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Duffy JMN, Ahmad G, Mohiyiddeen L, Nardo LG, Watson A

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[Intervention Review]

Growth hormone for in vitro fertilization

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ABSTRACT

Background

In an effort to improve outcomes of in-vitro fertilisation cycles the use of growth hormone has been considered. Improving the outcomes of in-vitro fertilisation is especially important for subfertile women who are considered 'poor responders'.

Objectives

To assess the effectiveness of adjuvant growth hormone in in-vitro fertilisation protocols.

Search methods

We searched the Cochrane Menstrual Disorders and Subfertility Groups trials register (June 2009), the Cochrane Central Register of Controlled Trials (Cochrane Library Issue 2, 2009), MEDLINE (1966 to June 2009), EMBASE (1988 to June 2009) and Biological Abstracts (1969 to June 2009).

Selection criteria

All randomised controlled trials were included if they addressed the research question and provided outcome data for intervention and control participants.

Data collection and analysis

Assessment of trial risk of bias and extraction of relevant data was performed independently by two reviewers.

Main results

Ten studies (440 subfertile couples) were included. Results of the meta-analysis demonstrated no difference in outcome measures and adverse events in the routine use of adjuvant growth hormone in in-vitro fertilisation protocols. However, meta-analysis demonstrated a statistically significant difference in both live birth rates and pregnancy rates favouring the use of adjuvant growth hormone in in-vitro fertilisation protocols in women who are considered poor responders without increasing adverse events, OR 5.39, 95% CI 1.89 to 15.35 and OR 3.28, 95% CI 1.74 to 6.20 respectively.

Authors' conclusions

Although the use of growth hormone in poor responders has been found to show a significant improvement in live birth rates, we were unable to identify which sub-group of poor responders would benefit the most from adjuvant growth hormone. The result needs to be

interpreted with caution, the included trials were few in number and small sample size. Therefore, before recommending growth hormone adjuvant in in-vitro fertilisation further research is necessary to fully define its role.

PLAIN LANGUAGE SUMMARY

Growth hormone in in-vitro fertilisation

Before starting an in-vitro fertilisation cycle, some women need help to ovulate and the use of growth hormone therapy may help these women. This aims to reduce the use of gonadotropin therapy to stimulate ovulation, a hormone that can cause multiple pregnancy. The review of trials found no evidence that growth hormone helps improve birth rates in women who are undergoing ovulation induction prior to in-vitro fertilisation. However there is some evidence of increased pregnancy and birth rates in women who are considered 'poor responders' to in-vitro fertilisation. More research is needed.

BACKGROUND

Description of the condition

Subfertility, usually defined as absence of conception after one year of regular intercourse, is a common problem affecting as many as one in six couples (Cahill 2002). Main causes include sperm dysfunction, ovulation disorder and fallopian tube damage (Cahill 2002). One method of treating infertile couples is assisted conception via in-vitro fertilisation (IVF). IVF involves using hormones to modify ovarian function 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. The oocytes are then fertilised outside the body (in vitro). The fertilised oocytes (embryos) are then transferred into the uterus after 36 hours after oocyte retrieval. IVF protocols are constantly under review in an attempt to decrease hormone (gonadotrophin) requirement, improve follicular recruitment, whilst primarily to increase live birth rates.

Description of the intervention

Some protocols have considered the role of growth hormone in IVF (Landolfi 1994; Jacobs 1995). Growth hormone is a biological peptide hormone, synthesised, stored and secreted by somatotroph cells located in the anterior pituitary gland. Growth hormone 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 growth hormone administration in IVF protocols.

How the intervention might work

The administration of growth hormone may potentate the effect of exogenous gonadotrophins (Homburg 1988). Growth hormone is reported to modulate the action of follicular stimulating hormone on granulosa cells by up-regulating the local synthesis of insulin-like growth factor-I (IGF-1). This interest has been stimulated by animal studies which suggest that growth hormone may increase the intra-ovarian production of the IGF-1 (Hsu 1987; Yoshimura 1996). IGF-1 displays growth hormone dependence both in-vivo and in-vitro (Blumenfeld 1996). The interaction between growth hormone 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).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). IGF-1 has also been found to stimulate follicular development, oestrogen production and oocyte maturation (Yoshimura 1996).

Why it is important to do this review

Improving the outcomes of IVF by the use of growth hormone adjuvant therapy is important particularly in those women who are considered poor responders. The aim of this review is to establish the role of growth hormone in IVF.

OBJECTIVES

To assess the effectiveness of adjuvant growth hormone in IVF.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials were eligible for inclusion.

Types of participants

Women who were part of a subfertile couple undergoing IVF.

Types of interventions

All studies comparing adjuvant growth hormone in IVF cycles with standard IVF cycles.

Types of outcome measures

Primary outcomes

1. Live birth rate per woman randomised

Number of women achieving a live birth divided by the number of women randomised.

Secondary outcomes

1. Pregnancy rate per woman randomised.

Number of women achieving a clinical pregnancy (established with a human chorionic gonadotropin test in blood or urine and/or confirmed by ultrasound) divided by the number of women randomised.

2. Oocytes retrieved per woman randomised.

Number of women with at least one oocyte retrieved divided by the number of women randomised.

3. Embryo transfer per woman randomised.

Number of women with at least one embryo transferred divided by the number of women randomised.

4. Ampoules of gonadotrophin used.

The mean number of ampoules used per woman.

5. Adverse events (e.g. ovarian hyperstimulation syndrome).

Search methods for identification of studies

Electronic searches

The following electronic databases, trial registers and web sites were searched up until June 2009: The Menstrual Disorders and Subfertility Group (MDSG) Specialised Register of Controlled Trials (Appendix 1), MEDLINE (Appendix 2), EMBASE (Appendix 3), the Cochrane Central Register of Controlled Trials (Appendix 4), and PSYCINFO (Appendix 5).

The MEDLINE search was combined with the Cochrane highly sensitive search strategy for identifying randomised trials, which appears in the searching chapter of The Cochrane Handbook of Systematic Reviews of Interventions. The EMBASE search was combined with trial filters developed by the Scottish Intercollegiate Guidelines Network (SIGN) (http://www.sign.ac.uk/methodology/filters.html#random)

Other electronic sources of trials were included:
Trial registers for ongoing and registered trials - 'Current Controlled Trials' (http://www.controlled-trials.com/), 'ClinicalTrials.gov' a service of the US national Institutes of Health (http://clinicaltrials.gov/ct2/home) and 'The World Health Organisation International Trials Registry Platform search portal' (http://www.who.int/trialsearch/Default.aspx)
Citation indexes (http://scientific.thomson.com/products/sci/)

Conference abstracts in the ISI Web of Knowledge (http://isiwebofknowledge.com/)
LILACS database, as a source of trials from the Portuguese and Spanish speaking world (http://bases.bireme.br/cgibin/wxislind.exe/iah/online/?IsisScript=iah/iah.xis&base=LILACS&lang=i&form=F)
ClinicalStudyResults for clinical trial results of marketed pharmaceuticals (http://www.clinicalstudyresults.org/)
PubMed (http://www.ncbi.nlm.nih.gov/pubmed/) , the random control filter for PubMed will be taken from the searching chapter of The Cochrane Handbook of Systematic.Reviews of Interventions
OpenSIGLE database(http://opensigle.inist.fr/) and Google for grey literature

Searching other resources

The reference lists of articles retrieved by the search were hand searched and personal contact was made with experts in the field and with the manufacturers of growth hormone to obtain any additional relevant data. Any relevant journals and conference abstracts that are not covered in the MDSG register was hand-searched in liaison with the Trial Search Coordinator.

