
Allocation concealment (selection bias)	Low risk	Closed envelope technique
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data reported per cycle started
Selective reporting (re-porting bias)	Low risk	There is no indication that the data were reported selectively
Other bias	Low risk	No other bias noted

Norman 2019

Study characteristics

Methods	Trial design - multicentre, double-blind, placebo-controlled trial performed in 10 participating centres throughout Australia and New Zealand.
	Analysis - Intention to treat

Participants	Total participants randomised - 130, 65 to GH and 65 to placebo

Norman 2019 *(Continued)*

- Inclusion criteria - poor responder defined as women who had at least one IVF cycle in which there was a poor response (5 or fewer oocytes) with recombinant FSH stimulation of more than 250 IU/day. Participants included were younger than 41 years of age, have a body mass index ≤32 kg/m2 and never have had a recorded FSH above 15 IU/L.
- Exclusion criteria: Participants were excluded if they had any clinically significant systemic disease, had undergone radiotherapyor chemotherapy, had any current history of malignant disease, pituitary or hypothalamic disease, had a current ovarian cyst >3 cm, or had any chronic infectious diseases, polycystic ovary syndrome or unexplained menstrual bleeding. Women who were undergoing preimplantation genetic testing or were smokers, using steroids, DHEA or prednisolone in the last 3 months were not eligible for the study.

Interventions	Study drug- GH (Recombinant GH- Saizen 8 mg, Merck, Australia), in a syringe of 24 IU with a daily administered dose of 12 IU.
	Placebo control- identical syringe provided by Merck but containing 0.3% metacresol in water.
	Gonadotrophin-releasing hormone (GnRH) antagonist cycle with the study drug being started at the same time as recombinant FSH on Day 2 or 3 of the cycle. GnRH antagonist was started on Day 5 or 6. When at least two follicles were available at 17 mm or more, injection of 250 µg recombinant HCG was given to trigger ovulation and an oocyte recovery organised for 36 h later.
Outcomes	Primary outcome -
	• live birth after 20 weeks' gestation.
	Secondary outcomes-
	• oocytes retrieval
	• time to oocyte retrieval from first administration of the study drug or placebo
	• total FSH dose
	• embryo quality by the Gardner criteria
	• embryos fertilized
	• embryo transferred, cryopreserved and discarded
	• miscarriage
	• safety profile
Notes	Australian New Zealand Clinical Trials Registry ACTRN12609001060235.
	Based on sample size calculation before the start of the study, sample size -195. These numbers were not reached and the study was ended early as provided drug had expired.
	A post hoc sub group analysis of poor ovarian response according to Bologna criteria was performed - no statistically significant differences were observed between the 2 groups.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation (1:1) was with a computer-generated block randomisation
Allocation concealment (selection bias)	Low risk	A prenumbered drug kit which was allocated on day 1 of the FSH stimulation. Sites telephoned a central office to obtain the randomisation numbers. Drugs were stored onsite and the code determined which injections were given to the participant
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants, study investigators, care providers and the trial statistician were all blinded to treatment allocation until the statistical analysis was completed.

Norman 2019 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcomes reported
Selective reporting (reporting bias)	Low risk	There is no indication the study has reported outcomes selectively
Other bias	Low risk	No other bias noted

Owen 1991

Study characteristics

Methods	Randomisation: two randomisation lists were made with 20 women on each list and block randomised into blocks of four. Allocation concealment: method unclear Blinding: double-blind Trial design: parallel. Analysis: no power calculation or intention to treat analysis performed. Study setting: single centre, location London. Withdrawals: none (< 10%). Cancelled Cycles: < 10%.
Participants	Number of women:n = 25 (13 GH, 12 placebo). • Inclusion criteria: one or more previous IVF cycles with poor response, defined as fewer than six oocytes retrieved from which fewer than three embryos developed. • Exclusion criteria: not statedCause of subfertility: 18 of 25 women found to have polycystic ovaries on ultrasound. Age: < 38
Interventions	Intervention: GH 24 IU intramuscular (IM), days 1, 3, 5, 7, 9, and 11 of hMG treatment, during long Gn-RHa protocol, vs placebo given IM on same cycle days as active treatment groups. Recombinant GH used. Dose of human chorionic gonadotropin: 5000 IU
Outcomes	• Live birth rate • pregnancy rate • adverse effects (multiple pregnancy and ectopic pregnancy).
Notes	Nature of placebo not described. Follicular fluid IG1 increased by 27% with GH treatment. The data from Jacobs 1995 are also presented in Owen 1991. Authors contacted regarding further information on allocation concealment - no reply received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Two randomisation lists were made with 20 women on each list and block randomised into blocks of four

Owen 1991 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not stated within the text
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawals: none (< 10%). Cancelled Cycles < 10%
Selective reporting (reporting bias)	Unclear risk	There is no indication the study has reported outcomes selectively
Other bias	High risk	Nature of placebo not described. Follicular fluid IG-1 increased by 27% with GH treatment Free supply of growth hormone received

Safdarian 2019

Study characteristics	
Methods	Randomisation: computerized random sampling table Allocation concealment: none Blinding: single blinded. Analysis: no power calculation or intention to treat analysis performed. Study setting: single centre, location Shariati Hospital of Tehran University of Medical Sciences. Withdrawals: none. Cancelled cycles: 14.2% (Failed fertilisation -7, no oocytes retrieved -3)
Participants	• Inclusion criteria- Poor Ovarian reserve (having at least two of the three following criteria): 1) age over 40 years, 2) the evidences of POR as having a maximum of three oocyte following induction protocol), and 3) low ovarian reserve score (AFC less than 5-7, AMH less than 0.5 – 1.1 ng/ml). • Exclusion criteria- Women with high FSH levels (more than 20 IU / L), a history of infertility due to known non-POR causes such as azoospermia, diabetes (type one or two), and those who were not willing to participant in the study.
Interventions	The patients in all groups received gonadotropin (Gonal-f 300 to 450 IU/day, subcutaneously, based on age, AFC, and the level of AMH) plus GnRH antagonist (Cetrotide, 0.25mg/day, subcutaneously, after production of 14mm follicles until HCG injection) from the third day of their cycle. In addition to common regimens, group A received recombinant GH (Somatropin, 2.5mg/day, subcutaneously from the eighth day of the cycle until the injection of HCG) and group C received placebo (normal saline, 0.1mg/day, subcutaneously) from the eighth day of the cycle until the injection of HCG).
Outcomes	• Duration of gonadotropin (Gonal-f) treatment • Duration of GnRH antagonist treatment • Total doses of Gonal-f • Endothelial thickness • No. of collected oocytes • No. of MII oocytes • No. of fertilized oocytes • No. of transferred embryos

Safdarian 2019 *(Continued)*

- clinical pregnancy
- live birth rate.

Notes	Study registered in Iranian Registry of Clinical Trials (IRCT20140818842N14).
	Third group - group B received GH (Somatropin, 0.1mg/day, subcutaneously from the third day of the previous cycle)- this group was excluded from analysis as GH was started in the previous cycle.
	Number of collected oocytes and embryo transfer given as average, hence could not be included in the analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computerised random sampling table
Allocation concealment (selection bias)	High risk	No allocation concealment
Blinding (performance bias and detection bias) All outcomes	High risk	'Single blinded' but mentioned patients' blinding was also considered. In one of the groups, intervention started in previous menstrual cycle, hence blinding not possible
Incomplete outcome data (attrition bias) All outcomes	High risk	Withdrawals: none. Cancelled cycles 14.2%
Selective reporting (reporting bias)	Low risk	There is no indication the study has reported outcomes selectively. Registered protocol
Other bias	Low risk	No other bias

Suikkari 1996

Study characteristics

Methods	Randomisation: stated as randomised.
	Allocation concealment: unclear.
	Blinding: double blind.
	Trial design: parallel.
	Analysis: no power calculation and no intention to treat analysis performed
	Study setting: two centres.
	Analysis: no power calculation or intention-to-treat analysis performed.
	Withdrawals: < 10%. Cancelled Cycles: > 10% (therefore include in meta-analysis but perform sensitivity analysis).
Participants	- Number of women: n = 22 (10 GH 4 IU, 6 GH 12 IU, 6 placebo)

Suikkari 1996 *(Continued)*

- Inclusion Criteria: previous poor response in ≥ two assisted cycles. Definition of poor response: ≤ two oocytes retrieved or ≥ 48 AMP hMG consumed in a stimulation cycle. Cause of subfertility: tubal (n = 10), endometriosis (n = 1), male factor (n = 2), idiopathic (n = 9).
- Exclusion criteria: not stated
- Age 25-40 years.

Interventions	Intervention: six women received 12 IU GH and 10 women received 4 IU GH daily SC from day three of spontaneous menstrual cycle. Recombinant GH used. Study Protocol: A boost "flare-up" protocol was used for ovarian stimulation. On day two of spontaneous menstrual cycle leuprolide acetate was administered SC 0.75mg in the morning. On day three gonadotrophin Metrodin was started at 300IU SC for four days then adjusted according to serum E2 and follicular growth. Dose of human chorionic gonadotropin 5000 IU IM given when the largest follicle(s) reached a diameter of 18 to 20mm.
Outcomes	- Live birth rate - pregnancy rate - embryo transfer - adverse effects (multiple pregnancy).
Notes	Twenty two women in total were included in Suikkari 1996 and they were divided into three groups, placebo, GH four IU and GH 12IU. Since only two groups could be compared for the table of comparisons the two GH groups were separated and compared with half the placebo data for the meta-analysis but throughout the text the trial is referred to singly as Suikkari 1996. Authors contacted for further information on allocation concealment - no reply received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated as randomised
Allocation concealment (selection bias)	Unclear risk	Not stated within the text
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Withdrawals < 10%. Cancelled Cycles > 10%
Selective reporting (reporting bias)	Unclear risk	There is no indication the study has reported outcomes selectively
Other bias	Low risk	No other bias

Tapanainen 1992

Study characteristics

Methods	Randomisation: Stated as randomised, method unclear. Allocation concealment: trial codes kept in sealed envelopes until the study was completed.

Tapanainen 1992 *(Continued)*

Blinding: double-blind

Trial design: parallel.

Analysis: power calculation not done, no intention to treat analysis but no withdrawals.

Study setting: single centre. Finland

Withdrawals: none (<10%). Cancelled cycles: <10%.

Participants	• Number of women randomised: n = 38 (19 GH, 19 placebo). • Inclusion criteria: normally cycling women with unexplained infertility, tubal infertility or mild to moderate endometriosis. • Exclusion criteria: not stated • Age: 27-37.
Interventions	Intervention: Recombinant GH 24 IU IM beginning on cycle day four, then every 2 days until human chorionic gonadotropin, vs sterile saline IM on same cycle days. Treatment Protocol: Short GnRHa protocol used for ovulation induction, 300 µg BA 3 times daily on cycle days 1-4. Three ampoules of hMG given IM on day 4 and then 150-223 IU daily until human chorionic gonadotropin injection. 5000 IU human chorionic gonadotropin given. Clinical Pregnancy Diagnosis: USS at six weeks gestation
Outcomes	• Live birth rate • adverse effects (multiple pregnancies)
Notes	There were two parts to this trial, A and B. Only data from part A was included as part B studied the effect of GH on gene expression of steroidogenic enzymes in granulosa cells and the women were not followed up for live birth or pregnancy data.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated as randomised, but method unclear
Allocation concealment (selection bias)	Unclear risk	Trial codes kept in sealed envelopes until the end of the study, no details as to whether centralised or envelopes opaque
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawals none, cancelled cycles < 10%
Selective reporting (reporting bias)	Unclear risk	There is no indication the study has reported outcomes selectively
Other bias	High risk	Free supply of growth hormone received

Tesarik 2005

Study characteristics

Methods	Randomisation: truly randomised, computer generated random number tables.

Tesarik 2005 *(Continued)*

Allocation concealment: clear, opaque envelopes.

Blinding: double-blinded.

Analysis: Power calculation performed and intention to treat analysis not performed.

Study setting: multi-centre, Spain and France.

Withdrawals: none. Cancelled cycles: <10%.

Participants	• Number of women: 100 (50, GH, 50 placebo). • Inclusion criteria: women > 40 years old asking for an assisted reproduction attempt by ICSI were assessed for eligibility.
Interventions	Intevention: Recombinant GH 8IU Subcut. Treatment Protocol: Long. Dose of human chorionic gonadotropin: 25mg when at least 1 follicle measured > 18mm in diameter.
Outcomes	• Live birth rate • pregnancy rate.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random number tables
Allocation concealment (selection bias)	Low risk	Opaque envelopes used
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawals none, cancelled cycles < 10%
Selective reporting (reporting bias)	High risk	The study did not report adverse events
Other bias	Low risk	No other bias noted

Younis 1992

Study characteristics

Methods	Randomisation: prospectively randomised, method unclear. Allocation concealment: allocation not revealed until all outcome measures were calculated and comparison between the two groups had been performed. Blinding: double-blind. Study design: placebo controlled trial.

Younis 1992 *(Continued)*

Sensitivity analysis: no power calculation or intention to treat analysis performed.

Study setting: single centre, location Israel.

Withdrawals: none (< 10%). Cancelled Cycles: < 10%.

Participants	• Number of women randomised: n = 42 (20 GH, 22 placebo). • Cause of subfertility: ovulating women with mechanical factor infertility. Normal serum FSH, LH, PRL, T and DHEAS. Normal semen (WHO criteria).Inclusion • Criteria: age: < or equal to 38 years
Interventions	• Intervention: recombinant GH 12 IU SC on days 1, 3, 5, and 7 of hMG treatment vs Mannitol 30 mg SC on same cycle days. • Treatment protocol: All women received GnRHa/hMG 0.5mg/day from day 21 of previous cycle ovulation induction protocol.
Outcomes	• Pregnancy rate • oocyte retrieval • embryo transfer • ampoules of Gonadotrophin used • adverse effects (multiple pregnancy).
Notes	Mannitol chosen as placebo.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated as randomised, but method unclear
Allocation concealment (selection bias)	Low risk	Allocation not revealed until all outcomes calculated and comparisons between groups performed
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawals none, cancelled cycles < 10%
Selective reporting (reporting bias)	Unclear risk	There is no indication the study has reported outcomes selectively
Other bias	High risk	Free supply of growth hormone received

Zhuang 1994

Study characteristics

Methods	Randomisation: stated as randomised, method unclear. Allocation concealment: unclear of method Blinding: outcome assessors were blind to treatment allocation.

Zhuang 1994 *(Continued)*

	Study design: parallel.
	Study setting: unclear.
	Analysis: power calculation done.
	Withdrawals: none. Cancelled cycles: none.
Participants	• Number of women randomised: n = 27 (12 GH, 15 control). Definition of poor response: not provided • Inclusion criteria: previous sub-optimal response to hyperstimulation cycles in IVF. • Exclusion criteria: cause of subfertility is tubal factor or unexplained. • Age: GH 33.2 ± 3.9, Placebo 32.3 ± 3.9.
Interventions	• Intervention: recombinant GH 12 IU IM on alternate days. • Treatment protocol: GnRH-a (Buserelin nasal spray) from day 21 of previous menstrual cycle to day of human chorionic gonadotropin injection (do not know dose of GnRH-a)2 IU hMG given on alternate days for 12 days (at same time as GH). Dose of human chorionic gonadotropin: 10000 IU.
Outcomes	• Live birth rate • pregnancy rate.
Notes	Some information will have been stated in the trial but was not translated. The sections that were translated were kindly done so by Teresa Gu.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated as randomised, but method unclear
Allocation concealment (selection bias)	Unclear risk	Not stated within the text
Blinding (performance bias and detection bias) All outcomes	High risk	Single-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	No cancelled cycles, no withdrawals
Selective reporting (reporting bias)	High risk	The study did not report adverse events
Other bias	Unclear risk	Translator used as publication was not in English

Only outcomes relevant to the review were stated in the table of included studies.
- hMG: human menopausal gonadotropin
- AFC: antral follicle count
- AMH: anti-Müllerian hormone
- FSH: follicle stimulating hormone
- GnRHa- gonadotropin-releasing hormone agonist
- GH: growth hormone
- IU: international units
- LH: luteinising hormone

- NaCl: sodium chloride
- COS: controlled ovarian stimulation
- Mii oocytes: metaphase 2 oocytes
- WHO: World Health Organisation
- IM: intramuscular
- SC: sub-cutaneous
- POR: poor ovarian response
- PRL: prolactin