Data collection and analysis

Data collection and analysis was conducted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2008).

Selection of studies

One review author scanned retrieved searches for relevant titles and abstracts . The full text of all potentially eligible studies were retrieved. Two review authors independently examined the full text articles for compliance with the inclusion criteria and elected studies eligible for inclusion in the review. Authors corresponded with study investigators to clarify study eligibility (for example, with respect to participant eligibility criteria and allocation method). Disagreements as to study eligibility was resolved by discussion with a third author (AW).

Data extraction and management

Data was extracted from eligible studies using a data extraction form designed and pilot-tested by the authors. Where studies have multiple publications, the main trial report was used as the reference and additional details supplemented from secondary papers. Review authors corresponded with study investigators in order to resolve data queries.Two review authors (one a methodologist and one a topic area specialist) independently extracted the data and any disagreement between these reviewer authors was resolved by a third review author (AW).

Assessment of risk of bias in included studies

The included studies were assessed for risk of bias using the Cochrane risk of bias assessment tool to assess: sequence generation; allocation concealment; blinding of participants, providers and outcome assessors; completeness of outcome data; selective outcome reporting; and other potential sources of bias. Two authors assessed these six domains, with any disagreements resolved by discussion with a third author (AW). The conclusions are presented in the Risk of Bias table and incorporated into the interpretation of review findings by means of sensitivity analyses (see below). Where identified studies failed to report the primary outcomes of live birth, but did report secondary outcomes such as clinical pregnancy, informal assessment was undertaken as to whether those reporting the primary outcomes have typical values of the secondary outcomes.

Measures of treatment effect

For dichotomous data the numbers of events in the control and intervention groups of each study was used to calculate Peto odds ratios. For continuous data standard mean differences between treatment groups was calculated if all studies report exactly the same outcomes. If similar outcomes are reported on different scales the standardised mean difference was calculated. Ordinal data was treated as continuous data. 95% confidence intervals were presented for all outcomes.

Unit of analysis issues

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

Dealing with missing data

The data was analysed on an intention-to-treat basis as far as possible and attempts were made to obtain missing data from the original investigators. Where these are unobtainable, imputation of individual values was undertaken for the primary outcomes only. Live births were assumed not to have occurred in participants with unreported outcomes. When studies reported sufficient detail to calculate mean differences but no information on associated standard deviation (SD), the outcome will be assumed to have standard deviation equal to the highest SD from other studies within the same analysis. For other outcomes, only the available data was analysed. Any imputation undertaken was subjected to sensitivity analysis (see below).

Assessment of heterogeneity

The authors considered whether the clinical and methodological characteristics of the included studies were sufficiently similar for meta-analysis to provide a meaningful summary. Statistical heterogeneity was assessed by the measure of the I^2. An I^2 measurement greater than 50% indicates substantial heterogeneity (Higgins 2008) and where present was addressed through sensitivity and/or subgroup analysis.

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 studies and by being alert for duplication of data.

Data synthesis

The data from primary studies was combined using fixed effect models in the following comparisons:

1. Routine use of adjuvant growth hormone in IVF protocols.

2. Non-routine use of adjuvant growth hormone in IVF protocols in poor responders as defined by the study.

Subgroup analysis and investigation of heterogeneity

Subgroup analyses was conducted in the second comparison to determine the evidence within the following sub-groups:
1. Sub-optimal response following controlled ovarian stimulation.

2. Poor ovarian reserve as demonstrated by abnormal ovarian reserve tests.

Sensitivity analysis

Sensitivity analyses were conducted for the primary outcomes to determine whether the conclusions are robust to arbitrary decisions made regarding the eligibility and analysis. These analyses considered whether conclusions would have differed if:
1. Eligibility were restricted to studies without high risk of bias;
2. Studies with outlying results had been excluded;
3. Alternative imputation strategies had been adopted;
4. A random effects model had been adopted.

RESULTS

Description of studies

Results of the search

Twenty-three randomised controlled trials were identified from the search strategy, ten of which were included in the meta-analysis.

Included studies

Ten trials were included in the meta-analysis. These are presented as 13 sets of data (Bergh 1994; Dor 1995; Hazout 2003; Hazout 2003 4 IU; Hazout 2003 8 IU; Kueuk 2008;Owen 1991; Suikkari 1996 ;Suikkari 1996 12 IU; Suikkari 1996 4 IU; Tapanainen 1992; Tesarik 2005;Younis 1992; Zhuang 1994). Further descriptive details about the included studies are provided in Characteristics of included studies table. All included trails were published reports (full papers or conference abstracts).

Routine use of growth hormone as an adjuvant in IVF protocols

Two trials concerned the routine use of growth hormone as an adjuvant in IVF protocols (Tapanainen 1992; Younis 1992).

Non-routine use of growth hormone as an adjuvant in IVF protocols in women considered poor responders

The remaining eight trials considered the non-routine use of adjuvant growth hormone in IVF protocols for subfertile couples subgrouped as:-

1. Poor responders as described by the study (Bergh 1994; Dor 1995; Kueuk 2008; Owen 1991; Suikkari 1996; Hazout 2003; Tesarik 2005; Zhuang 1994).

2. Poor responders because of previous sub-optimal response following controlled ovarian stimulation (Bergh 1994; Dor 1995; Kueuk 2008; Owen 1991; Suikkari 1996).

3. Poor responders because of poor ovarian reserve as demonstrated by abnormal ovarian reserve tests - no trials identified.

Participants

Ten trials with a total of 440 subfertile couples were included in the meta-analysis. The number of couples included in each trial ranged from 14 (Dor 1995) to 61 (Kueuk 2008). All studies detailed the age ranges and included women aged 30 to 40 years old with exception of Tesarik 2005 who included women aged forty years or older. Exclusion criteria were not stated in Dor 1995, Hazout 2003, Owen 1991, Suikkari 1996, Tapanainen 1992 and Zhuang 1994. The remaining trials based their exclusion criteria on serum FSH concentrations (Kueuk 2008; Tesarik 2005), obesity (Bergh 1994), ovarian pathology (Bergh 1994), endometriosis (Bergh 1994), severe intercurrent illness (Bergh 1994) and unsatisfactory sperm quality (Tesarik 2005).

Interventions

There was no consistency as to the dose or timing of growth hormone administration (Please see Characteristics of included studies table). The dose of growth hormone ranged from 8IU (Tesarik 2005) to 24IU (Owen 1991; Tapanainen 1992). Both Hazout 2003 and Suikkari 1996 conducted a multi-arm trail comparing two different doses of growth hormone to a control arm. For the purposes of comparison the separate arms were allocated two different study IDs. The timing of growth hormone administration varied between studies from daily administration to alternate days.

Outcomes

Primary outcome measure

Live birth rates were reported by seven of the included trials (Dor 1995; Owen 1991; Tapanainen 1992; Tesarik 2005; Suikkari 1996; Younis 1992; Zhuang 1994).

Secondary outcomes measures

Pregnancy rates were reported by eight of the included trials (Bergh 1994; Hazout 2003; Kueuk 2008; Owen 1991; Suikkari 1996; Tesarik 2005; Younis 1992; Zhuang 1994) . Two trials reported the number of oocytes retrieved per woman (Bergh 1994; Younis 1992). Three trials reported the embryo transfer rate (Bergh 1994; Younis 1992; Suikkari 1996). Two trials reported the mean number of ampoules of gonadotrophin used per woman randomised (Tapanainen 1992; Younis 1992). Adverse effects were reported by four of the trials (Owen 1991; Suikkari 1996; Tapanainen 1992; Younis 1992).

Excluded studies

Thirteen trials were excluded outlined in the Characteristics of excluded studies table. Six trials were excluded because the participants did not undergo IVF (Blumenfeld 1994; Busacca 1996; Homburg 1990b; Homburg 1995; Jacobs 1995; Landolfi 1994; Tulandi 1993). A further trial were excluded because growth hormone was not the intervention (Howles 1999; Schoolcraft 1997). Three trials were excluded because the study was not truly randomised (Homburg 1990; Owen 1991b; Rinehart 1999).

Risk of bias in included studies

Please refer to Characteristics of included studies table, Figure 1 and Figure 2.

Figure 1. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

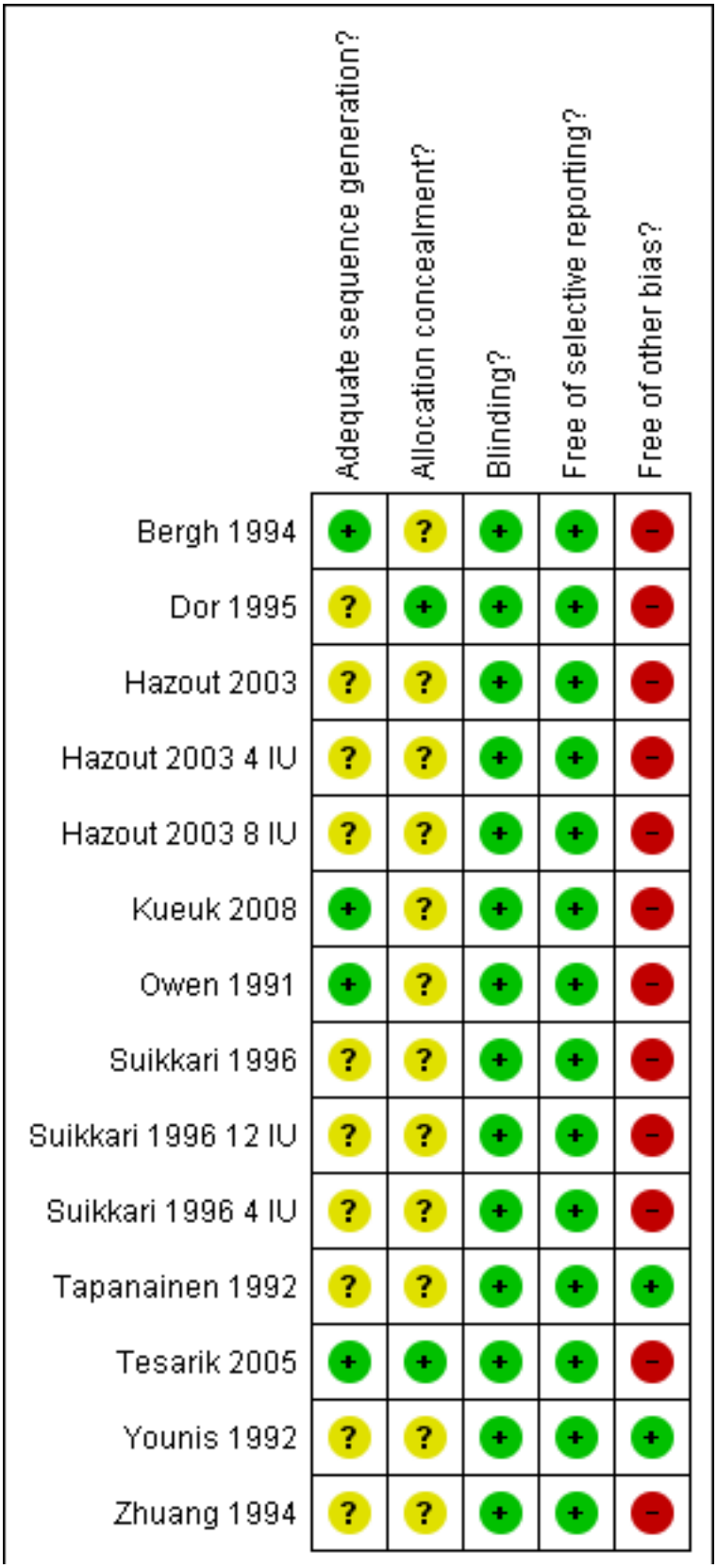


Figure 1. (Continued)

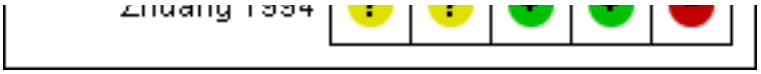
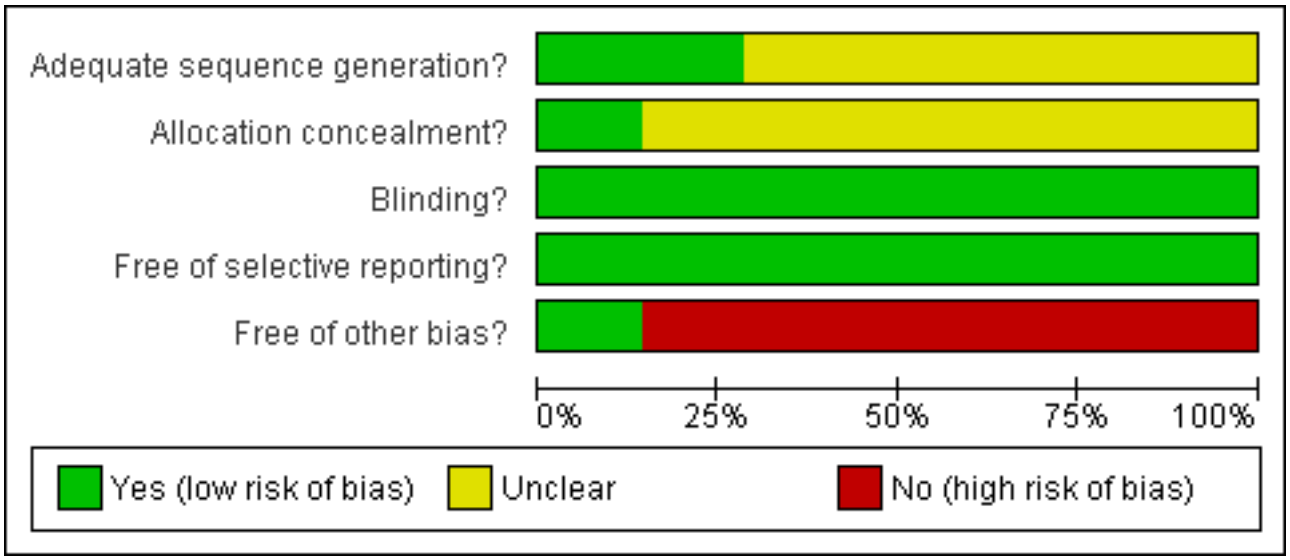


Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.



Allocation

The method of randomisation was clearly stated in five trials (Kueuk 2008; Tapanainen 1992, Tesarik 2005, Suikkari 1996 & Younis 1992). The method of randomisation was unclear in the remaining trails.

Allocation concealment was unclear in all the included trails, except Kueuk 2008, Tapanainen 1992, Tesarik 2005 and Younis 1992.