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Balasubramanyam 2017	Case series. Testosterone gel and GH used together
Bhattacharya 2014	Not a RCT; non-randomised, case-control study
Blumenfeld 1994	Additional data were sought to clarify which women included in the trial received which method of assisted conception and the definition of "poor responder" used, but a response was not received
Busacca 1996	Method of assisted conception used was not IVF, but artificial insemination by husband or GIFT
Cui 2018	Role of GH in frozen embryo replacement cycle in women with thin endometrium
Dakhly 2016	All four groups received GH as adjuvant with different protocols to compare outcomes
Demoulin 1992	Not randomised, published abstract with no data available
European and Australian Multicentre study 1995	All hypogonadotropic hypogonadism participants included in the study for comparison of various doses of GH with hMG versus placebo with hMG to evaluate the dose-response relationship
Fernandez 2015	Pre-implantation genetic testing done on all embryos, therefore prone to bias
Guan 2007	Co-administration of GH and aspirin
Hassan 1998	The study involved identifying poor responders on day 10 and then alteration of the protocol by stopping GnRH agonist and adding GH/no GH at that stage. Abstract published
Hassan 2001	Study on effect of GH on in vitro maturation
Hazout 2009	Not randomised and non-comparative
Homburg 1990a	Not stated as randomised, no useful outcomes reported
Homburg 1990b	Women did not undergo IVF
Homburg 1995	Women did not undergo IVF
Howles 1999	Intervention is GH-releasing factor, not GH
Hughes 1994	Stimulation cycles with less that 3 follicles > 20 mm after ovarian stimulation were cancelled. These women were not included in the analysis. This unpublished information could not be obtained from the author.
Jacobs 1995	Only concerns ovulation induction, not IVF

Study	Reason for exclusion
Landolfi 1994	Only concerns ovulation induction, not IVF
Latte 2013	Study not randomised
Li 2020	The participants included had a history of poor embryonic development; not based on ovarian response
Matsumoto 2020	Retrospective study
Merdassi 2010	Non-randomised retrospective study
Nayar 2018	Comparison of two adjuvants: GH versus rLH instead of placebo, hence not included
Ob'edkova 2017	Prospective observational study
Owen 1991b	There are two publications for this trial. The analysis used women randomised to receive GH in the trial and retrospective cases of women who had also received GH in the past.
Regan 2018	Laboratory study; pregnancy rates mentioned but included the fresh as well as frozen cycles
Rinehart 1999	Allocation was stated as "alternating randomisation", suggesting allocation to groups by alternation, not randomisation.
Sakr 2012	Comparative study of the effect of GH versus corticosteroids to ICSI in low responding patient (instead of placebo)
Schoolcraft 1997	Both treatment groups received the same dose of GH, the intervention was oral contraceptive
Tulandi 1993	Method of assisted conception was intrauterine insemination, not IVF
Viardot-Foucault 2016	Retrospective study, 3 different regimens compared: FSH, FSH + LH, FSH + GH
Xue-Mei 2016	Effect of GH on clinical outcomes in frozen embryo replacement cycles
Yovich 2010	Study was non-randomised sequential cross-over study

- FSH: follicle stimulating hormone
- GH: growth hormone
- GnRH: gonadotropin-releasing hormone
- IVF: in vitro fertilisation
- LH: luteinising hormone
- GIFT: Gamete intrafallopian transfer
- hMG: human menopausal gonadotropin
- ICSI: Intracytoplasmic sperm injection

Characteristics of studies awaiting classification [ordered by study ID]

Bassiouny 2016

Methods	Trial design: parallel
	Analysis: no power calculation or intention-to-treat analysis performed
	Study setting: single study centre (Egypt)

Bassiouny 2016 *(Continued)*

	Withdrawals: none
	Cancelled cycles: 25 (17.73%), failed egg collection: 9, failed fertilisation: 16
Participants	Number of women: 141 (68 GH, 73 gonadotropin only). IVF previous poor responders as defined by study design (ESHRE consensus): • age > 40 years • previous treatment that resulted with < 3 oocytes • AMH level < 0.5 ng/mL to 1.1 ng/mL • AFC < 5 to 7 follicles
Interventions	GnRH antagonist protocol • hMG (300 IU to 450 IU) according to patient's age, AFC, and AMH level started from day 2 of cycle, GnRH antagonist added daily when leading follicle was 12 mm to 14 mm. GH introduced in treatment group from day 6 2.5 mg (7.5 IU) sc daily until HCG triggering. Trigger injection, HCG 10,000 IU given when leading follicle reached ≥ 18 mm
Outcomes	• Total HMG dose and duration of HMG and antagonist stimulation (in days) • Endometrial thickness • E2, LH and P levels on the day of hCG administration • Mean number of oocytes retrieved • number of metaphase II and fertilised oocytes • Fertilisation rate • Chemical and clinical pregnancy rates • Early miscarriage rate • Ongoing pregnancy and live birth rates per cycle start and per ET
Notes	Registered protocol NCT02195947

Bayoumi 2015

Methods	Randomisation: using a computerised list women were randomised to one of four arms
	Allocation concealment: unclear
	Blinding: non-blind
	Trial design: parallel
	Analysis: no power calculation or intention-to-treat analysis performed
	Study setting: single study centre (Egypt)
	Withdrawals: none
	Cancelled cycles: 27 patients (15.6%)
Participants	Number of women: 172 (84 GH, 88 placebo). IVF previous poor responders as defined by study design (ESHRE consensus): • age > 40 years • previous treatment that resulted with < 4 oocytes • AMH level < 0.5 ng/mL to 1.1 ng/mL • AFC < 5 to 7 follicles

Bayoumi 2015 *(Continued)*

Interventions	Intervention: GH 2.5 mg subcutaneously daily until ovulation induction with HCG trigger
	Treatment protocol: microflare stimulation protocol - combined OCP (drosperinone plus ethinyl estradiol) for 21 days before ovarian stimulation. Short GnRHa (0.05 mg triptorelin/hMG 300 IU to 450 IU intramuscularly daily from day 3. Dose of HCG: 10000 IU when at least two follicles were > 17 mm in diameter
Outcomes	• Mean number of mature oocytes retrieved and fertilised • Chemical and clinical pregnancy
Notes	Registered protocol NCT02185326
	Method: inserted 3 embryos per cycle. Primary outcome of clinical pregnancy was changed after 3 months into the trial. No data for live birth rate obtained

Eftekhar 2012

Methods	Randomisation: stated as randomised
	Allocation concealment: sealed opaque identical envelopes
	Blinding: not blinded
	Trial design: parallel
	Analysis: no power calculation or intention-to-treat analysis performed
	Study setting: single centre, location Iran
	Withdrawals: none. Cancelled cycles: 40%
Participants	Number of women: 82 (40 GH, 42 not treated)
	Inclusion criteria: women who had one or more previous failed IVF-ET cycles with three or fewer retrieved oocytes and with subsequent three or less obtained embryos using GnRH agonist long protocol, and/or E2 levels B 500 pg/mL on the day of HCG injection
	Age: unlimited
Interventions	Intervention
	• Group I (GH/HMG/GnRH antagonist group) received daily injection of 4 IU GH (Eutropin, LG, Korea) from day 21 of previous cycle until the day of HCG injection • Group II (n = 42) received same gonadotropin/GnRH antagonist protocol without GH
	Treatment protocol
	• Antagonist/HMG protocol given subcutaneously • Dose of HCG: 10,000 IU given when at least two follicles were > 17 mm in diameter
Outcomes	• Clinical pregnancy rate
Notes	Waiting for additional information from trial authors

Gong 2020

Methods	Prospective randomised open-label study
Participants	Total participants in POR group: 105, GH (52), no adjuvant POR control (53) Inclusion criteria • Patients with POR (aged 33 to 43 years) diagnosed according to the Bologna criteria Exclusion criteria • Hydrosalpinx, congenital uterine malformations and/or endometrial disease such as tuberculosis or hyperplasia • Basal follicle-stimulating hormone level ≥ 15 IU/L • Systemic lupus erythematosus, sicca syndrome, or polycystic ovarian syndrome • Uncontrolled endocrinopathy such as diabetes, hyperthyroidism, hypothyroidism, or hyperprolactinaemia • IVF-ET treatment within three months • ICSI cycle due to male infertility • Supplementation with any antioxidants such as vitamin E, vitamin C, CoQ10, betacarotene or selenium Women with tubal factor infertility (aged 20 to 35 years) with a normal ovarian reserve and regular menstrual cycles who underwent IVF-ET were recruited as non-POR controls during the same period. The exclusion criteria for the non-POR group were the same as those for the POR group.
Interventions	• GnRH antagonist protocol - Gonal F from day 2 • POR GH group 4 IU GH/day started from day 2 of previous menstrual cycle before IVF until trigger day • No placebo was used in the control group
Outcomes	• Endometrial thickness on trigger day • Number of cleaved embryos • Number of higher-quality embryos • Rates of embryo formation • Higher-quality embryo formation • Implantation • Clinical pregnancy rates
Notes	Chinese Clinical Trial Registry Centre Registration No. ChiCTR1900021269 The sample size calculation was based on assumption that the clinical pregnancy rate would increase 3-fold after GH pretreatment. Rationale for the proposed GH treatment: low physiological dose and longer treatment (from the antral follicle stage) might be more beneficial to follicular growth and development. Oxidative stress makers studied: follicular fluid malondialdehyde, superoxide dismutase, total oxidant status, oxidative stress index and total antioxidant capacity were significantly lower in the POR-C group (P < 0.05).

- AFC: antral follicle count
- AMH: anti-mullerian hormone
- ESHRE: European Society of Human Reproduction and Embryology
- ET: embryo transfer
- GH: growth hormone
- GnRH: gonadotropin releasing hormone
- HCG: human chorionic gonadotropin

- hMG:human menopausal gonadotropin
- ICSI: intracytoplasmic sperm injection
- IVF: in vitro fertilisation
- OCP: oral contraceptive pills
- POR: poor ovarian response

Characteristics of ongoing studies *[ordered by study ID]*

ChiCTR1800016106

Study name	Application of growth hormone in patients with poor ovarian response and study of mechanism
Methods	
Participants	Patients with poor ovarian response
Interventions	• A: GH 4.5 IU/d subcutaneous injection every day from the menstrual day before last menstruation period • B: GH 4.5 IU/d subcutaneous injection every day from initiation day to trigger day • C: no use of GH
Outcomes	Primary outcomes • Clinical pregnancy rate • Follicular fluid level of estradiol • mRNA of FSH receptor in granular cell Secondary outcome • Gonadotropins usage duration
Starting date	2018
Contact information	Not available
Notes	

CTRI/2019/03/018047

Study name	Study to compare the effect of giving growth hormone in poor responders during IVF
Methods	
Participants	• Previous failed IVF with < 5 oocytes retrieved or poor ovarian reserve • AMH ≤ 1.2 ng/ml or Antral follicle count less than or equal to 5
Interventions	Intervention 1 • GH • Recombinant FSH (Gonal-F) • Recombinant LH (luveris) given: GH 5 mg (novitropin) subcutaneous plus recombinant FSH (Gonal-F) 300 IU and luteinising hormone 75 IU (luveris) subcutaneous both given from day 1 of stimulation to the day of trigger (approximately 10 days) in patients who are poor responders Control • No GH in comparator arm

CTRI/2019/03/018047 *(Continued)*

- Only recombinant FSH (Gonal-F) and recombinant LH (luveris) given
- No GH given to poor responders
- Recombinant FSH (Gonal-F) 300 IU and luteinizing hormone 75 IU (luveris) subcutaneous both given from day 1 of stimulation to the day of trigger (approximately 10 days) in patients who are poor responders

Outcomes	Primary outcome
	- Clinical pregnancy rate (4 weeks after embryo transfer)
	Secondary outcomes
	- Live birth rate
	- Response to controlled ovarian stimulation
	- Fertilization rate
	- Cleavage rate
	- Embryo number and grade
	- Number of embryos available for cryopreservation
	- Implantation rate
Starting date	2019
Contact information	Not available
Notes	

NCT01715324

Study name	Adjuvant growth therapy in vitro fertilization
Methods	Randomised, parallel, open-label interventional trial
Participants	528 participants
	- Women between the ages of 35 to 42
	- Primary or secondary infertility (no previous treatment IVF cycle using the same proposed protocol)
	- Negative pregnancy test at randomisation (urine or blood)
Interventions	The treatment group will receive 2.5 mg of saizen daily via subcutaneous injections, from the beginning of the ovarian reserve stimulation until the day of the ovulation triggering
Outcomes	Aim: to determine if the clinical pregnancy rate during the course of one treatment cycle in women receiving GH daily in addition to gonadotropin-releasing hormone antagonist protocol is significantly higher than those receiving only gonadotropin-releasing hormone antagonist protocol (control group)
	Primary outcomes
	- Clinical pregnancy rate (time frame: 7 weeks)
	Aim: to evaluate the effectiveness of GH adjuvant therapy in gonadotropin-releasing hormone antagonist protocol when compared to the control group
	Secondary outcomes
	- Total dose of gonadotropins (time frame: 7 weeks)

NCT01715324 *(Continued)*

- Number of observed follicles (time frame: 7 weeks)
- Number of mature (metaphase II) oocytes retrieved (time frame: 7 weeks)
- Oocyte morphology (time frame: 7 weeks)
- Fertilization rate (time frame: 7 weeks)
- Embryo morphology (time frame: 7 weeks)
- Embryo cleavage rate (time frame: 7 weeks)
- Number of embryos available (time frame: 7 weeks)
- Number of supernumerary embryos available for cryopreservation (time frame: 7 weeks)
- Implantation rate (time frame: 7 weeks)
- Miscarriage rate (time frame: 7 weeks)
- Live birth rate (time frame: 7 weeks)
- Adverse side effects in women (time frame: 7 weeks)

Starting date	October 2012
Contact information	Jacques Kadoch, MD. Clinique Ovo, Montreal, Quebec, Canada
Notes	

NCT02179255

Study name	Human growth hormone pre-treatment for 6 weeks prior to ovulation induction for IVF
Methods	Randomised, parallel, open-label interventional trial
Participants	30 participants - The study will be limited to women with poor response to prior treatment with evidence of diminished ovarian reserve with 2 or fewer oocytes in a previous ovulation induction cycles with maximal gonadotrophin stimulation - All women in this study will be < 45 years old
Interventions	1.9 mg (5.7 units) daily injection of rHGH for at least 6 weeks (42 days) plus FSH 450 to 600 units per day administered subcutaneous. Daily dose adjusted based on the patients response starting on day 2 of the 28 day menstrual cycle and continued until ovulation trigger
Outcomes	Primary outcomes - Oocytes retrieved for IVF (time frame: 8 weeks after starting intervention) Secondary outcomes - Clinical pregnancy rates (time frame: 12 weeks after starting intervention). Presence of an established clinical pregnancy as evidenced by gestational sac with active fetal heart beat
Starting date	July 2017
Contact information	David H Barad, MD, Center for Human Reproduction New York, New York, USA
Notes	This study is for pretreatment unlike other trials where GH has been used during stimulation

NCT03027843

Study name	The effect of growth hormone in assisted reproductive technology clinical outcome of poor responder
Methods	Randomised, parallel, open-label, interventional trial
Participants	80 participants • Age ≥ 35 years and ≤ 40 years • 2 ≤ AFC ≤ 6, and AMH level ≥ 0.5 ng/mL and ≤ 1.1 ng/mL • Previous failed transfer cycle ≥ 2 • Did not participate in other clinical subjects in three months • Written informed consent
Interventions	GH group patients have weekly injections of GH dose 14 IU, until the day of hCG
Outcomes	Primary outcomes • Live birth rate (time frame: 1 to 2 years) • Live birth rate (%): number of live births/transferred cycle Secondary outcomes • Clinical pregnancy rate (%): number of clinical pregnancies/transferred cycle (time frame: 1 to 2 years) • Number of oocytes retrieved (time frame: 1 to 2 years) • Fertility rate (%): number of oocyte fertilised/number of oocytes retrieved (time frame: 1 to 2 years) • Normal fertility rate (%): number of oocyte normally fertilised/number of oocytes retrieved (time frame: 1 to 2 years) • Transferable embryo rate(%): number of transferable embryo/number of fertilized oocytes. Cleavage embryo grades 1 or 2 with at least 5 blastomeres are considered as transferable embryo (time frame: 1 to 2 years) • Good quality embryo rate (%): number of good quality embryo/number of fertilised oocytes. Cleavage embryo grades 1 or 2 with 6-10 blastomeres were considered good quality embryos (time frame: 1 to 2 years)
Starting date	January 2017
Contact information	Xing Yang, MD, PhD. The Sixth Affiliated Hospital, Sun Yat-Sen University
Notes	

NCT03373149

Study name	Growth hormone co-treatment within a GnRH antagonist protocol in patients with poor ovarian response
Methods	Randomised, parallel, single-blind interventional trial
Participants	228 participants • Patients who responded poorly to high-dose gonadotropin treatment in their first cycles (peak E ≤ 500 pg/mL, or retrieval of < 4 oocytes) • Age > 40 years, bilateral antral follicle count < 6 • Serum AMH < 0.66 ng/mL