Blinding

One trial (Zhuang 1994) reported single blinding, seven trials were double blinded (Bergh 1994; Dor 1995; Hazout 2003; Owen 1991; Suikkari 1996; Tapanainen 1992; Tesarik 2005) and a two trials reported triple-blinded (Kueuk 2008; Younis 1992).

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. The remaining trials reported no losses. Several study authors replied to requests for additional information including Bergh 1994, Dor 1995, Tapanainen 1992, Younis 1992 and Zhuang 1994.

Selective reporting

No selective reporting was identified.

Other potential sources of bias

A number of trials received a free supply of growth hormone from the manufacture including Owen 1991, Tapanainen 1992 and Younis 1992. One trial reported a withdrawal or cycle cancellation rate greater than 10% of participants (Suikkari 1996). Owen 1991 did not describe the nature of the placebo.

Effects of interventions

The effects of adjuvant growth hormone in IVF protocols are reported in the following populations:-

1. Women who are not considered poor responders.

2. Women who are considered poor responders as defined by the study.

3. Women who are considered poor responders because of a previous sub-optimal response following controlled ovarian stimulation.

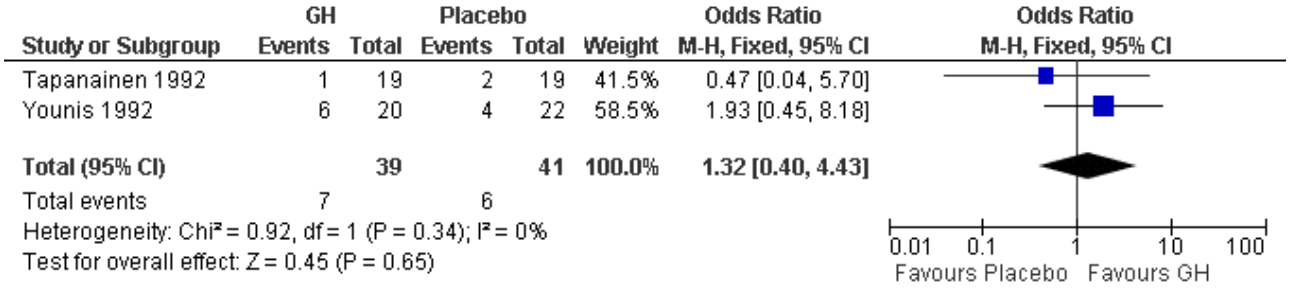
The use of adjuvant growth hormone in IVF protocols in women who are not considered poor responders.

Main outcome measure

Live birth rate per woman randomised

Two trials reported the live birth rate per woman randomised (Tapanainen 1992; Younis 1992). Meta-analysis demonstrated no difference in the use growth hormone adjuvant in IVF protocols when compared to standard IVF protocols OR 1.32, 95% CI 0.40 to 4.43 ; 80 participants , 2 trials Analysis 1.1 (Figure 3).

Figure 3. Forest plot of comparison: 1 Growth hormone versus placebo: Routine use, outcome: 1.1 Live birth rate per woman randomised.

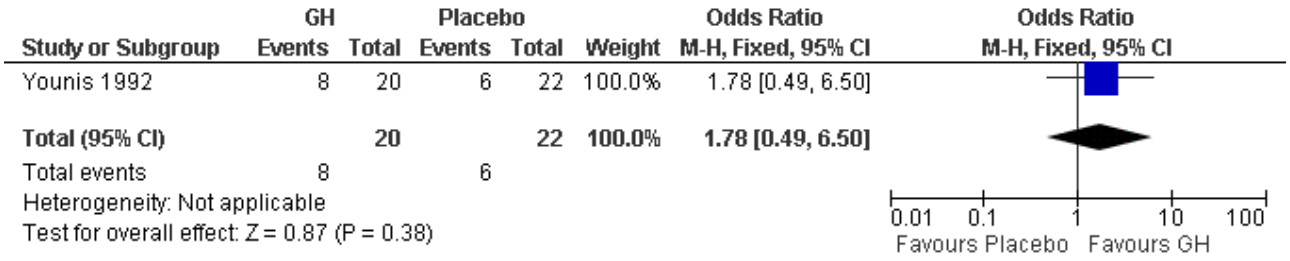


Additional outcomes measures

Pregnancy rate per woman randomised

One trial reported the pregnancy rate per woman randomised (Younis 1992). Analysis demonstrated no difference in the use growth hormone adjuvant in IVF protocols when compared to standard IVF protocols OR 1.78, 95% CI 0.49 to 6.50 ; 42 participants , 1 trials , Analysis 1.2 (Figure 4).

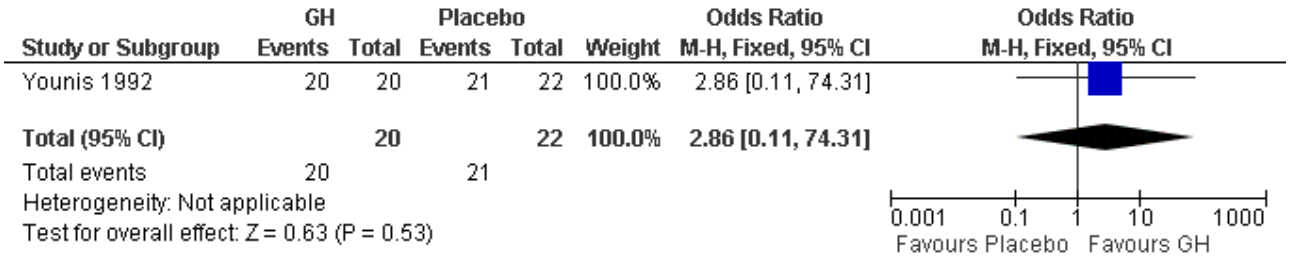
Figure 4. Forest plot of comparison: 1 Growth hormone versus placebo: Routine use, outcome: 1.2 Pregnancy rate per woman randomised.



Oocytes retrieved per woman randomised.

One trial reported the live birth rate per woman randomised (Younis 1992). Analysis demonstrated no difference in the use growth hormone adjuvant in IVF protocols when compared to standard IVF protocols OR 2.86, 95% CI 0.11 to 74.31 ; 42 participants , 1 trial Analysis 1.3 (Figure 5).

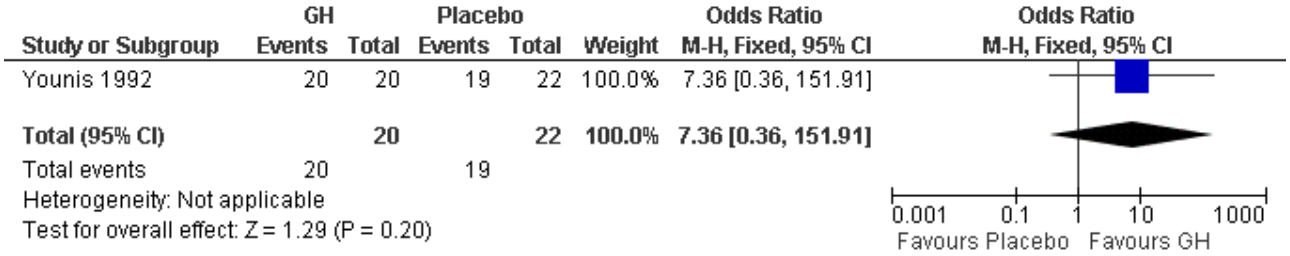
Figure 5. Forest plot of comparison: 1 Growth hormone versus placebo: Routine use, outcome: 1.3 Number of women with at least one oocyte retrieved per woman randomised.