NCT03373149 *(Continued)*

Interventions	• GH (somatropin) 4 IU/day and highly purified urinary FSH (HPuFSH) (fostimon) 300 IU/day will be started on cycle day 3 and will be continued until and including the day of HCG administration. Starting from cycle day 8, the dose of HPuFSH will be adjusted individually according to ovarian response which will be monitored using transvaginal ultrasound and serum estradiol (E2). • GnRH antagonist (cetrorelix acetate: cetrotide) 0.25 mg subcutaneously once daily will be started when the leading follicle is 14 mm in mean diameter and will be continued until and including the day of HCG administration.
Outcomes	**Primary outcomes** • Number of participants who achieved a clinical pregnancy in a transfer cycle (time frame: 5 weeks after embryo transfer) **Secondary outcomes** • Number of participants who achieved an ongoing pregnancy in a transfer cycle (time frame: 18 weeks after embryo transfer)
Starting date	December 2017
Contact information	Usama M Fouda, Prof Riyadh Fertility and Reproductive Health Center, Giza, Egypt
Notes	

NCT03759301

Study name	Efficacy of growth hormone supplementation with gonadotrophins in IVF/ICSI for poor responders
Methods	Randomised, parallel, triple-blind, interventional trial
Participants	156 participants. • Age: 25 to 38 years old • IVF previous poor responders: at least two failed cycles with < 5 oocytes or abnormal ORT e.g. AMH < 1 • Patients with unexplained infertility • Normal FSH, LH, prolactin and ovarian ultrasound • Normal pelvic ultrasound including 3D ultrasound of the uterus with no detected hydrosalpinx
Interventions	• GHs somatropin recombinant 4 IU/day subcutaneous from the second day of the cycle and stopped 1 day before ovum pickup
Outcomes	**Primary outcomes** • Clinical pregnancy rate (time frame: 3 weeks) **Secondary outcomes** • E2 levels (time frame: day 1 of COS, the same day of HCG injection) • Number of oocytes collected (time frame: day 6 of COS) • Metaphase I and Metaphase II oocyte number (time frame: day 6 of COS) • Number of pronucleus (time frame: day 6 of COS) • Multiple pregnancy (time frame: 6 weeks from last period
Starting date	November 2018

NCT03759301 *(Continued)*

Contact information	Mohamed M Shafeek, MSc Al Azhar University Hospitals (Kasr Al-Aini), Cairo, Egypt

Notes	

- AMH: anti-Müllerian hormone
- COS: controlled ovarian stimulation
- FSH: follicle stimulating hormone
- GH: growth hormone
- GnRH:gonadotropin releasing hormone
- HCG: human chorionic gonadotropin
- HPuFSH: highly purified urinary FSH
- ICSI:intracytoplasmic sperm injection
- IVF: in vitro fertilization
- LH: luteinising hormone
- mRNA: messenger ribonucleic acid
- ORT: ovarian reserve test
- PCOS: polycystic ovarian syndrome
- rHGH: recombinant human growth hormone
- E: estradiol

DATA AND ANALYSES

Comparison 1. Adjuvant GH compared to no adjuvant: routine use for IVF

Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
1.1 Live birth rate per woman ran- domised	2	80	Odds Ratio (M-H, Fixed, 95% CI)	1.32 [0.40, 4.43]
1.2 Clinical pregnancy rate per woman randomised	1	42	Odds Ratio (M-H, Fixed, 95% CI)	1.78 [0.49, 6.50]
1.3 Number of women with at least one oocyte retrieved per woman ran- domised	1	42	Odds Ratio (M-H, Fixed, 95% CI)	2.86 [0.11, 74.31]
1.4 Mean number of oocytes retrieved	2	80	Mean Difference (IV, Fixed, 95% CI)	-0.02 [-0.79, 0.74]
1.5 Embryo transfer achieved per woman randomised	1	42	Odds Ratio (M-H, Fixed, 95% CI)	7.36 [0.36, 151.91]
1.6 Mean units of gonadotrophin used	2	80	Mean Difference (IV, Fixed, 95% CI)	13.57 [-112.88, 140.01]

Analysis 1.1.   Comparison 1: Adjuvant GH compared to no adjuvant: routine use for IVF, Outcome 1: Live birth rate per woman randomised
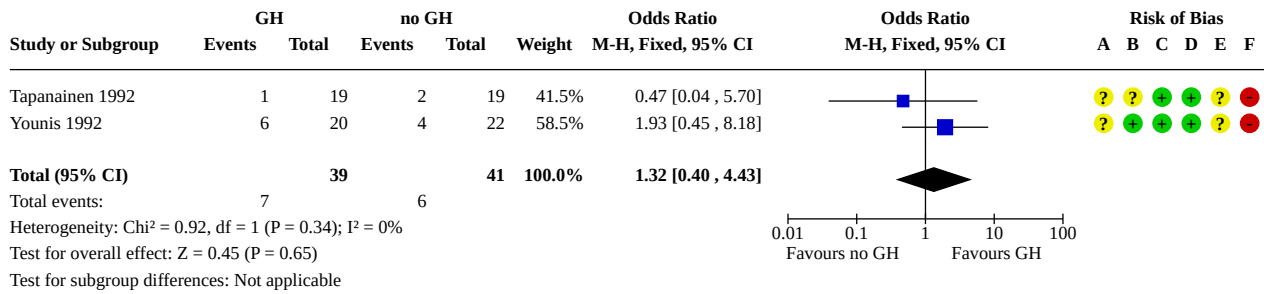
Study or Subgroup	GH Events	GH Total	no GH Events	no GH Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
Tapanainen 1992	1	19	2	19	41.5%	0.47 [0.04 , 5.70]		? ? + + ? −
Younis 1992	6	20	4	22	58.5%	1.93 [0.45 , 8.18]		? + + + ? −
Total (95% CI)		**39**		**41**	**100.0%**	**1.32 [0.40 , 4.43]**		
Total events:	7		6					

Heterogeneity: Chi² = 0.92, df = 1 (P = 0.34); I² = 0%
Test for overall effect: Z = 0.45 (P = 0.65)
Test for subgroup differences: Not applicable

0.01   0.1   1   10   100
Favours no GH   Favours GH

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding (performance bias and detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

Analysis 1.2.   Comparison 1: Adjuvant GH compared to no adjuvant: routine use for IVF, Outcome 2: Clinical pregnancy rate per woman randomised
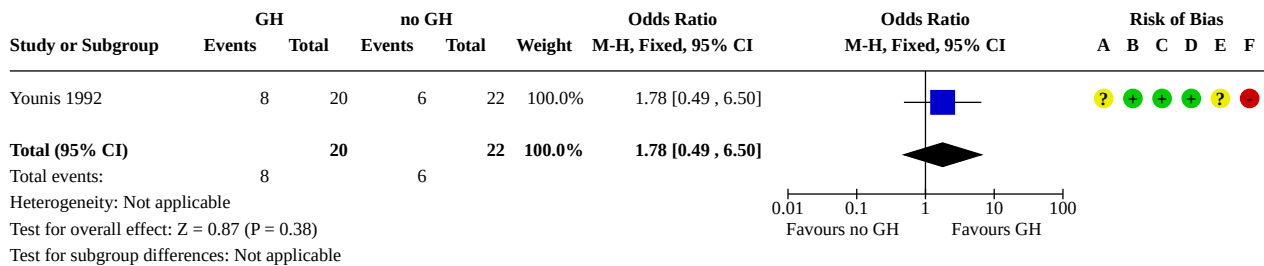
Study or Subgroup	GH Events	GH Total	no GH Events	no GH Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
Younis 1992	8	20	6	22	100.0%	1.78 [0.49 , 6.50]		? + + + ? −
Total (95% CI)		**20**		**22**	**100.0%**	**1.78 [0.49 , 6.50]**		
Total events:	8		6					

Heterogeneity: Not applicable
Test for overall effect: Z = 0.87 (P = 0.38)
Test for subgroup differences: Not applicable

0.01   0.1   1   10   100
Favours no GH   Favours GH

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding (performance bias and detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

Analysis 1.3. Comparison 1: Adjuvant GH compared to no adjuvant: routine use for IVF, Outcome 3: Number of women with at least one oocyte retrieved per woman randomised

Study or Subgroup	GH Events	GH Total	no GH Events	no GH Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
Younis 1992	20	20	21	22	100.0%	2.86 [0.11 , 74.31]		? + + + ? −
Total (95% CI)		**20**		**22**	**100.0%**	**2.86 [0.11 , 74.31]**		
Total events:	20		21					

Heterogeneity: Not applicable
Test for overall effect: Z = 0.63 (P = 0.53)
Test for subgroup differences: Not applicable

0.001   0.1   1   10   1000
Favours no GH   Favours GH

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding (performance bias and detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

Analysis 1.4. Comparison 1: Adjuvant GH compared to no adjuvant: routine use for IVF, Outcome 4: Mean number of oocytes retrieved
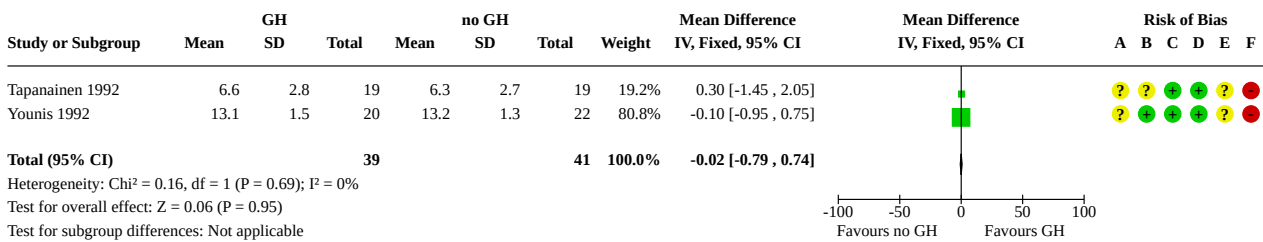
Study or Subgroup	GH Mean	GH SD	GH Total	no GH Mean	no GH SD	no GH Total	Weight	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
Tapanainen 1992	6.6	2.8	19	6.3	2.7	19	19.2%	0.30 [-1.45 , 2.05]		? ? + + ? −
Younis 1992	13.1	1.5	20	13.2	1.3	22	80.8%	-0.10 [-0.95 , 0.75]		? + + + ? −
Total (95% CI)			**39**			**41**	**100.0%**	**-0.02 [-0.79 , 0.74]**		

Heterogeneity: Chi² = 0.16, df = 1 (P = 0.69); I² = 0%
Test for overall effect: Z = 0.06 (P = 0.95)
Test for subgroup differences: Not applicable

-100   -50   0   50   100
Favours no GH   Favours GH

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding (performance bias and detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

Analysis 1.5. Comparison 1: Adjuvant GH compared to no adjuvant: routine use for IVF, Outcome 5: Embryo transfer achieved per woman randomised
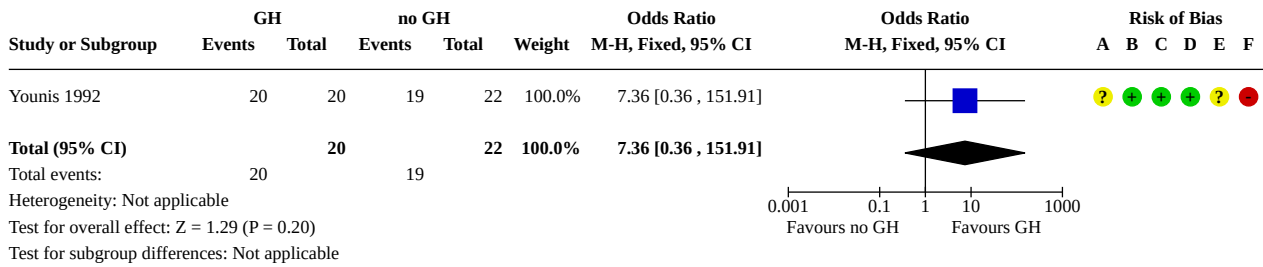
Study or Subgroup	GH Events	Total	no GH Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
Younis 1992	20	20	19	22	100.0%	7.36 [0.36 , 151.91]		? + + + ? −
Total (95% CI)		**20**		**22**	**100.0%**	**7.36 [0.36 , 151.91]**		

Total events: 20 (GH), 19 (no GH)
Heterogeneity: Not applicable
Test for overall effect: Z = 1.29 (P = 0.20)
Test for subgroup differences: Not applicable

0.001 0.1 1 10 1000
Favours no GH   Favours GH

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding (performance bias and detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

Analysis 1.6.   Comparison 1: Adjuvant GH compared to no adjuvant: routine use for IVF, Outcome 6: Mean units of gonadotrophin used

Study or Subgroup	GH Mean	SD	Total	no GH Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
Tapanainen 1992	1425	420	19	1327.5	367.5	19	25.4%	97.50 [-153.44 , 348.44]		? ? + + ? −
Younis 1992	2805	277.5	20	2820	195	22	74.6%	-15.00 [-161.39 , 131.39]		? + + + ? −
Total (95% CI)			**39**			**41**	**100.0%**	**13.57 [-112.88 , 140.01]**		

Heterogeneity: Chi² = 0.58, df = 1 (P = 0.45); I² = 0%
Test for overall effect: Z = 0.21 (P = 0.83)
Test for subgroup differences: Not applicable

-20 -10 0 10 20
Favours no GH   Favours GH

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding (performance bias and detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

Comparison 2.   Adjuvant GH compared to no adjuvant: poor responders for IVF

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Live birth rate per woman randomised	8	737	Odds Ratio (M-H, Fixed, 95% CI)	1.77 [1.17, 2.70]
2.1.1 Poor responder by definition	3	400	Odds Ratio (M-H, Fixed, 95% CI)	1.85 [1.02, 3.38]
2.1.2 Poor responder based on previous response	5	337	Odds Ratio (M-H, Fixed, 95% CI)	1.70 [0.95, 3.06]
2.2 Clinical pregnancy rate per woman randomised	11	1033	Odds Ratio (M-H, Fixed, 95% CI)	1.85 [1.35, 2.53]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.2.1 Poor responder by definition	5	711	Odds Ratio (M-H, Fixed, 95% CI)	1.70 [1.16, 2.50]
2.2.2 Poor responder based on previous response	6	322	Odds Ratio (M-H, Fixed, 95% CI)	2.19 [1.26, 3.81]
2.3 Number of women with at least one oocyte retrieved per woman randomised	2	148	Odds Ratio (M-H, Fixed, 95% CI)	5.67 [1.54, 20.83]
2.3.1 Poor responder based on previous response	2	148	Odds Ratio (M-H, Fixed, 95% CI)	5.67 [1.54, 20.83]
2.4 Mean number of oocytes retrieved	12	1153	Mean Difference (IV, Fixed, 95% CI)	1.40 [1.16, 1.64]
2.4.1 Poor responder based on definition	5	721	Mean Difference (IV, Fixed, 95% CI)	1.42 [1.12, 1.73]
2.4.2 Poor responder based on previous response	7	432	Mean Difference (IV, Fixed, 95% CI)	1.35 [0.96, 1.74]
2.5 Embryo transfer acheived per woman randomised	4	214	Odds Ratio (M-H, Fixed, 95% CI)	2.32 [1.08, 4.96]
2.5.1 Poor responder based on previous response	4	214	Odds Ratio (M-H, Fixed, 95% CI)	2.32 [1.08, 4.96]
2.6 Mean units gonadotropin used	8	685	Mean Difference (IV, Fixed, 95% CI)	-1088.19 [-1203.20, -973.18]
2.6.1 Poor responder based on definition	3	437	Mean Difference (IV, Fixed, 95% CI)	-1246.99 [-1388.24, -1105.74]
2.6.2 Poor responder based on previous response	5	248	Mean Difference (IV, Fixed, 95% CI)	-775.79 [-973.90, -577.67]

Analysis 2.1. Comparison 2: Adjuvant GH compared to no adjuvant: poor responders for IVF, Outcome 1: Live birth rate per woman randomised

Study or Subgroup	GH Events	GH Total	No GH Events	No GH Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
2.1.1 Poor responder by definition								
Dakhly 2018	21	120	17	120	41.8%	1.29 [0.64 , 2.58]		
Safdarian 2019	1	34	0	26	1.6%	2.37 [0.09 , 60.65]		
Tesarik 2005	11	50	2	50	4.6%	6.77 [1.42 , 32.37]		
Subtotal (95% CI)		**204**		**196**	**48.0%**	**1.85 [1.02 , 3.38]**		
Total events:	33		19					
Heterogeneity: Chi² = 3.72, df = 2 (P = 0.16); I² = 46%								
Test for overall effect: Z = 2.01 (P = 0.04)								
2.1.2 Poor responder based on previous response								
Mohammad 2019	15	78	11	78	26.5%	1.45 [0.62 , 3.40]		
Norman 2019	9	62	7	51	19.6%	1.07 [0.37 , 3.10]		
Owen 1991	4	13	0	12	1.0%	11.84 [0.57 , 247.83]		
Suikkari 1996 (1)	2	10	0	6	1.4%	3.82 [0.16 , 94.13]		
Zhuang 1994	4	12	2	15	3.5%	3.25 [0.48 , 22.00]		
Subtotal (95% CI)		**175**		**162**	**52.0%**	**1.70 [0.95 , 3.06]**		
Total events:	34		20					
Heterogeneity: Chi² = 3.12, df = 4 (P = 0.54); I² = 0%								
Test for overall effect: Z = 1.78 (P = 0.08)								
Total (95% CI)		**379**		**358**	**100.0%**	**1.77 [1.17 , 2.70]**		
Total events:	67		39					
Heterogeneity: Chi² = 6.86, df = 7 (P = 0.44); I² = 0%								
Test for overall effect: Z = 2.68 (P = 0.007)								
Test for subgroup differences: Chi² = 0.04, df = 1 (P = 0.84), I² = 0%								