Embryo transfer per woman randomised

One trial reported the number of embryos transferred per woman randomised (Younis 1992). Analysis demonstrated no difference in the use growth hormone adjuvant in IVF protocols when compared to standard IVF protocols OR 7.36, 95% CI 0.36 to 151.91 ; 42 participants , 1 trial Analysis 1.4 (Figure 6).

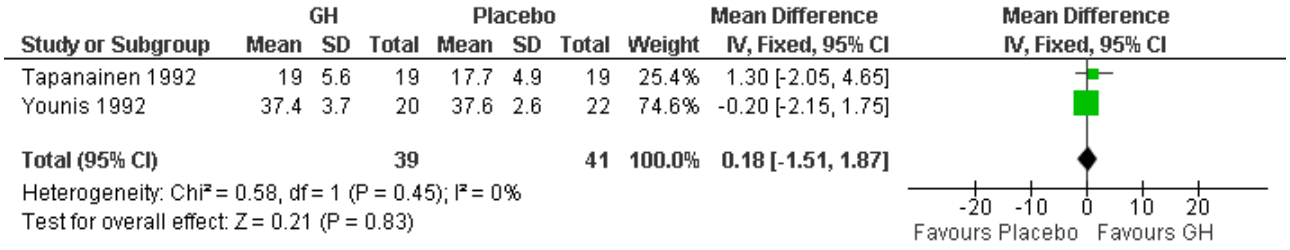
Figure 6. Forest plot of comparison: 1 Growth hormone versus placebo: Routine use, outcome: 1.4 Embryo transfer per woman randomised.



Mean ampoules of gonadotrophin used.

Two trials (Tapanainen 1992; Younis 1992) reported the mean number of ampoules of gonadotrophin used per woman randomised. Meta-analysis demonstrated no difference in the use growth hormone adjuvant in IVF protocols when compared to standard IVF protocols OR 0.18, 95% CI -1.53 to 1.87 ; 80 participants , 2 trials Analysis 1.5 (Figure 7).

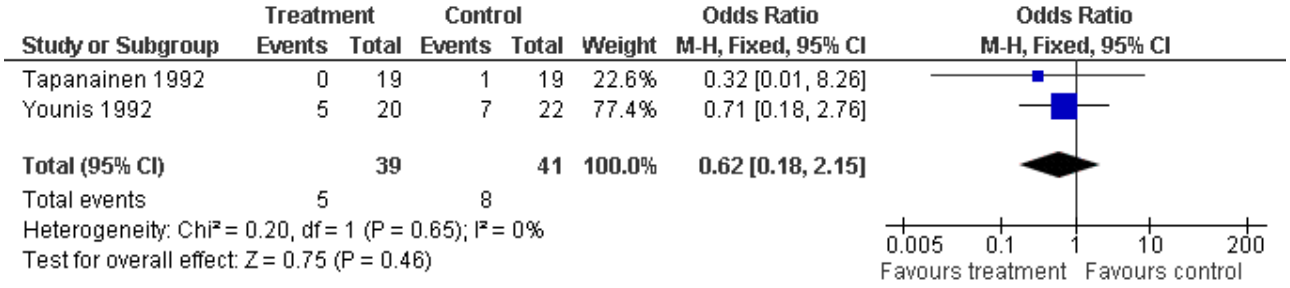
Figure 7. Forest plot of comparison: 1 Growth hormone versus placebo: Routine use, outcome: 1.5 Mean number of ampoules of gonadotrophin used per woman.



Adverse events

Two trials reported the occurrence of adverse events (Tapanainen 1992; Younis 1992). Meta-analysis demonstrated no difference in the use growth hormone adjuvant in IVF protocols when compared to standard IVF protocols OR 0.62, 95% CI 0.18 to 2.15 ; 80 participants , 2 trials Analysis 1.6 (Figure 8).

Figure 8. Forest plot of comparison: 1 Growth hormone versus placebo: Routine use, outcome: 1.6 Adverse Events.



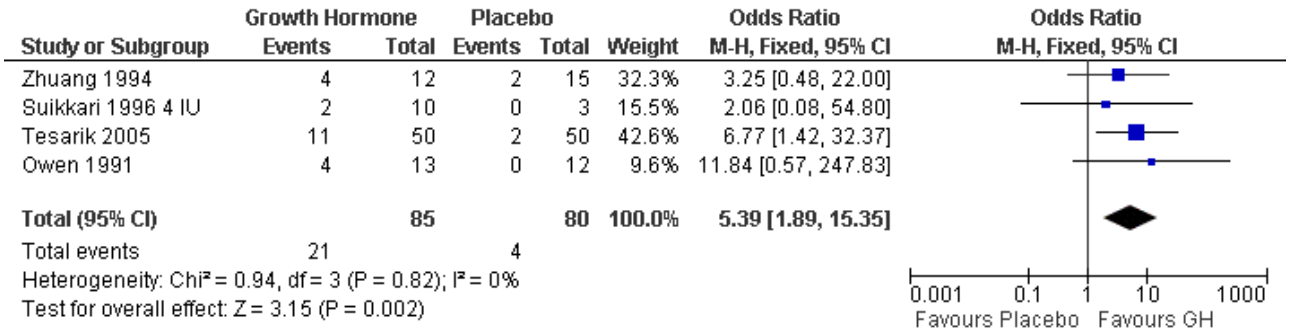
The use of adjuvant growth hormone in IVF protocols in women who are considered poor responders as defined by the included study.

Main outcome measure

Live birth rate per woman randomised

Four trials reported the live birth rate per woman randomised (Owen 1991; Suikkari 1996 4 IU; Tesarik 2005; Zhuang 1994). Meta-analysis demonstrated a statistically significant difference favouring the use growth hormone adjuvant in IVF protocols when compared to IVF protocols in women with a poor prognosis as defined by the included study OR 5.39, 95% CI 1.89 to 15.35 ; 165 participants , 4 trials , Analysis 2.1 (Figure 9).

Figure 9. Forest plot of comparison: 2 Growth hormone versus placebo: Poor responder as defined by the study, outcome: 2.1 Live birth rate per woman randomised.