0.02 0.1 1 10 50
Favours no GH   Favours GH

Footnotes

(1) This is data from 4 IU arm of Suikkari 1996

Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding (performance bias and detection bias)

(D) Incomplete outcome data (attrition bias)

(E) Selective reporting (reporting bias)

(F) Other bias

Analysis 2.2. Comparison 2: Adjuvant GH compared to no adjuvant: poor responders for IVF, Outcome 2: Clinical pregnancy rate per woman randomised

Study or Subgroup	GH Events	GH Total	No GH Events	No GH Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
2.2.1 Poor responder by definition								
Choe 2017	6	62	11	65	16.7%	0.53 [0.18 , 1.52]		
Dakhly 2018	29	120	23	120	30.0%	1.34 [0.72 , 2.49]		
Lee 2019	30	94	15	90	18.0%	2.34 [1.16 , 4.74]		
Safdarian 2019	5	34	1	26	1.7%	4.31 [0.47 , 39.40]		
Tesarik 2005	13	50	3	50	3.8%	5.50 [1.46 , 20.76]		
Subtotal (95% CI)		**360**		**351**	**70.2%**	**1.70 [1.16 , 2.50]**		
Total events:	83		53					
Heterogeneity: Chi² = 9.73, df = 4 (P = 0.05); I² = 59%								
Test for overall effect: Z = 2.72 (P = 0.006)								
2.2.2 Poor responder based on previous response								
Bergh 1994	3	9	2	9	2.3%	1.75 [0.22 , 14.22]		
Hazout 2003 (1)	6	12	2	6	2.3%	2.00 [0.26 , 15.38]		
Hazout 2003 (2)	6	11	1	6	1.0%	6.00 [0.52 , 69.75]		
Kucuk 2008	10	31	5	30	5.9%	2.38 [0.70 , 8.07]		
Mohammad 2019	15	78	11	78	15.3%	1.45 [0.62 , 3.40]		
Owen 1991	4	13	1	12	1.2%	4.89 [0.46 , 51.87]		
Zhuang 1994	5	12	2	15	1.8%	4.64 [0.71 , 30.42]		
Subtotal (95% CI)		**166**		**156**	**29.8%**	**2.19 [1.26 , 3.81]**		
Total events:	49		24					
Heterogeneity: Chi² = 2.68, df = 6 (P = 0.85); I² = 0%								
Test for overall effect: Z = 2.77 (P = 0.006)								
Total (95% CI)		**526**		**507**	**100.0%**	**1.85 [1.35 , 2.53]**		
Total events:	132		77					
Heterogeneity: Chi² = 12.94, df = 11 (P = 0.30); I² = 15%								
Test for overall effect: Z = 3.82 (P = 0.0001)								
Test for subgroup differences: Chi² = 0.53, df = 1 (P = 0.46), I² = 0%								

0.01 0.1 1 10 100
Favours no GH   Favours GH

Footnotes
(1) This is data from 4 IU study arm of Hazout 2003
(2) This data is from 8 IU study arm of Hazout 2003

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding (performance bias and detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

Analysis 2.3. Comparison 2: Adjuvant GH compared to no adjuvant: poor responders for IVF,
Outcome 3: Number of women with at least one oocyte retrieved per woman randomised

Study or Subgroup	GH Events	GH Total	No GH Events	No GH Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
2.3.1 Poor responder based on previous response								
Bergh 1994	9	9	9	9		Not estimable		+ ? + – ? +
Norman 2019	62	65	51	65	100.0%	5.67 [1.54 , 20.83]		+ + + + + +
Subtotal (95% CI)		**74**		**74**	**100.0%**	**5.67 [1.54 , 20.83]**		
Total events:	71		60					
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.62 (P = 0.009)								
Total (95% CI)		**74**		**74**	**100.0%**	**5.67 [1.54 , 20.83]**		
Total events:	71		60					
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.62 (P = 0.009)								
Test for subgroup differences: Not applicable								

0.01 0.1 1 10 100
Favours no GH   Favours GH

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding (performance bias and detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

Analysis 2.4. Comparison 2: Adjuvant GH compared to no adjuvant: poor responders for IVF, Outcome 4: Mean number of oocytes retrieved

Study or Subgroup	GH Mean	GH SD	GH Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
2.4.1 Poor responder based on definition										
Choe 2017	3.7	2.6	62	3.4	2.5	65	7.4%	0.30 [-0.59 , 1.19]		
Dakhly 2018	5.4	1.7	120	4.3	2.1	120	24.9%	1.10 [0.62 , 1.58]		
Lee 2019	5.5	3.3	94	2.1	0.7	90	12.5%	3.40 [2.72 , 4.08]		
Safdarian 2019	7.14	2.03	35	5.17	1.82	35	7.1%	1.97 [1.07 , 2.87]		
Tesarik 2005	5.8	2	50	5.6	1.9	50	9.9%	0.20 [-0.56 , 0.96]		
Subtotal (95% CI)			**361**			**360**	**61.8%**	**1.42 [1.12 , 1.73]**		
Heterogeneity: Chi² = 51.32, df = 4 (P < 0.00001); I² = 92%										
Test for overall effect: Z = 9.10 (P < 0.00001)										
2.4.2 Poor responder based on previous response										
Bergh 1994	3.5	1.75	9	6.75	3.77	9	0.8%	-3.25 [-5.97 , -0.53]		
Dor 1995	2	1.15	7	2.25	1.61	7	2.7%	-0.25 [-1.72 , 1.22]		
Kucuk 2008	6.5	2.1	31	3.2	1.4	30	7.3%	3.30 [2.41 , 4.19]		
Mohammad 2019	4.97	1.77	78	3.74	1.82	78	18.3%	1.23 [0.67 , 1.79]		
Norman 2019	5.2	3.5	65	4.1	3.7	65	3.8%	1.10 [-0.14 , 2.34]		
Owen 1991	5	2.38	13	3.75	1.16	12	2.8%	1.25 [-0.20 , 2.70]		
Suikkari 1996 (1)	2.25	1.44	6	2.75	1.5	6	2.1%	-0.50 [-2.16 , 1.16]		
Suikkari 1996 (2)	6.75	5.7	10	2.75	1.5	6	0.4%	4.00 [0.27 , 7.73]		
Subtotal (95% CI)			**219**			**213**	**38.2%**	**1.35 [0.96 , 1.74]**		
Heterogeneity: Chi² = 40.96, df = 7 (P < 0.00001); I² = 83%										
Test for overall effect: Z = 6.79 (P < 0.00001)										
Total (95% CI)			**580**			**573**	**100.0%**	**1.40 [1.16 , 1.64]**		
Heterogeneity: Chi² = 92.36, df = 12 (P < 0.00001); I² = 87%										
Test for overall effect: Z = 11.35 (P < 0.00001)										
Test for subgroup differences: Chi² = 0.08, df = 1 (P = 0.77), I² = 0%										

-4 -2 0 2 4
Favours GH   Favours no GH

Footnotes
(1) This data is from 12 IU study arm of Suikkari 1996
(2) This data is from 4 IU study arm of Suikkari 1996

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding (performance bias and detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

Analysis 2.5. Comparison 2: Adjuvant GH compared to no adjuvant: poor responders for IVF, Outcome 5: Embryo transfer acheived per woman randomised

Study or Subgroup	GH Events	GH Total	No GH Events	No GH Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
2.5.1 Poor responder based on previous response								
Bergh 1994	9	9	8	9	4.7%	3.35 [0.12 , 93.83]		
Kucuk 2008	31	31	22	30	3.9%	23.80 [1.31 , 433.85]		
Norman 2019	53	62	42	51	74.0%	1.26 [0.46 , 3.46]		
Suikkari 1996 (1)	1	6	1	3	12.3%	0.40 [0.02 , 10.02]		
Suikkari 1996 (2)	7	10	1	3	5.1%	4.67 [0.30 , 73.38]		
Subtotal (95% CI)		118		96	100.0%	**2.32 [1.08 , 4.96]**		
Total events:	101		74					

Heterogeneity: Chi² = 5.31, df = 4 (P = 0.26); I² = 25%

Test for overall effect: Z = 2.17 (P = 0.03)

Total (95% CI)		118		96	100.0%	**2.32 [1.08 , 4.96]**		
Total events:	101		74					

Heterogeneity: Chi² = 5.31, df = 4 (P = 0.26); I² = 25%

Test for overall effect: Z = 2.17 (P = 0.03)

Test for subgroup differences: Not applicable

0.01   0.1   1   10   100
Favours no GH   Favours GH

Footnotes

(1) This data is from 4 IU study arm of Suikkari 1996

(2) This data is from 12 IU study arm of Suikkari 1996

Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding (performance bias and detection bias)

(D) Incomplete outcome data (attrition bias)

(E) Selective reporting (reporting bias)

(F) Other bias

Analysis 2.6. Comparison 2: Adjuvant GH compared to no adjuvant: poor responders for IVF, Outcome 6: Mean units gonadotropin used

Study or Subgroup	GH Mean	GH SD	Total	no GH/ Placebo Mean	no GH/ Placebo SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
2.6.1 Poor responder based on definition										
Choe 2017	2409.8	991.7	62	2548.8	814.4	65	13.2%	-139.00 [-455.44 , 177.44]		? ? ● ● ● ●
Dakhly 2018	3386.2	1113.7	120	4789.3	1332.2	120	13.7%	-1403.10 [-1713.78 , -1092.42]		● ● ● ● ● ?
Safdarian 2019	3098.57	510.26	35	4662.86	213.61	35	39.4%	-1564.29 [-1747.55 , -1381.03]		● ● ● ● ● ●
Subtotal (95% CI)			**217**			**220**	**66.3%**	**-1246.99 [-1388.24 , -1105.74]**		
Heterogeneity: Chi² = 59.58, df = 2 (P < 0.00001); I² = 97%										
Test for overall effect: Z = 17.30 (P < 0.00001)										
2.6.2 Poor responder based on previous response										
Bergh 1994	3246.25	1109.58	9	5590	4687.64	9	0.1%	-2343.75 [-5490.91 , 803.41]		● ? ● ● ? ●
Dor 1995	3187.5	951.88	7	4031.25	1648.47	7	0.7%	-843.75 [-2253.90 , 566.40]		? ● ● ● ? ●
Kucuk 2008	3187.1	232.3	31	4070.8	598.2	30	25.2%	-883.70 [-1112.85 , -654.55]		● ? ● ● ? ?
Norman 2019	3383	1073	65	3786	1684	65	5.6%	-403.00 [-888.43 , 82.43]		● ● ● ● ● ●
Owen 1991	2437.5	1014.81	13	2793.75	1009.07	12	2.1%	-356.25 [-1150.14 , 437.64]		? ? ● ● ? ●
Subtotal (95% CI)			**125**			**123**	**33.7%**	**-775.79 [-973.90 , -577.67]**		
Heterogeneity: Chi² = 5.15, df = 4 (P = 0.27); I² = 22%										
Test for overall effect: Z = 7.68 (P < 0.00001)										
Total (95% CI)			**342**			**343**	**100.0%**	**-1088.19 [-1203.20 , -973.18]**		
Heterogeneity: Chi² = 79.14, df = 7 (P < 0.00001); I² = 91%										
Test for overall effect: Z = 18.54 (P < 0.00001)										
Test for subgroup differences: Chi² = 14.41, df = 1 (P = 0.0001), I² = 93.1%										

-1000 -500 0 500 1000
Favours no GH   Favours GH

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding (performance bias and detection bias)
(D) Incomplete outcome data (attrition bias)
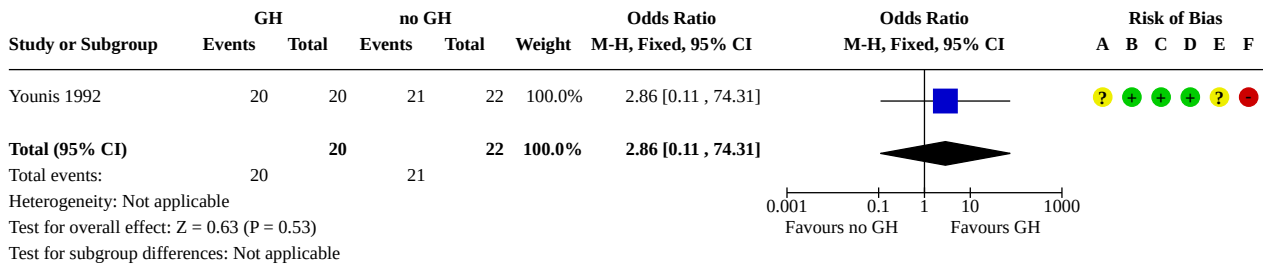(E) Selective reporting (reporting bias)
(F) Other bias

Comparison 3.   Adjuvant GH compared to no adjuvant: subgroup analysis based on age

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Live birth rate per woman randomised	10	817	Odds Ratio (IV, Fixed, 95% CI)	1.62 [1.07, 2.44]
3.1.1 Age < 40 years	6	390	Odds Ratio (IV, Fixed, 95% CI)	1.45 [0.82, 2.56]
3.1.2 Age > 40 years	2	340	Odds Ratio (IV, Fixed, 95% CI)	1.69 [0.90, 3.20]
3.1.3 Age criteria not defined	2	87	Odds Ratio (IV, Fixed, 95% CI)	3.00 [0.58, 15.56]
3.2 Clinical pregnancy rate per woman randomised	12	1087	Odds Ratio (M-H, Fixed, 95% CI)	1.87 [1.38, 2.52]
3.2.1 Age < 40 years	5	288	Odds Ratio (M-H, Fixed, 95% CI)	1.98 [1.12, 3.50]
3.2.2 Age > 40 years	4	651	Odds Ratio (M-H, Fixed, 95% CI)	1.64 [1.11, 2.42]
3.2.3 Age criteria not defined	3	148	Odds Ratio (M-H, Fixed, 95% CI)	3.15 [1.25, 7.94]
3.3 No of women with at least one oocyte retrieved per woman randomised	3	190	Odds Ratio (M-H, Fixed, 95% CI)	5.19 [1.56, 17.32]
3.3.1 Age < 40 years	3	190	Odds Ratio (M-H, Fixed, 95% CI)	5.19 [1.56, 17.32]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.4 Mean number of oocytes retrieved	15	1260	Mean Difference (IV, Fixed, 95% CI)	1.27 [1.04, 1.49]
3.4.1 Age < 40 years	7	437	Mean Difference (IV, Fixed, 95% CI)	0.73 [0.34, 1.13]
3.4.2 Age > 40 years	4	651	Mean Difference (IV, Fixed, 95% CI)	1.35 [1.03, 1.68]
3.4.3 Age criteria not defined	4	172	Mean Difference (IV, Fixed, 95% CI)	2.12 [1.55, 2.69]
3.5 Embryo transfer achieved per woman randomised	5	262	Odds Ratio (M-H, Fixed, 95% CI)	2.50 [1.24, 5.03]
3.5.1 Age < 40 years	4	201	Odds Ratio (M-H, Fixed, 95% CI)	1.73 [0.80, 3.74]
3.5.2 Age criteria not defined	1	61	Odds Ratio (M-H, Fixed, 95% CI)	23.80 [1.31, 433.85]
3.6 Mean units of gonadotropin used	10	765	Mean Difference (IV, Fixed, 95% CI)	-589.38 [-674.47, -504.30]
3.6.1 Age < 40 years	5	253	Mean Difference (IV, Fixed, 95% CI)	-24.30 [-145.14, 96.55]
3.6.2 Age > 40 years	2	367	Mean Difference (IV, Fixed, 95% CI)	-782.66 [-1004.35, -560.97]
3.6.3 Age criteria not defined	3	145	Mean Difference (IV, Fixed, 95% CI)	-1294.15 [-1436.54, -1151.77]

Analysis 3.1. Comparison 3: Adjuvant GH compared to no adjuvant: subgroup analysis based on age, Outcome 1: Live birth rate per woman randomised