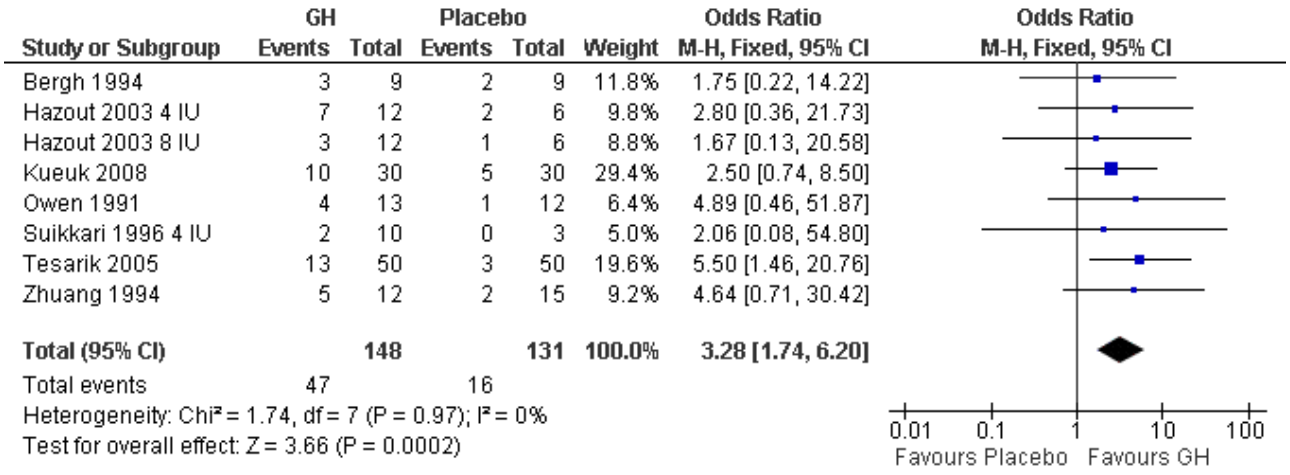


Additional outcomes measures

Pregnancy rate per woman randomised

Seven of the trials reported the pregnancy birth rate per woman randomised (Bergh 1994; Hazout 2003 4 IU; Hazout 2003 8 IU; Kueuk 2008; Owen 1991; Suikkari 1996 4 IU; Tesarik 2005; Zhuang 1994). Meta-analysis demonstrated a statistically significant difference favouring the use growth hormone adjuvant in IVF protocols when compared to IVF protocols in women with a poor prognosis as defined by the included study OR 3.28, 95% CI 1.74 to 6.20 ; 279 participants , 7 trials , Analysis 2.2 (Figure 10).

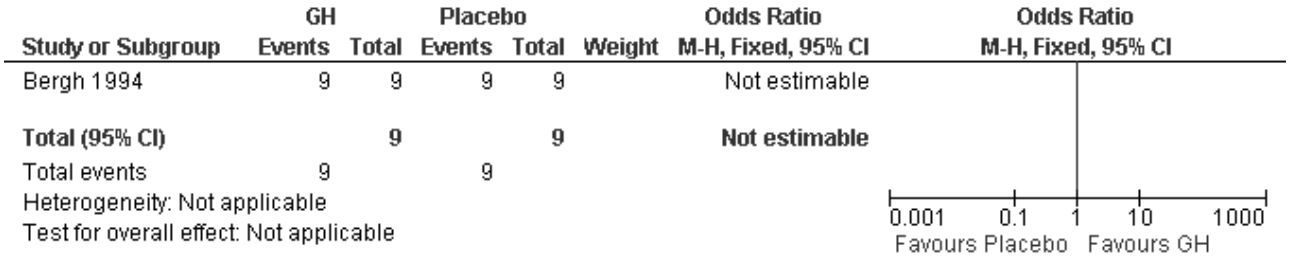
Figure 10. Forest plot of comparison: 2 Growth hormone versus placebo: Poor responder as defined by the study, outcome: 2.2 Pregnancy rate per woman randomised.



Oocytes retrieved per woman randomised

One trial reported the oocytes retrieved per woman randomised (Bergh 1994). Analysis could not be performed because the same number of events occurred in each group, and the groups involved the same number of couples Analysis 3.3 (Figure 11).

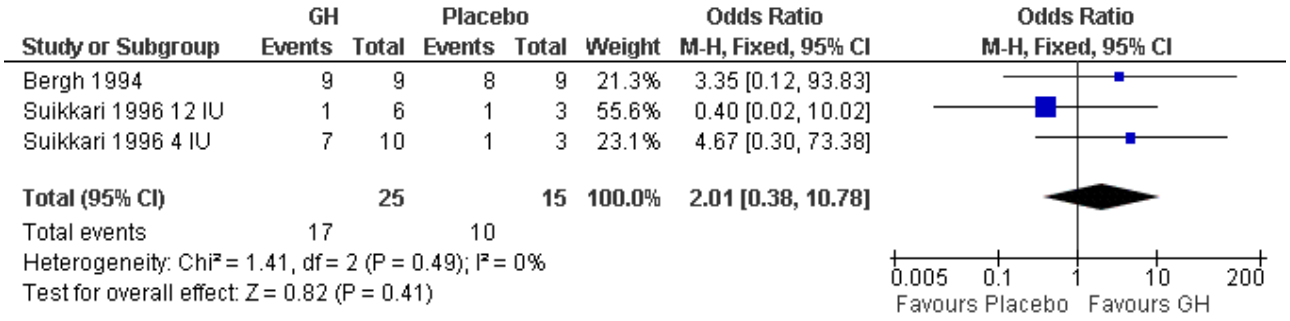
Figure 11. Forest plot of comparison: 3 Growth hormone versus placebo: Poor responder as demonstrated by previous sub-optimal response following controlled ovarian stimulation, outcome: 3.3 Number of women with at least one oocyte retrieved per woman randomised.



Embryo transfer per woman randomised

Two trials reported the number of embryos transferred per woman randomised (Bergh 1994; Suikkari 1996 4 IU; Suikkari 1996 12 IU). Meta-analysis demonstrated no difference in the use growth hormone adjuvant in IVF protocols when compared to IVF protocols in women with a sub-optimal response following controlled ovarian stimulation OR 2.01, 95% CI 0.38 to 10.78 ; 40 participants , 2 trials , Analysis 3.4 (Figure 12).

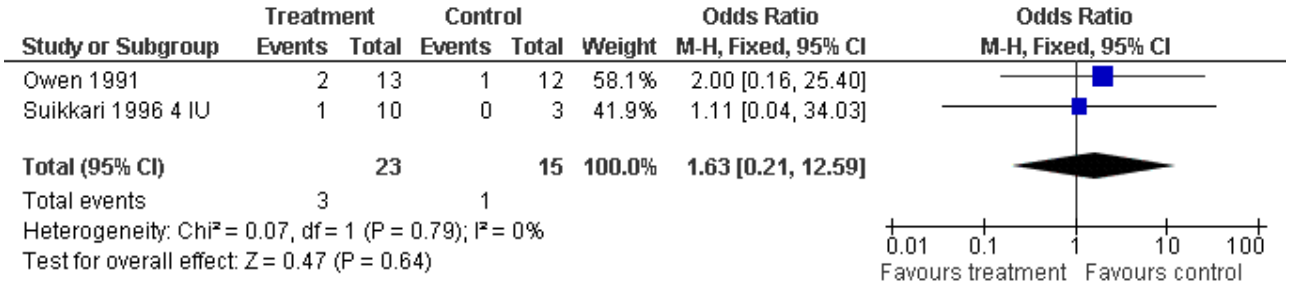
Figure 12. Forest plot of comparison: 3 Growth hormone versus placebo: Poor responder as demonstrated by previous sub-optimal response following controlled ovarian stimulation, outcome: 3.4 Embryo transfer per woman randomised.



Adverse events

One trial reported the oocytes retrieved per woman randomised (Owen 1991). Analysis demonstrated no difference in the use growth hormone adjuvant in IVF protocols when compared to IVF protocols in women with a sub-optimal response following controlled ovarian stimulation OR 2.00, 95% CI 0.16 to 25.40 ; 116 participants , 1 trial , Analysis 3.5 (Figure 13).

Figure 13. Forest plot of comparison: 3 Growth hormone versus placebo: Poor responder as demonstrated by previous sub-optimal response following controlled ovarian stimulation, outcome: 3.5 Adverse Events.



Sensitivity Analysis

One trial reported a withdrawal or cycle cancellation rate greater than 10% of participants (Suikkari 1996). A sensitivity analysis was performed to detect whether the inclusion of this randomised controlled trials affected the results. There was no difference in results when the meta-analysis was re-calculated.

The use of adjuvant growth hormone in IVF protocols in women who are considered poor responders because of a

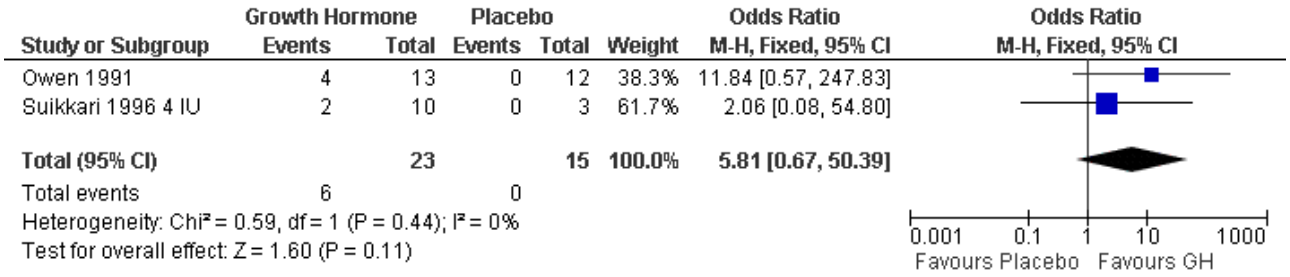
previous *sub-optimal response following controlled ovarian stimulation*

Main outcome measure

Live birth rate per woman randomised

Two trials reported the live birth rate per woman randomised (Owen 1991; Suikkari 1996 4 IU). Meta-analysis demonstrated no difference in the use growth hormone adjuvant in IVF protocols when compared to IVF protocols in women with a sub-optimal response following controlled ovarian stimulation OR 5.81, 95% CI 0.67 to 50.39 ; 38 participants , 2 trials , Analysis 3.1 (Figure 14).

Figure 14. Forest plot of comparison: 3 Growth hormone versus placebo: Poor responder as demonstrated by previous sub-optimal response following controlled ovarian stimulation, outcome: 3.1 Live birth rate per woman randomised.

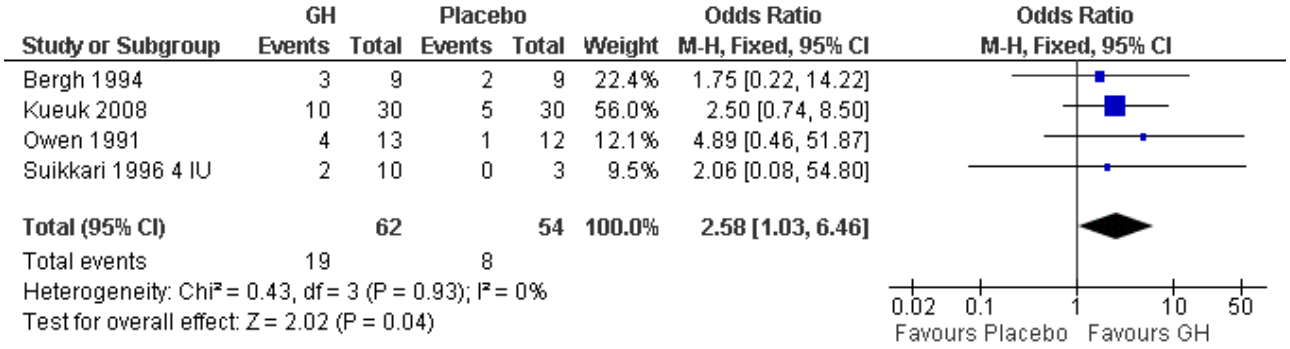


Additional outcomes measures

Pregnancy rate per woman randomised

Four of the trials reported the pregnancy birth rate per woman randomised (Bergh 1994; Kueuk 2008; Owen 1991; Suikkari 1996 4 IU). Meta-analysis demonstrated a statistically significant difference favouring the use growth hormone adjuvant in IVF protocols when compared to IVF protocols in women with a sub-optimal response following controlled ovarian stimulation OR 2.58, 95% CI 1.03 to 6.46 ; 116 participants , 4 trials , Analysis 3.2 (Figure 15).

Figure 15. Forest plot of comparison: 3 Growth hormone versus placebo: Poor responder as demonstrated by previous sub-optimal response following controlled ovarian stimulation, outcome: 3.2 Pregnancy rate per woman randomised.



Oocytes retrieved per woman randomised

One trial reported the oocytes retrieved per woman randomised (Bergh 1994). Analysis could not be performed because the same number of events occurred in each group, and the groups involved the same number of couples Analysis 3.3 (Figure 11).

Embryo transfer per woman randomised

Two trials reported the number of embryos transferred per woman randomised (Bergh 1994; Suikkari 1996 4 IU; Suikkari 1996 12 IU). Meta-analysis demonstrated no difference in the use growth hormone adjuvant in IVF protocols when compared to IVF protocols in women with a sub-optimal response following controlled ovarian stimulation OR 2.01, 95% CI 0.38 to 10.78 ; 40 participants , 2 trials , Analysis 3.4 (Figure 12).

Adverse events

One trial reported the oocytes retrieved per woman randomised (Owen 1991). Analysis demonstrated no difference in the use growth hormone adjuvant in IVF protocols when compared to IVF protocols in women with a sub-optimal response following controlled ovarian stimulation OR 2.00, 95% CI 0.16 to 25.40 ; 116 participants , 1 trial , Analysis 3.5 (Figure 13).

Sensitivity Analysis

One trial reported a withdrawal or cycle cancellation rate greater than 10% of participants (Suikkari 1996). A sensitivity analysis was

performed to detect whether the inclusion of this randomised controlled trials affected the results. There was no difference in results when the meta-analysis was re-calculated.

DISCUSSION

Summary of main results

This review was undertaken to establish the role of growth hormone adjuvant therapy for IVF in improving IVF outcomes particularly in those women who are considered poor responders. Results of this meta-analysis demonstrated no difference in IVF outcome measures and adverse events in the routine use of growth hormone adjuvant therapy in IVF. However, meta-analysis demonstrated a statistically significant difference in both live birth rates and pregnancy rates favouring the use of growth hormone adjuvant therapy in IVF in women who are considered poor responders without increasing adverse events (Analysis 2.1, Analysis 2.2, Analysis 3.5). Although these results have to be interpreted with caution, the trials included in the meta-analysis were few and of small sample size.

Defining which sub-group or sub-groups of poor responder benefited the most from growth hormone adjuvant therapy in IVF proved challenging due to the diverse definitions of poor responder used by the included studies. Sub-group analysis demonstrated a statistically significant difference in pregnancy rates favouring the use of growth hormone adjuvant in IVF in women who are considered poor responders because of previous sub-optimal response following controlled ovarian stimulation without increasing adverse events. Although these results have to be interpreted with caution, the trials included in the meta-analysis were few and of small sample size. (Analysis 3.2, Analysis 3.5). However, meta-analysis demonstrated no difference in the other IVF outcome measures, including live birth rate, in the use of growth hormone adjuvant in IVF in these women (Analysis 3.1).

Overall completeness and applicability of evidence

Meta-analysis demonstrated a statistically significant difference in both live birth rates and pregnancy rates favouring the use of growth hormone adjuvant in IVF in women who are considered poor responders without increasing adverse events (Analysis 2.1, Analysis 2.2, Analysis 3.5). Sub-group analysis demonstrated a statistically significant difference in pregnancy rates favouring the use of growth hormone adjuvant in IVF in women who are considered poor responders because of previous sub-optimal response following controlled ovarian stimulation without increasing adverse events (Analysis 3.2, Analysis 3.5). The width of the confidence interval should be taken into account when considering the results. The wide confidence interval emphasises the lack of available evidence, the included trials were few in number and of small sample size for the primary outcome, live birth rates, in the sub-group analysis.