Study or Subgroup	GH Events	GH Total	no GH Events	no GH Total	Weight	Odds Ratio IV, Fixed, 95% CI	Odds Ratio IV, Fixed, 95% CI	Risk of Bias A B C D E F
3.1.1 Age < 40 years								
Mohammad 2019	15	78	11	78	23.2%	1.45 [0.62 , 3.40]		+ + + + + +
Norman 2019	9	62	7	51	14.8%	1.07 [0.37 , 3.10]		+ + + + + +
Owen 1991	4	13	0	12	1.8%	11.84 [0.57 , 247.83]		? ? + + ? −
Suikkari 1996 (1)	2	10	0	6	1.6%	3.82 [0.16 , 94.13]		? ? + − ? +
Tapanainen 1992	1	19	2	19	2.7%	0.47 [0.04 , 5.70]		? ? + + + ? −
Younis 1992	6	20	4	22	8.1%	1.93 [0.45 , 8.18]		? + + + ? −
Subtotal (95% CI)		**202**		**188**	**52.3%**	**1.45 [0.82 , 2.56]**		
Total events:	37		24					
Heterogeneity: Chi² = 3.43, df = 5 (P = 0.63); I² = 0%								
Test for overall effect: Z = 1.29 (P = 0.20)								
3.1.2 Age > 40 years								
Dakhly 2018	21	120	17	120	34.7%	1.29 [0.64 , 2.58]		+ + − − − ?
Tesarik 2005	11	50	2	50	6.9%	6.77 [1.42 , 32.37]		+ + + + − +
Subtotal (95% CI)		**170**		**170**	**41.5%**	**1.69 [0.90 , 3.20]**		
Total events:	32		19					
Heterogeneity: Chi² = 3.61, df = 1 (P = 0.06); I² = 72%								
Test for overall effect: Z = 1.62 (P = 0.11)								
3.1.3 Age criteria not defined								
Safdarian 2019	1	34	0	26	1.6%	2.37 [0.09 , 60.65]		+ − − − + +
Zhuang 1994	4	12	2	15	4.6%	3.25 [0.48 , 22.00]		? ? − + − ?
Subtotal (95% CI)		**46**		**41**	**6.2%**	**3.00 [0.58 , 15.56]**		
Total events:	5		2					
Heterogeneity: Chi² = 0.03, df = 1 (P = 0.87); I² = 0%								
Test for overall effect: Z = 1.31 (P = 0.19)								
Total (95% CI)		**418**		**399**	**100.0%**	**1.62 [1.07 , 2.44]**		
Total events:	74		45					
Heterogeneity: Chi² = 7.77, df = 9 (P = 0.56); I² = 0%								
Test for overall effect: Z = 2.30 (P = 0.02)								
Test for subgroup differences: Chi² = 0.69, df = 2 (P = 0.71), I² = 0%								

0.1 0.2 0.5 1 2 5 10
Favours no GH   Favours GH

Footnotes

(1) This is data from 4 IU study arm of Suikkari 1996

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding (performance bias and detection bias)
(D) Incomplete outcome data (attrition bias)
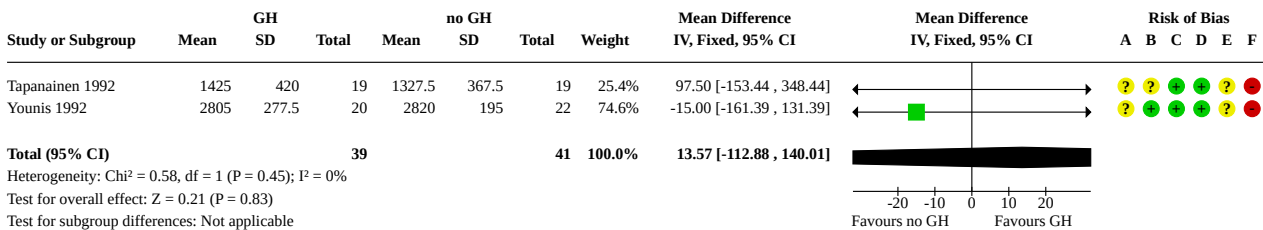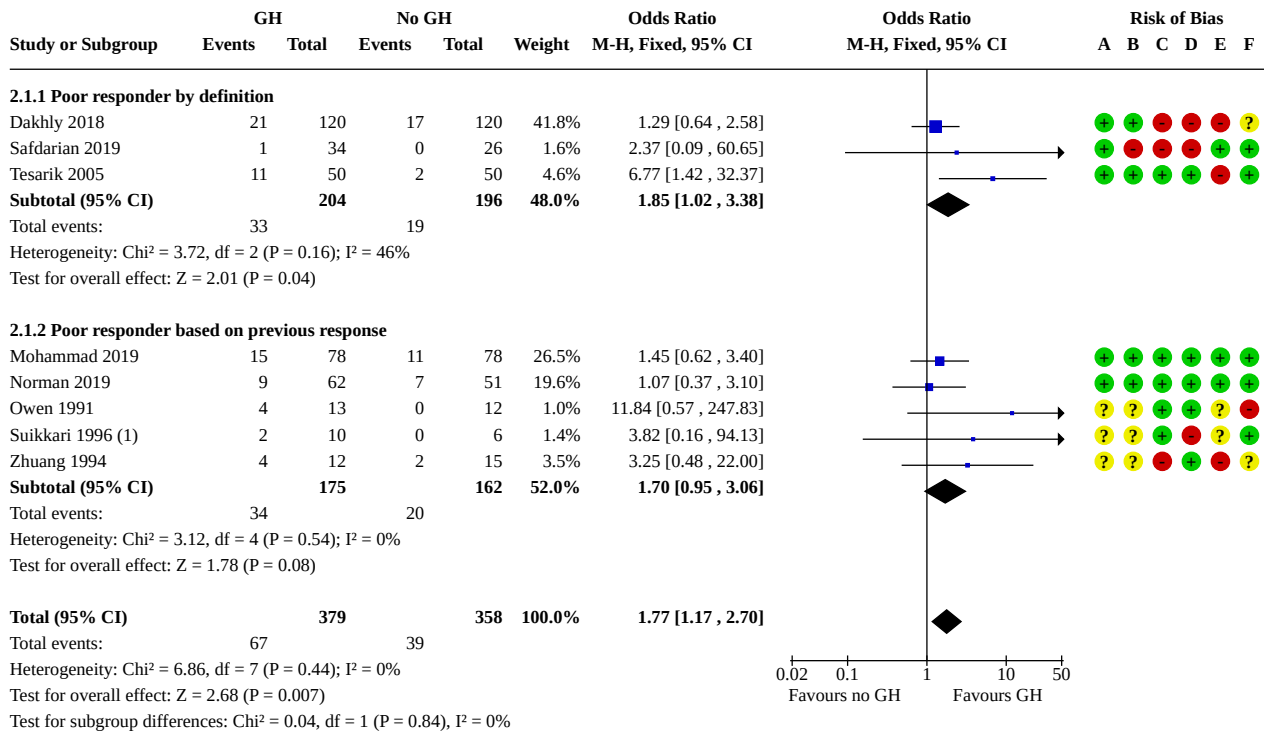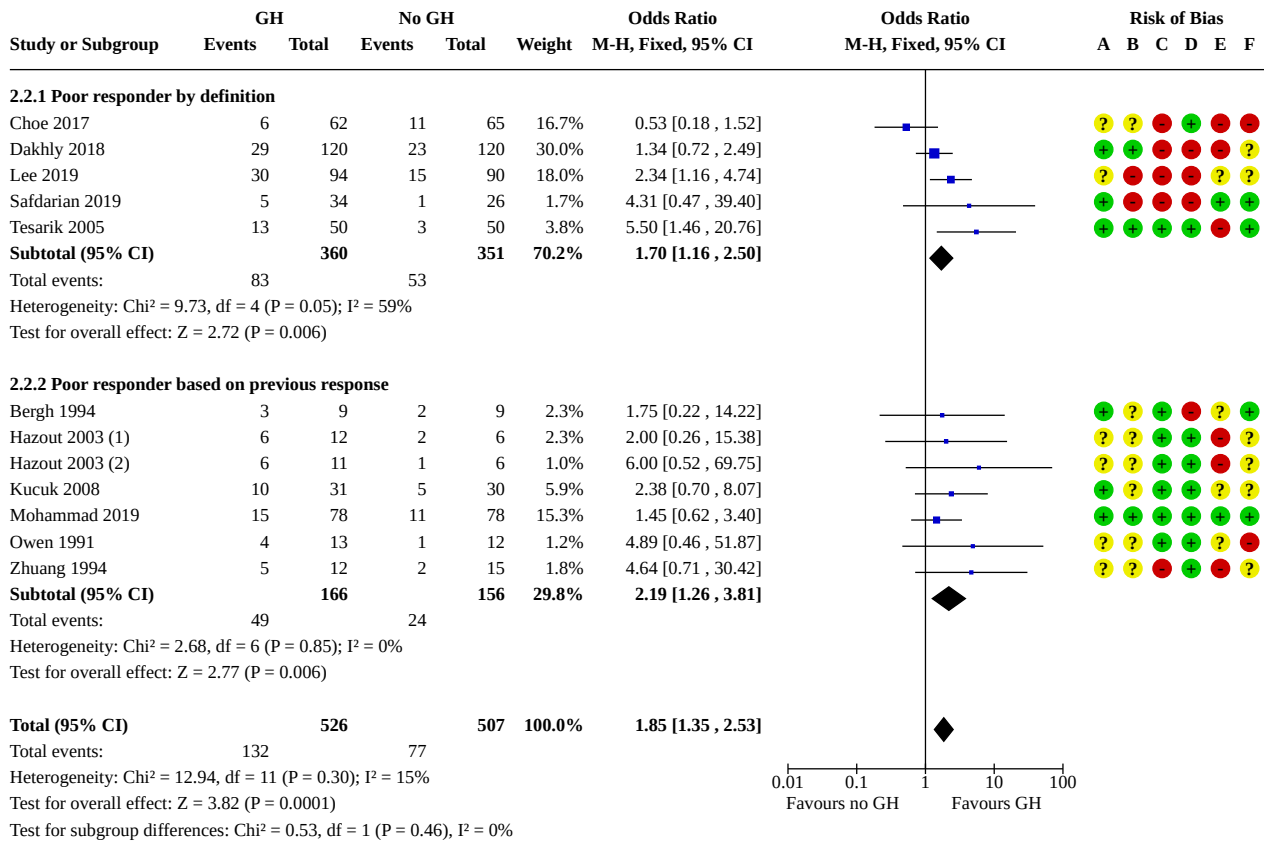(E) Selective reporting (reporting bias)
(F) Other bias

Analysis 3.2.   Comparison 3: Adjuvant GH compared to no adjuvant: subgroup analysis based on age, Outcome 2: Clinical pregnancy rate per woman randomised

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
3.2.1 Age < 40 years								
Bergh 1994	3	9	2	9	2.1%	1.75 [0.22 , 14.22]		+ ? + ● ? +
Hazout 2003 (1)	6	11	3	12	2.1%	3.60 [0.62 , 21.03]		? ? + + ● ?
Hazout 2003 (2)	6	12	3	12	2.4%	3.00 [0.53 , 16.90]		? ? + + ● ?
Mohammad 2019	15	78	11	78	14.2%	1.45 [0.62 , 3.40]		+ + + + + +
Owen 1991	4	13	1	12	1.2%	4.89 [0.46 , 51.87]		? + + + ? ●
Younis 1992	8	20	6	22	5.5%	1.78 [0.49 , 6.50]		? + + + ? ●
Subtotal (95% CI)		**143**		**145**	**27.5%**	**1.98 [1.12 , 3.50]**		
Total events:	42		26					
Heterogeneity: Chi² = 1.78, df = 5 (P = 0.88); I² = 0%								
Test for overall effect: Z = 2.36 (P = 0.02)								
3.2.2 Age > 40 years								
Choe 2017	6	62	11	65	15.5%	0.53 [0.18 , 1.52]		? ? ● + ● ●
Dakhly 2018	29	120	23	120	27.9%	1.34 [0.72 , 2.49]		+ + ● ● + ?
Lee 2019	30	94	15	90	16.7%	2.34 [1.16 , 4.74]		? ● ● + ? ?
Tesarik 2005	13	50	3	50	3.6%	5.50 [1.46 , 20.76]		+ + + + ● +
Subtotal (95% CI)		**326**		**325**	**63.8%**	**1.64 [1.11 , 2.42]**		
Total events:	78		52					
Heterogeneity: Chi² = 8.98, df = 3 (P = 0.03); I² = 67%								
Test for overall effect: Z = 2.48 (P = 0.01)								
3.2.3 Age criteria not defined								
Kucuk 2008	10	31	5	30	5.5%	2.38 [0.70 , 8.07]		+ ? + + ? ?
Safdarian 2019	5	34	1	26	1.5%	4.31 [0.47 , 39.40]		+ ● ● ● + +
Zhuang 1994	5	12	2	15	1.7%	4.64 [0.71 , 30.42]		? + ● + ● ?
Subtotal (95% CI)		**77**		**71**	**8.7%**	**3.15 [1.25 , 7.94]**		
Total events:	20		8					
Heterogeneity: Chi² = 0.44, df = 2 (P = 0.80); I² = 0%								
Test for overall effect: Z = 2.44 (P = 0.01)								
Total (95% CI)		**546**		**541**	**100.0%**	**1.87 [1.38 , 2.52]**		
Total events:	140		86					
Heterogeneity: Chi² = 12.91, df = 12 (P = 0.38); I² = 7%								
Test for overall effect: Z = 4.04 (P < 0.0001)								
Test for subgroup differences: Chi² = 1.71, df = 2 (P = 0.43), I² = 0%								

0.01   0.1   1   10   100
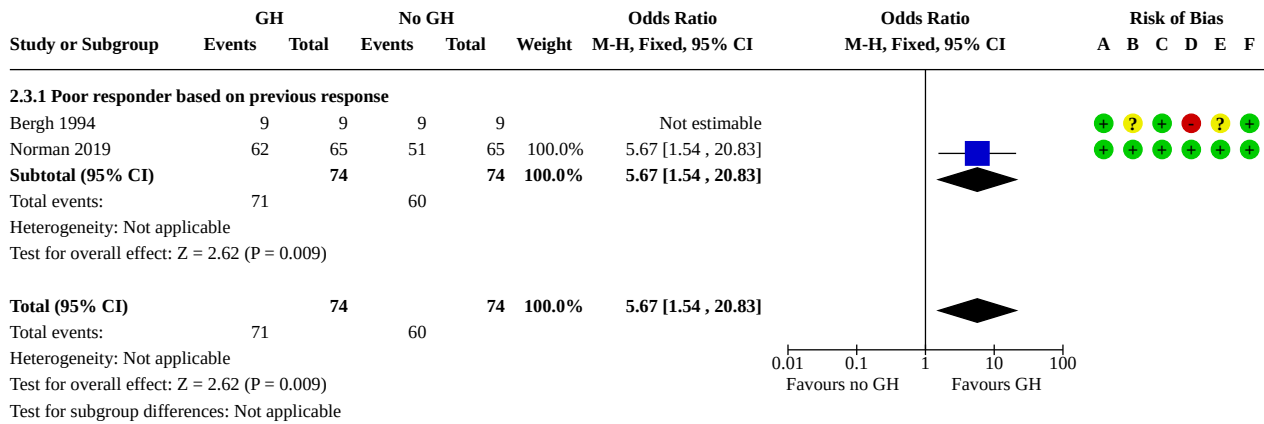Favours no GH   Favours GH

Footnotes

(1) This data is from 8 IU study arm of Hazout 2003

(2) This data is from 4 IU study arm of Hazout 2003

Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding (performance bias and detection bias)

(D) Incomplete outcome data (attrition bias)
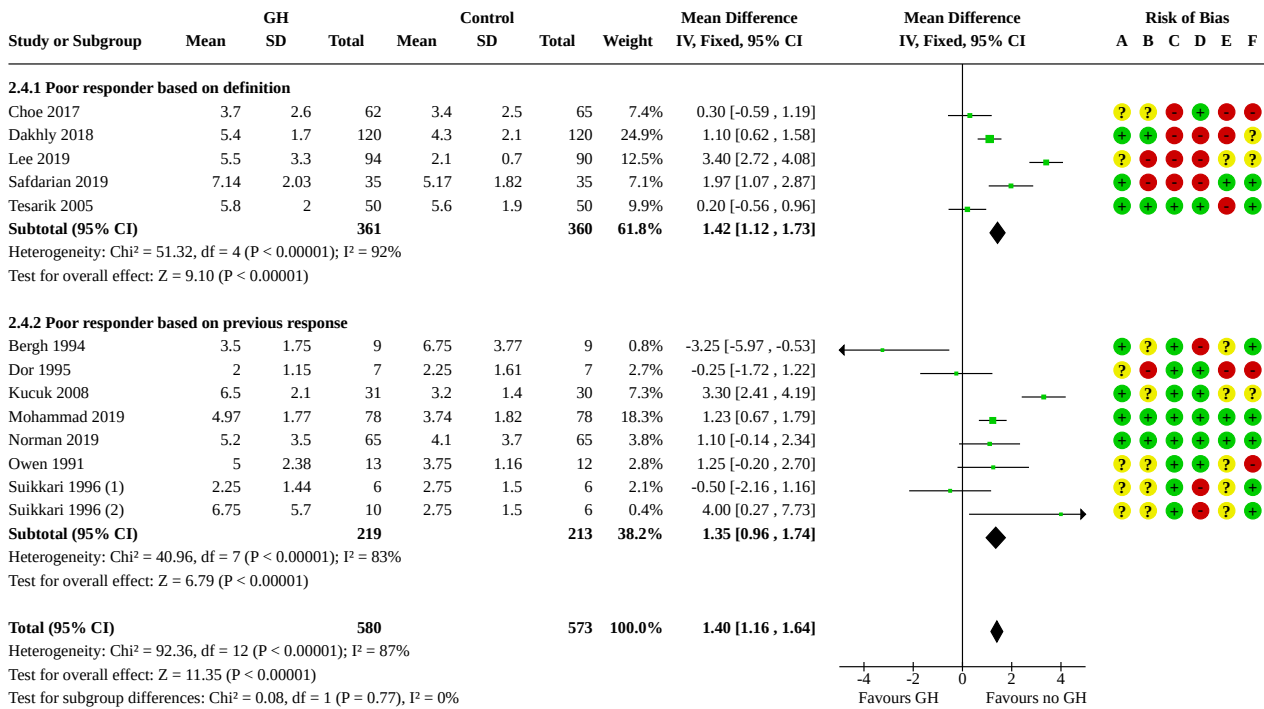
(E) Selective reporting (reporting bias)

(F) Other bias

Analysis 3.3. Comparison 3: Adjuvant GH compared to no adjuvant: subgroup analysis based on age, Outcome 3: No of women with at least one oocyte retrieved per woman randomised

Study or Subgroup	GH Events	GH Total	no GH Events	no GH Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
3.3.1 Age < 40 years								
Bergh 1994	9	9	9	9		Not estimable		+ ? + − ? +
Norman 2019	62	65	51	65	82.8%	5.67 [1.54 , 20.83]		+ + + + + +
Younis 1992	20	20	21	22	17.2%	2.86 [0.11 , 74.31]		? + + + ? −
Subtotal (95% CI)		94		96	100.0%	**5.19 [1.56 , 17.32]**		
Total events:	91		81					
Heterogeneity: Chi² = 0.15, df = 1 (P = 0.70); I² = 0%								
Test for overall effect: Z = 2.68 (P = 0.007)								
Total (95% CI)		94		96	100.0%	**5.19 [1.56 , 17.32]**		
Total events:	91		81					
Heterogeneity: Chi² = 0.15, df = 1 (P = 0.70); I² = 0%								
Test for overall effect: Z = 2.68 (P = 0.007)								
Test for subgroup differences: Not applicable								

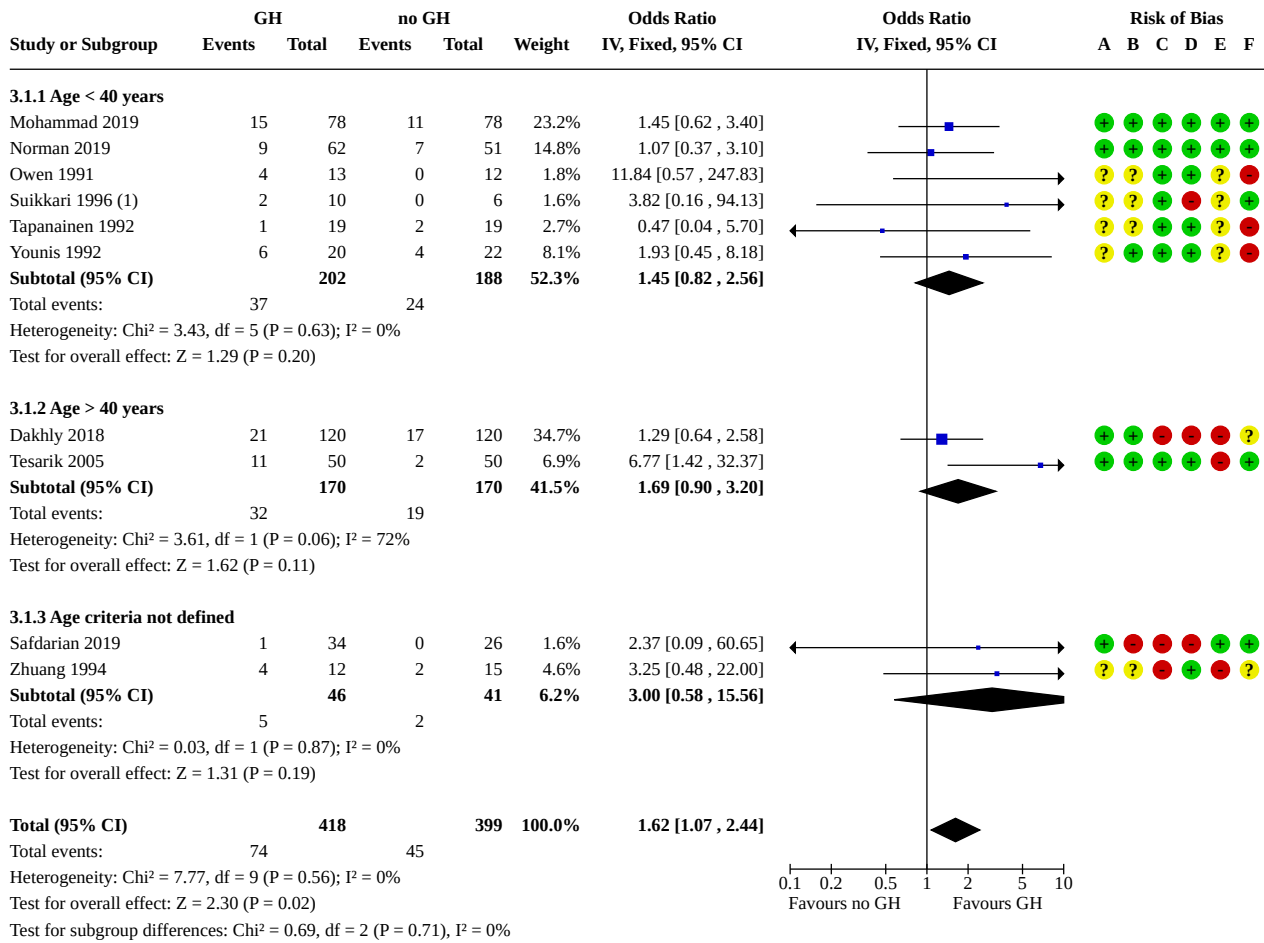0.01 0.1 1 10 100
Favours no GH   Favours GH

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding (performance bias and detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

Analysis 3.4. Comparison 3: Adjuvant GH compared to no adjuvant: subgroup analysis based on age, Outcome 4: Mean number of oocytes retrieved

Study or Subgroup	GH Mean	GH SD	GH Total	no GH Mean	no GH SD	no GH Total	Weight	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
3.4.1 Age < 40 years										
Bergh 1994	3.5	1.75	9	6.75	3.77	9	0.7%	-3.25 [-5.97 , -0.53]		+ ? + ● ? +
Mohammad 2019	4.97	1.77	78	3.74	1.82	78	16.5%	1.23 [0.67 , 1.79]		+ + + + + +
Norman 2019	5.2	3.5	65	4.1	3.7	65	3.4%	1.10 [-0.14 , 2.34]		+ + + + + +
Owen 1991	5	2.38	13	3.75	1.16	12	2.5%	1.25 [-0.20 , 2.70]		? ? + + ? ●
Suikkari 1996 (1)	6.75	5.7	10	2.75	1.5	6	0.4%	4.00 [0.27 , 7.73]		? ? + ● ? +
Suikkari 1996 (2)	2.25	1.44	6	2.75	1.5	6	1.9%	-0.50 [-2.16 , 1.16]		? ? + ● ? +
Tapanainen 1992	6.6	2.8	19	6.3	2.7	19	1.7%	0.30 [-1.45 , 2.05]		? ? + + ? ●
Younis 1992	13.1	1.5	20	13.2	1.3	22	7.2%	-0.10 [-0.95 , 0.75]		? + + + ? ●
Subtotal (95% CI)			**220**			**217**	**34.4%**	**0.73 [0.34 , 1.13]**		
Heterogeneity: Chi² = 21.03, df = 7 (P = 0.004); I² = 67%										
Test for overall effect: Z = 3.69 (P = 0.0002)										
3.4.2 Age > 40 years										
Choe 2017	3.7	2.6	62	3.4	2.5	65	6.7%	0.30 [-0.59 , 1.19]		? ? ● + ● ●
Dakhly 2018	5.4	1.7	120	4.3	2.1	120	22.5%	1.10 [0.62 , 1.58]		+ + + ● ● ?
Lee 2019	5.5	3.3	94	2.1	0.7	90	11.3%	3.40 [2.72 , 4.08]		? ● ● ● ? ?
Tesarik 2005	5.8	2	50	5.6	1.9	50	9.0%	0.20 [-0.56 , 0.96]		+ + + + ● +
Subtotal (95% CI)			**326**			**325**	**49.3%**	**1.35 [1.03 , 1.68]**		
Heterogeneity: Chi² = 49.74, df = 3 (P < 0.00001); I² = 94%										
Test for overall effect: Z = 8.13 (P < 0.00001)										
3.4.3 Age criteria not defined										
Dor 1995	2	1.15	7	2.25	1.61	7	2.4%	-0.25 [-1.72 , 1.22]		? ● + + ● ●
Kucuk 2008	6.5	2.1	31	3.2	1.4	30	6.6%	3.30 [2.41 , 4.19]		+ ? + + ? ?
Safdarian 2019	7.14	2.03	35	5.17	1.82	35	6.4%	1.97 [1.07 , 2.87]		+ ● ● + + +
Zhuang 1994	6.7	3.4	12	5.8	3.1	15	0.9%	0.90 [-1.58 , 3.38]		? ? ● + ● ?
Subtotal (95% CI)			**85**			**87**	**16.3%**	**2.12 [1.55 , 2.69]**		
Heterogeneity: Chi² = 17.79, df = 3 (P = 0.0005); I² = 83%										
Test for overall effect: Z = 7.32 (P < 0.00001)										
Total (95% CI)			**631**			**629**	**100.0%**	**1.27 [1.04 , 1.49]**		
Heterogeneity: Chi² = 104.60, df = 15 (P < 0.00001); I² = 86%										
Test for overall effect: Z = 10.83 (P < 0.00001)										
Test for subgroup differences: Chi² = 16.04, df = 2 (P = 0.0003), I² = 87.5%										

-4 -2 0 2 4
Favours no GH   Favours GH

Footnotes
(1) This data is from 12 IU study arm of Suikkari 1996
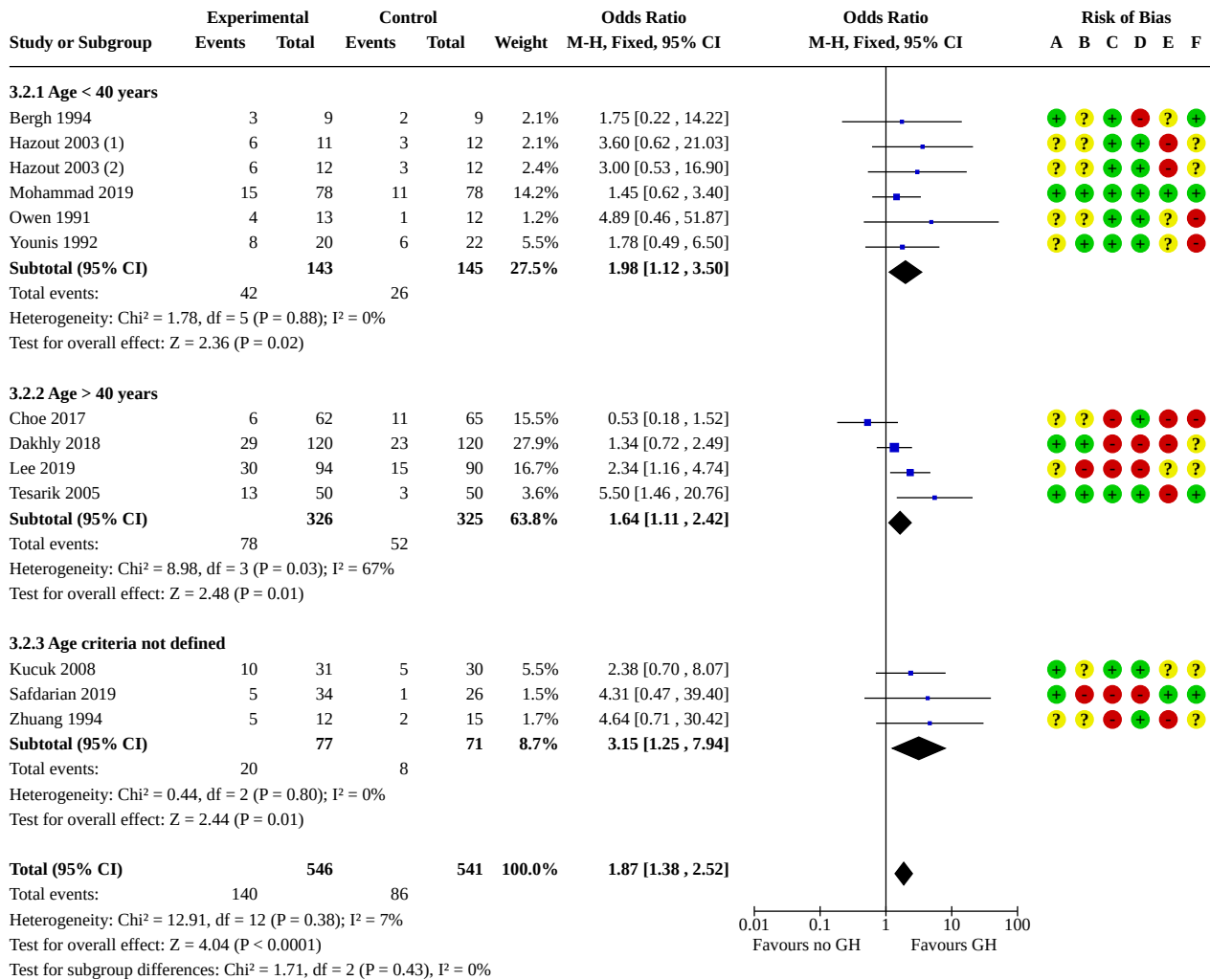(2) This data is from 4 IU study arm of Suikkari 1996

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding (performance bias and detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

Analysis 3.5. Comparison 3: Adjuvant GH compared to no adjuvant: subgroup analysis based on age, Outcome 5: Embryo transfer achieved per woman randomised
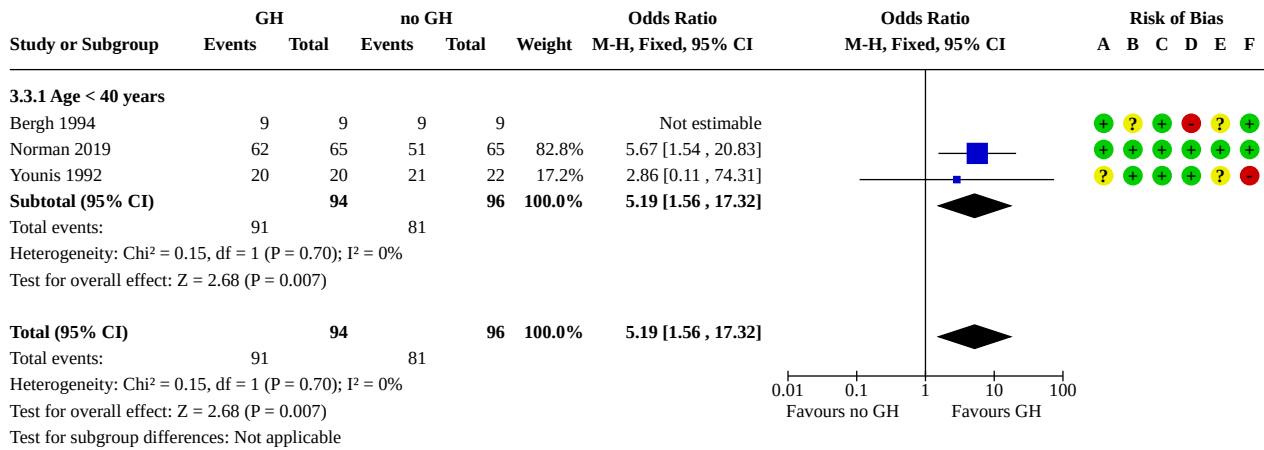
Study or Subgroup	GH Events	GH Total	no GH Events	no GH Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
3.5.1 Age < 40 years								
Bergh 1994	9	9	8	9	4.1%	3.35 [0.12 , 93.83]		+ ? + – ? +
Norman 2019	53	62	42	51	64.8%	1.26 [0.46 , 3.46]		+ + + + + +
Suikkari 1996 (1)	1	6	2	6	16.1%	0.40 [0.03 , 6.18]		? ? + – ? +
Suikkari 1996 (2)	7	10	2	6	7.3%	4.67 [0.53 , 40.89]		? ? + – ? +
Younis 1992	20	20	19	22	4.3%	7.36 [0.36 , 151.91]		? + + + ? –
Subtotal (95% CI)		**107**		**94**	**96.5%**	**1.73 [0.80 , 3.74]**		
Total events:	90		73					
Heterogeneity: Chi² = 3.31, df = 4 (P = 0.51); I² = 0%								
Test for overall effect: Z = 1.40 (P = 0.16)								
3.5.2 Age criteria not defined								
Kucuk 2008	31	31	22	30	3.5%	23.80 [1.31 , 433.85]		+ ? + + ? ?
Subtotal (95% CI)		**31**		**30**	**3.5%**	**23.80 [1.31 , 433.85]**		
Total events:	31		22					
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.14 (P = 0.03)								
Total (95% CI)		**138**		**124**	**100.0%**	**2.50 [1.24 , 5.03]**		
Total events:	121		95					
Heterogeneity: Chi² = 6.63, df = 5 (P = 0.25); I² = 25%								
Test for overall effect: Z = 2.56 (P = 0.01)								
Test for subgroup differences: Chi² = 2.92, df = 1 (P = 0.09), I² = 65.8%								

0.01   0.1   1   10   100
Favours no GH   Favours GH

Footnotes
(1) This data is from 12 IU study arm of Suikkari 1996
(2) This data is from 4 IU study arm of Suikkari 1996

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding (performance bias and detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

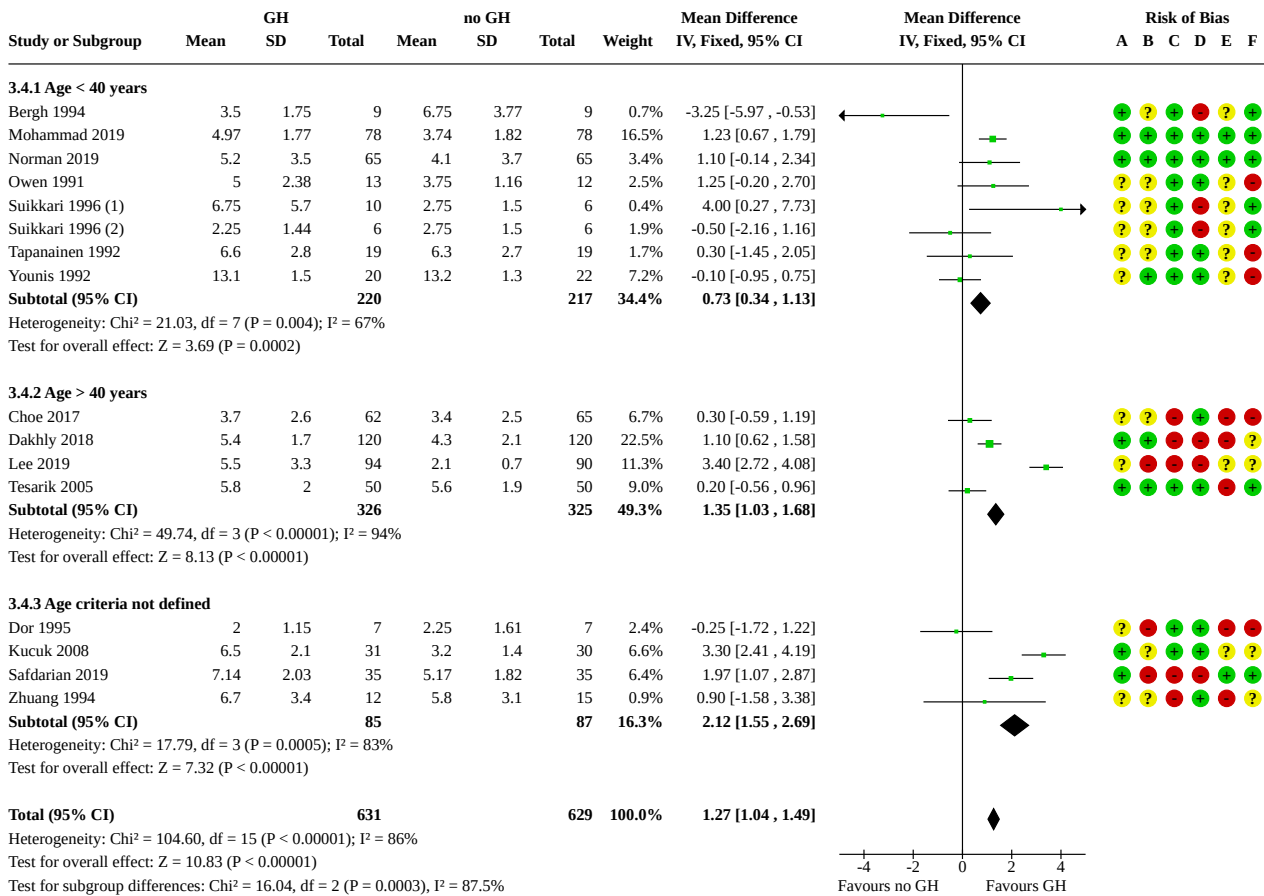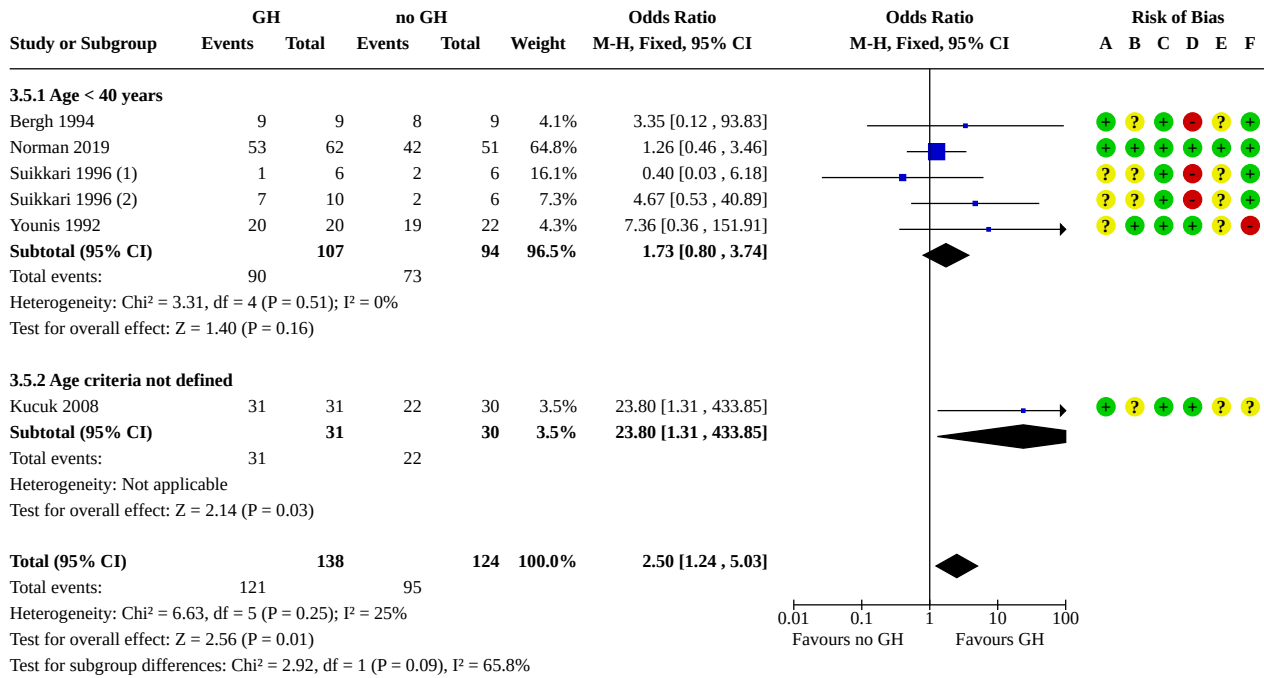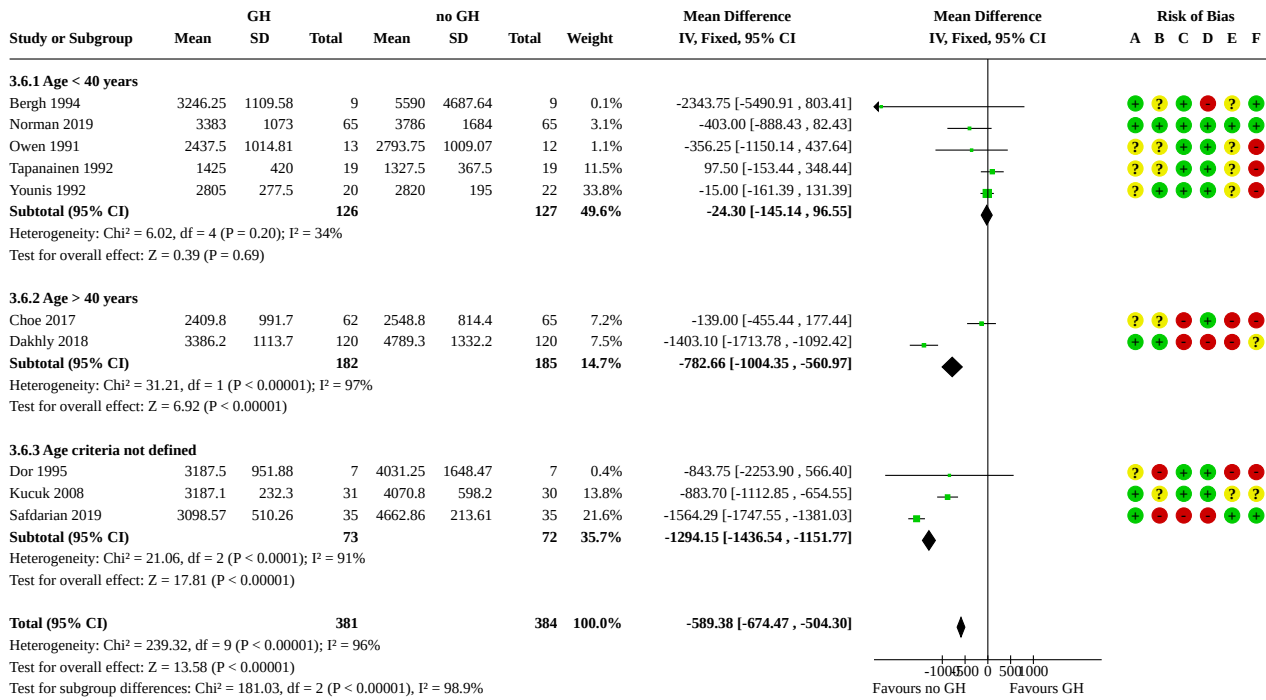## Analysis 3.6. Comparison 3: Adjuvant GH compared to no adjuvant: subgroup analysis based on age, Outcome 6: Mean units of gonadotropin used

Study or Subgroup	GH Mean	GH SD	GH Total	no GH Mean	no GH SD	no GH Total	Weight	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
3.6.1 Age < 40 years										
Bergh 1994	3246.25	1109.58	9	5590	4687.64	9	0.1%	-2343.75 [-5490.91 , 803.41]		+ ? + ● ? +
Norman 2019	3383	1073	65	3786	1684	65	3.1%	-403.00 [-888.43 , 82.43]		+ + + + + +
Owen 1991	2437.5	1014.81	13	2793.75	1009.07	12	1.1%	-356.25 [-1150.14 , 437.64]		? ? + + ? ●
Tapanainen 1992	1425	420	19	1327.5	367.5	19	11.5%	97.50 [-153.44 , 348.44]		? ? + + ? ●
Younis 1992	2805	277.5	20	2820	195	22	33.8%	-15.00 [-161.39 , 131.39]		? + + + ? ●
Subtotal (95% CI)			**126**			**127**	**49.6%**	**-24.30 [-145.14 , 96.55]**		
Heterogeneity: Chi² = 6.02, df = 4 (P = 0.20); I² = 34%										
Test for overall effect: Z = 0.39 (P = 0.69)										
3.6.2 Age > 40 years										
Choe 2017	2409.8	991.7	62	2548.8	814.4	65	7.2%	-139.00 [-455.44 , 177.44]		? ? + + ● ●
Dakhly 2018	3386.2	1113.7	120	4789.3	1332.2	120	7.5%	-1403.10 [-1713.78 , -1092.42]		+ + ● ● ● ?
Subtotal (95% CI)			**182**			**185**	**14.7%**	**-782.66 [-1004.35 , -560.97]**		
Heterogeneity: Chi² = 31.21, df = 1 (P < 0.00001); I² = 97%										
Test for overall effect: Z = 6.92 (P < 0.00001)										
3.6.3 Age criteria not defined										
Dor 1995	3187.5	951.88	7	4031.25	1648.47	7	0.4%	-843.75 [-2253.90 , 566.40]		? ● + + ● ●
Kucuk 2008	3187.1	232.3	31	4070.8	598.2	30	13.8%	-883.70 [-1112.85 , -654.55]		+ ? + + ? ?
Safdarian 2019	3098.57	510.26	35	4662.86	213.61	35	21.6%	-1564.29 [-1747.55 , -1381.03]		+ ● ● ● + +
Subtotal (95% CI)			**73**			**72**	**35.7%**	**-1294.15 [-1436.54 , -1151.77]**		
Heterogeneity: Chi² = 21.06, df = 2 (P < 0.0001); I² = 91%										
Test for overall effect: Z = 17.81 (P < 0.00001)										
Total (95% CI)			**381**			**384**	**100.0%**	**-589.38 [-674.47 , -504.30]**		
Heterogeneity: Chi² = 239.32, df = 9 (P < 0.00001); I² = 96%										
Test for overall effect: Z = 13.58 (P < 0.00001)										
Test for subgroup differences: Chi² = 181.03, df = 2 (P < 0.00001), I² = 98.9%										

-1000 -500 0 500 1000
Favours no GH   Favours GH

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding (performance bias and detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

ADDITIONAL TABLES

Table 1. Adverse events

Trial	Response type	AE reported	Ectopic		Multiple pregnancy		Congenital anomalies		OHSS		Oedema	
			GH	Control	GH	Control	GH	Control	GH	Control	GH	Control
Bergh 1994	Poor	Yes	0	0	0	0	0	0	0	0	2/29	0
Choe 2017	Poor	No										
Dakhly 2018	Poor	No										
Dor 1995	Poor	No										
Hazout 2003	Poor	No										
Kucuk 2008	Poor	Yes	0	0	0	0	0	0	0	0	0	0
Lee 2019	Poor	Yes	0	0	0	0	0	0	0	0	0	0
Mohammad 2019	Poor	Yes	0	0	1/78	1/78	0	0	0	0	0	0
Norman 2019	Poor	Yes	0	0	0	0	1/65	1/65	0	0	0	0
Owen 1991	Poor	Yes	0/13	1/12	2/13	0/12	0	0	0	0		
Safdarian 2019	Poor	Yes	0	0	0	0	0	0	0	0	0	0
Suikkari 1996	Poor	Yes	0	0	1/10 (4IU group)	0/6	0	0	0	0	0	0
Tapanainen 1992	Normal	Yes	0		0/19	1/19	0		0		0	
Tesarik 2005	Poor	No										
Younis 1992	Normal	Yes	0/20	2/22	5/20	2/22	0	0	0/20	0/22	0	0
Zhuang 1994	Poor	No										

- IU: international units
- AE: adverse effects

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- OHSS: ovarian hyperstimulation syndrome

Table 2. Trial characteristics

Trial	Age	Poor response type	GH	Dose	Schedule	Placebo	ET day	GH	Total
	BMI		Protocol					Control	
Bergh 1994	< 38	Response x 2	HGH Agonist	0.1 IU/kg	Pre- treatment for 7 days followed by with/without stimulation	Saline	Day 2/3	10 x 4 groups	40
Choe 2017	≥ 40 < 30	Bologna	Sustained-re-lease GH Antagonist	20 mg	3 doses - previous cycle mid luteal, late luteal and D2	No	Not stated	62 65	127
Dakhly 2018	≥ 40	Bologna	HGH Agonist	7.5 IU	Daily from D21 of previous cycle	No	Day 3 up to 3	120 120	240
Dor 1995		Response	HGH Flare	18 IU	Days 2, 4, 6, 8	Mannitol	Day 2	7 7	14
Hazout 2003	< 39	Oocyte dysmor-phia > 50%	HGH Agonist	3 groups 4 IU, 8 IU, placebo	Daily from day 1 of stimulation until trigger	Yes - not stated what	Day 3	4 IU: 12 8 IU: 11 12	35
Kucuk 2008		Response	HGH Agonist	12 IU	Daily from D21 of previous cycle	No	Day 3	31 30	61
Lee 2019	≥ 40	Bologna	HGH Agonist ul-tra-long pro-tocol	4 IU, 4 IU, 2 IU - total 10 IU	3 consecutive days with stimulation	No	Day 3	94 90	184
Moham-mad 2019	25-38	Response	HGH Antagonist	4 IU	D2 until 1 day before egg collection	Saline	Day 2/3	78 78	156

Table 2. Trial characteristics (Continued)

Norman 2019	< 41	Response	HGH Antagonist	12 IU	D1 until 1 day before egg collection	Metacresol in water	Not stated	65	130
	< 33							65	
Owen 1991	< 38	Response	HGH Agonist	24 IU	Alternate day from D1 stimulation (maximum 2 weeks)	Yes - not stated what	Day 2 (1-4)	13	25
								12	
Safdarian 2019		Bologna	HGH Antagonist	3 groups: 7.5 IU from day 8 0.3 IU from day 3 previous cycle saline from day 8	3 groups: 7.5 IU from day 8 X 5 d 0.3 IU from day 3 previous cycle x 20 d saline from day 8 X 5 d	Saline	Day 5 up to 3	Group 1: 34 Group 2: 32 Group 3: 26	105
Suikkari 1996	< 40	Response x 2	HGH Flare	3 groups 4 IU, 12 IU, placebo	Daily from day 3	Saline	Day 2	4 IU: 10 12 IU: 6	22
	< 27							6	
Tapanainen 1992	27-37	N	HGH Flare	24 IU	Alternate day from D4 stimulation until last HMG	Saline	Not stated	19	38
								19	
Tesarik 2005	> 40	As per study	HGH Agonist	8 IU	Daily from D7 of stimulation until 1 day before egg collection	Yes - not stated what	Day 3 (1-5)	50	100
								50	
Younis 1992	< 38	N	HGH Agonist	12 IU	Days 1, 3, 5, 7	Mannitol	Not stated	20	42
								22	
Zhuang 1994		Response	HGH Agonist	12 IU	Alternate day	No	Not stated	12	27
								15	

- HMG: human menopausal gonadotropin
- IU: international units
- HGH: human recombinant growth hormone

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- GH: growth hormone

APPENDICES

Appendix 1. Cochrane Gynaecology and Fertility Specialised Register search strategy

ProCite platform

Searched 11 November 2020

Keywords CONTAINS "growth hormone" or "growth hormone derivative" or "human growth hormone" or "growth hormone releasing factor" or "grf" or r-hGH or rhGH or Title CONTAINS "growth hormone" or "growth hormone derivative" or "human growth hormone" or "growth hormone releasing factor" or "grf" or r-hGH or rhGH

(102 records)

Appendix 2. CENTRAL via the Cochrane Register of Studies Online (CRSO) search strategy

Web platform

Searched 11 November 2020

#1 MESH DESCRIPTOR Fertilization in Vitro EXPLODE ALL TREES 2062

#2 MESH DESCRIPTOR Embryo Transfer EXPLODE ALL TREES 1097

#3 (embryo transfer*):TI,AB,KY 3809

#4 MESH DESCRIPTOR Sperm Injections, Intracytoplasmic EXPLODE ALL TREES 538

#5 (vitro fertili?ation):TI,AB,KY 3460

#6 (intracytoplasmic sperm injection*):TI,AB,KY 1933

#7 ((Ivf or icsi)):TI,AB,KY 6604

#8 (blastocyst* adj2 transfer*):TI,AB,KY 417

#9 MESH DESCRIPTOR Ovulation Induction EXPLODE ALL TREES 1349

#10 (ovulat* adj3 stimulat*):TI,AB,KY 82

#11 (ovar* adj3 stimulat*):TI,AB,KY 2364

#12 (ovar* adj3 induc*):TI,AB,KY 661

#13 (ovulat* adj3 induc*):TI,AB,KY 2666

#14 (infertil* or subfertil*):TI,AB,KY 9043

#15 (assisted reproduct*):TI,AB,KY 1430

#16 (poor adj3 respon*):TI,AB,KY 2423

#17 (sub-optimal respon*):TI,AB,KY 37

#18 (ovar* adj3 function*):TI,AB,KY OR (ovar* adj3 reserv*):TI,AB,KY 1385

#19 (ovar* adj2 hyperstimulat*):TI,AB,KY 1646

#20 (implantation failure*):TI,AB,KY 452

#21 superovulat*:TI,AB,KY 218

#22 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #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 17409

#23 MESH DESCRIPTOR Human Growth Hormone EXPLODE ALL TREES 1541

#24 MESH DESCRIPTOR Growth Hormone EXPLODE ALL TREES 3135

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#25 somatotrop*:TI,AB,KY 289

#26 somatrop*:TI,AB,KY 195

#27 (growth hormone):TI,AB,KY 5917

#28 grf:TI,AB,KY 159

#29 rHGH:TI,AB,KY 520

#30 HGH:TI,AB,KY 403

#31 sermorelin:TI,AB,KY 32

#32 norditropin:TI,AB,KY 102

#33 #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 6167

#34 #22 AND #33 163

Appendix 3. MEDLINE search strategy

Ovid platform

Searched from 1946 to 11 November 2020
1 exp Reproductive Techniques, Assisted/ (70255)
2 embryo transfer$.tw. (12474)
3 in vitro fertili?ation.tw. (23676)
4 ivf.tw. (24222)
5 icsi.tw. (8622)
6 intracytoplasmic sperm injection$.tw. (7378)
7 (blastocyst adj2 transfer$).tw. (1140)
8 exp Ovulation Induction/ (13241)
9 ((ovar$ or ovulat$) adj5 (induct$ or stimulat$)).tw. (16271)
10 (infertil$ or subfertil$).tw. (65487)
11 assisted reproduct$.tw. (15458)
12 (poor adj2 respon$).tw. (17407)
13 (ovar$ adj2 respon$).tw. (4652)
14 (ovar$ adj2 reserv*).tw. (3386)
15 sub-optimal respon$.tw. (102)
16 ovar$ function$.tw. (7465)
17 (ovar$ adj2 hyperstimulat$).tw. (5223)
18 poor prognosis.tw. (83842)
19 implantation failure$.tw. (1705)
20 or/1-19 (248311)
21 growth hormone/ or human growth hormone/ (55298)
22 exp growth hormone-releasing hormone/ or sermorelin/ (5017)
23 somatotrop$.tw. (7495)
24 (somatrop$ or norditropin).tw. (363)
25 (growth adj3 hormone$).tw. (63161)
26 grf.tw. (2951)
27 rHGH.tw. (1852)
28 GHRF.tw. (102)
29 HGH.tw. (4380)
30 sermorelin.tw. (10)
31 Humatrope.tw. (26)
32 or/21-31 (84325)
33 20 and 32 (1346)
34 randomized controlled trial.pt. (516636)
35 controlled clinical trial.pt. (93916)
36 randomized.ab. (498254)
37 randomised.ab. (99429)
38 placebo.tw. (218158)
39 clinical trials as topic.sh. (193603)

40 randomly.ab. (344514)
41 trial.ti. (228357)
42 (crossover or cross-over or cross over).tw. (86662)
43 or/34-42 (1392770)
44 exp animals/ not humans.sh. (4754125)
45 43 not 44 (1282851)
46 33 and 45 (145)

Appendix 4. Embase search strategy

Ovid platform

Searched from 1980 to 11 November 2020
1 exp embryo transfer/ or exp fertilization in vitro/ or exp intracytoplasmic sperm injection/ (72124)
2 embryo$ transfer$.tw. (22137)
3 in vitro fertili?ation.tw. (31361)
4 icsi.tw. (16653)
5 intracytoplasmic sperm injection$.tw. (9979)
6 (blastocyst adj2 transfer$).tw. (2561)
7 ivf.tw. (41854)
8 assisted reproduct$.tw. (23687)
9 ovulation induc$.tw. (5714)
10 (ovari$ adj2 stimulat$).tw. (11462)
11 superovulat$.tw. (3952)
12 ovarian hyperstimulation.tw. (7612)
13 COH.tw. (2567)
14 infertil$.tw. (87096)
15 subfertil$.tw. (7145)
16 (ovari$ adj2 induction).tw. (332)
17 exp ovulation induction/ (14827)
18 assisted reproduct$.tw. (23687)
19 (poor adj2 respon$).tw. (28231)
20 (ovar$ adj2 respon$).tw. (6617)
21 (ovar$ adj2 reserv*).tw. (6549)
22 sub-optimal respon$.tw. (304)
23 ovar$ function$.tw. (8958)
24 ovar$ reserv$.tw. (6362)
25 (ovar$ adj2 hyperstimulat$).tw. (7737)
26 implantation failure$.tw. (3394)
27 poor prognosis.tw. (128750)
28 or/1-27 (342471)
29 exp growth hormone/ (55943)
30 exp human growth hormone/ (11631)
31 exp growth hormone releasing factor/ (7244)
32 exp sermorelin/ (317)
33 somatotrop$.tw. (7094)
34 (somatrop$ or norditropin).tw. (1212)
35 (growth adj3 hormone$).tw. (67557)
36 grf.tw. (3322)
37 rHGH.tw. (2631)
38 GHRF.tw. (100)
39 HGH.tw. (4691)
40 sermorelin.tw. (23)
41 Humatrope.tw. (442)
42 or/29-41 (95989)
43 28 and 42 (1852)
44 Clinical Trial/ (982892)
45 Randomized Controlled Trial/ (627750)
46 exp randomization/ (89123)
47 Single Blind Procedure/ (40905)
48 Double Blind Procedure/ (175571)
49 Crossover Procedure/ (65151)

50 Placebo/ (345175)
51 Randomi?ed controlled trial$.tw. (242701)
52 Rct.tw. (39309)
53 random allocation.tw. (2090)
54 randomly allocated.tw. (36699)
55 allocated randomly.tw. (2593)
56 (allocated adj2 random).tw. (833)
57 Single blind$.tw. (25671)
58 Double blind$.tw. (207879)
59 ((treble or triple) adj blind$).tw. (1229)
60 placebo$.tw. (311063)
61 prospective study/ (640581)
62 or/44-61 (2266870)
63 case study/ (73510)
64 case report.tw. (418898)
65 abstract report/ or letter/ (1129538)
66 or/63-65 (1610773)
67 62 not 66 (2211744)
68 (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.) (6108712)
69 67 not 68 (2131981)
70 43 and 69 (233)

Appendix 5. PsycINFO search strategy

Ovid platform

Searched from 1806 to 11 November 2020

1 exp Somatotropin/ (1302)
2 somatotrop$.tw. (259)
3 (somatrop$ or norditropin).tw. (9)
4 (growth adj5 hormone$).tw. (2667)
5 1 or 2 or 3 or 4 (2869)
6 exp reproductive technology/ (1881)
7 in vitro fertili?ation.tw. (772)
8 ivf-et.tw. (20)
9 (ivf or et).tw. (143737)
10 icsi.tw. (75)
11 intracytoplasmic sperm injection$.tw. (57)
12 (blastocyst adj2 transfer$).tw. (4)
13 assisted reproduct$.tw. (1014)
14 artificial insemination.tw. (262)
15 iui.tw. (44)
16 intrauterine insemination$.tw. (34)
17 ovulation induc$.tw. (33)
18 (ovari$ adj2 stimulat$).tw. (60)
19 ovarian hyperstimulation.tw. (13)
20 COH.tw. (135)
21 superovulat$.tw. (8)
22 infertil$.tw. (3633)
23 subfertil$.tw. (97)
24 (ovari$ adj2 induction).tw. (8)
25 poor responder$.tw. (131)
26 or/6-25 (148811)
27 5 and 26 (112)
28 random.tw. (59858)
29 control.tw. (453410)
30 double-blind.tw. (23231)
31 clinical trials/ (11806)
32 placebo/ (5779)
33 exp Treatment/ (1068486)
34 or/28-33 (1472642)
35 27 and 34 (37)

Appendix 6. CINAHL search strategy

Ebsco platform

Searched from 1961 until 20 January 2020. Search output from the 11 November 2020 search is included in the CENTRAL output

#	Query	Results
S50	S26 AND S49	19
S49	S48 NOT S47	622,364
S48	S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41	650,729
S47	S45 NOT S46	166,691
S46	MH (human)	2,022,943
S45	S42 OR S43 OR S44	189,382
S44	TI (animal model*)	2,879
S43	MH (animal studies)	110,140
S42	MH animals+	87,026
S41	AB (cluster W3 RCT)	317
S40	MH (crossover design) OR MH (comparative studies)	251,708
S39	AB (control W5 group)	98,479
S38	PT (randomized controlled trial)	86,212
S37	MH (placebos)	11,573
S36	MH (sample size) AND AB (assigned OR allocated OR control)	3,753
S35	TI (trial)	98,599
S34	AB (random*)	279,402
S33	TI (randomised OR randomized)	96,562
S32	MH cluster sample	3,996
S31	MH pretest-posttest design	39,260
S30	MH random assignment	56,981
S29	MH single-blind studies	13,027
S28	MH double-blind studies	43,273
S27	MH randomized controlled trials	89,512

(Continued)

S26	S16 AND S25	57
S25	S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24	5,505
S24	TX HGH	157
S23	TX HGH	157
S22	TX rHGH	155
S21	TX grf	574
S20	TX (somatrop* or norditropin)	64
S19	TX somatotrop*	152
S18	TX growth N3 hormone*	4,803
S17	(MM "Human Growth Hormone")	1,552
S16	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15	15,741
S15	TX (ovari* N2 induction)	34
S14	TX COH	244
S13	TX ovarian hyperstimulation	835
S12	TX superovulat*	86
S11	TX ovulation induc*	1,756
S10	TX assisted reproduct*	3,853
S9	(MM "Reproduction Techniques+")	8,993
S8	TX intracytoplasmic sperm injection*	902
S7	TX embryo* N3 transfer*	3,102
S6	TX ovar* N3 hyperstimulat*	840
S5	TX ovari* N3 stimulat*	1,007
S4	TX IVF or TX ICSI	5,030
S3	(MM "Fertilization in Vitro")	3,439
S2	TX vitro fertilization	7,002
S1	TX vitro fertilisation	7,002

WHAT'S NEW

Date	Event	Description
28 September 2021	New citation required but conclusions have not changed	The addition of 6 new trials has not led to any changes in the conclusions of this review. Also, we added a separate subgroup analysis based on age at the request of a referee. Methods updated to current Cochrane standards, including provision for summary of findings tables, sensitivity analyses and a funnel plot.
28 September 2021	New search has been performed	We updated our contact details. We added 6 trials to the review (Choe 2017; Dakhly 2018; Lee 2019; Mohammad 2019; Norman 2019; Safdarian 2019). We made a list of ongoing research and contacted all authors.

HISTORY

Protocol first published: Issue 1, 1995
Review first published: Issue 1, 1995

Date	Event	Description
24 August 2009	New citation required but conclusions have not changed	Authors changed
11 August 2009	New citation required but conclusions have not changed	New authors added
14 June 2009	New search has been performed	Since the last published review (1995 & 2003), the authorship of the review has changed. New authors involved in updating the review in 2009 included G Ahmad, J Brown, JMN Duffy, L Nardo, I Salim and AJ Watson. New randomised controlled trials were included in the review, resulting from repeating the search strategy In June 2009. Subgroup analysis of poor responders was performed in the 2009 update, the first subgroup defined as poor responders as demonstrated by sub-optimal response following controlled ovarian stimulation and the second subgroup defined as poor ovarian performance as demonstrated by abnormal ovarian reserve tests.
28 April 2008	Amended	Converted to new review format.
28 May 2003	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

D Kotarba, J Kotarba, and E Hughes prepared the original version of this review published in 1995. The 2003 update of the review was prepared by K Harper and M Proctor. The 2009 update of the review was prepared by G Ahmad, J Brown, JMN Duffy and L Nardo, L Mohiyiddeen and AJ Watson.

The 2021 update was prepared by A Sood, G Mohiyiddeen and L Mohiyiddeen. AS and GM retrieved the searches, selected studies, extracted and analysed the data with guidance from LM. CF, GA and AW made contributions to concept and design, reading and approving the draft.

DECLARATIONS OF INTEREST

AS has no conflicts of interest to declare.

GM has no conflicts of interest to declare.

GA has no conflicts of interest to declare.

CF has no conflicts of interest to declare.

AW has no conflicts of interest to declare.

LM has no conflicts of interest to declare.

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  £5000 initiative fund

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

New authors of the protocol were added for the first full review; additional authors were included in the 2009 update: G Ahmad, J Brown, JMN Duffy, L Nardo, L Mohiyiddeen and AJ Watson. Further additional authors for the 2021 review were A Sood and G Mohiyiddeen.

We added a separate analysis for subgroups, based on age, at the request of a referee in the 2021 update.

The protocol stated that Peto ORs would be used. We used Maentel-Haenszel ORs for the 2021 update, as the *Cochrane Handbook for Systematic Reviews of Interventions* recommends this as the default method for meta-analysis (Higgins 2021).

At the 2021 update we updated the methods to current Cochrane standards, including provision for summary of findings tables, sensitivity analyses and a funnel plot.

INDEX TERMS

Medical Subject Headings (MeSH)

*Abortion, Spontaneous; Fertilization in Vitro; *Growth Hormone [therapeutic use]; Live Birth [epidemiology]; Ovulation Induction; Pregnancy Rate; Sperm Injections, Intracytoplasmic

MeSH check words

Female; Humans; Pregnancy