Adverse effects were also considered as a secondary outcome. Frequency of reporting of adverse effects varied between the trials and different adverse effects were recorded. In general adverse effects were not well documented making the meta-analysis result fairly unreliable as emphasised by the wide confidence intervals. For those that were documented, growth hormone adjuvant in IVF protocols did not significantly reduce the incidence of any of the adverse effects in either group.

The causative factors for poor response to controlled controlled ovarian hyperstimulation 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. Therefore we have been unable to identify the particular sub-group of poor responders who would benefit the most from growth hormone augmentation in IVF protocols in terms of live birth rates.

Quality of the evidence

Of the ten randomised controlled trials included in the review differences in participant number, cause of subfertility, treatment protocol and outcomes measured all varied considerably between the trials. There was no uniformity of dose and timing of the intervention. A large scale trial with a standardised treatment protocol and intervention protocol is required (Please refer to Implications for research section).

There was a lack of large high quality trials comparing growth hormone to placebo in ovarian stimulation protocols in IVF cycles. If a new large randomised controlled trial was performed the results of this review could be significantly different.

Potential biases in the review process

Critical to the limitation of bias in these included randomised controlled trials are the randomisation method and allocation concealment strategy deployed, both of which provide similar comparison groups achieving a balance of both known and unknown factors that may influence the outcome. Six of the ten included trials did not state explicitly the method of randomisation used. Failure to report how women were randomised does not allow us to evaluate the adequacy of the method deployed. Furthermore, seven of the ten included randomised controlled trials did not state a method of allocation concealment. This could undermine further the quality of the included randomised controlled trial. With poor methods of concealing the allocation, knowledge of the treatment codes may be gained in advance, increasing the likelihood of selection bias (Li 2005).

One trial reported a withdrawal or cycle cancellation rate greater than 10% of participants (Suikkari 1996). A sensitivity analysis was performed to detect whether the inclusion of this randomised controlled trial affected the results. There was no difference in results when the meta-analysis was re-calculated.

Owen 1991 did not describe the nature of the placebo which could have lead to bias if the placebo had an action mechanism similar to growth hormone

Agreements and disagreements with other studies or reviews

Currently no national or international guidelines recommend the routine use of growth hormone augmentation in IVF protocols. However a recent systematic review and meta-analysis concerning the evaluation of strategies to improve the pregnancy rates in poor responders undergoing IVF concluded that there was some evidence to suggest the addition of growth hormone could improve live birth rates but further research was required (Kyrou 2009). Kyrou and colleagues analysis and conclusions broadly agree with our own.

Other studies have reported mixed results. Rinehart and colleagues reported that growth hormone did not significantly increase the pregnancy rates for women who were defined as 'poor responders' to gonadotrophin stimulation on previous IVF cycles. The study, which was non-randomised in design, and defined a poor responder as one whose follicles did not reach 18mm in diameter or an E2 of less than 500 pg/ml (Rinehart 1999). In a cross-over trial Blumenfeld 1996 (Blumenfeld 1996) examined the role of growth hormone augmentation in poor responders to gonadotrophin stimulation on previous IVF cycles. Interestingly the study concluded that the addition of growth hormone was only beneficial in terms of pregnancy and live birth rates in women who were not 'endocrinologically normal' as illustrated by being identified as clonidine positive.

Other studies have evaluated the potential for the use of growth hormone releasing factor. Growth hormone releasing factor may also have a role in ovulation induction for IVF. Pituitary growth hormone secretion is controlled by growth hormone releasing factor which may also have a direct effect on the ovary. A pilot study demonstrated that growth hormone releasing factor was associated with improvement in ovarian response and resulted in slight increases in recruited follicles and retrieved oocytes (Hughes 1994). Growth hormone releasing factor seems to have a similar effect as growth hormone on ovarian response (Howles 1999). Howles and colleagues performed a randomised controlled trial and reported that growth hormone releasing factor did not significantly increase the pregnancy or live birth rates for women who demonstrate as poor responders to gonadotrophin stimulation on previous IVF cycles.

AUTHORS' CONCLUSIONS

Implications for practice

In women who are not considered poor responders undergoing in IVF there is no evidence from randomised controlled trials to support the use of growth hormone. In women who are considered poor responders the use of growth hormone has been shown to significantly improve live birth and pregnancy rates. Although the exact sub-group of poor responders who would benefit from growth hormone augmentation needs to be identified. The result needs to be interpreted with caution, the included trials were few in number and small with significant clinical heterogeneity.

Implications for research

With regards to women who are known poor responders to IVF, a multi-centre randomised double blinded trial is warranted to investigate the effect of growth hormone augmentation. Key elements of design should include power calculation to ensure the minimum number of participants needed for a significant result are included, the standardisation of controlled controlled ovarian hyperstimulation protocols, dose of growth hormone and the definition of a poor responder - <4 oocytes retrieved in a previous IVF attempt might be appropriate. The primary outcome of live birth rate should be measured. Only by considering such outcomes can this therapy be truly tested. Also, adverse effects, for example OHSS and miscarriage, should be routinely reported. Given the high hormone cost of treatment, one component of this study should also be an economic evaluation.

ACKNOWLEDGEMENTS

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CHARACTERISTICS OF STUDIES

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

Bergh 1994

Methods	Randomisation: Using a computerised list women were randomised to one of four arms. Allocation Concealment: unclear. Blinding: double-blind. Trial Design: Parallel. Analysis: power calculation was performed, no intention to treat analysis performed. Study Setting: Multicentre study - three IVF programs in Sweden. Withdrawals: two women (< 10%). Cancelled cycles: one woman in placebo group (<10%).
Participants	Number of women: 18 (nine growth hormone, nine placebo). IVF previous poor responders: at least two failed cycles with < five oocytes. Regular menstrual cycle, normal FSH, LH, PRL and ovarian ultrasound. BMI less than or equal to 28, age 25 to 38 years. Normal semen quality, (WHO criteria).
Interventions	Intervention: growth hormone 0.1 IU/kg daily subcutaneous. Treatment Protocol: seven days pretreatment with placebo; pre-treatment was started after ovarian down regulation was established (achieved with BA beginning on day one or two of cycle administered intranasally six/day or in a few cases by s/c injection two per day for a total dose of 1.2mg/day. Treatment with BA continued during the pre-treatment and stimulation periods). Ovarian stimulation was performed by hMG 225 to 300 IU/day IM and/or FSH in a dose of 75 to 300 IU/day for 10 to 25 days. Protocol, n=10 women and cycles. Dose of human chorionic gonadotropin: 10000 IU when at least one follicle was >18mm diameter and there had been seven to eight days of continued rise of serum E2.
Outcomes	Pregnancy rate, oocyte retrieval and embryo transfer.

Bergh 1994 *(Continued)*

Notes	This trial involved four treatment arms (and 40 women) but only data comparing growth hormone use in conjunction with GnRHa / hMG vs standard treatment (groups I, II) were included. Groups III and IV involved growth hormone pretreatment and were excluded. The placebo used was NaCl.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Randomisation: Using a computerised list women were randomised to one of four arms
Allocation concealment?	Unclear risk	Not stated within the text
Blinding? All outcomes	Low risk	Double-blinded
Free of selective reporting?	Low risk	There is no indication the study has reported outcomes selectively
Free of other bias?	High risk	The study does not report on adverse effects or multiple pregnancies

Dor 1995

Methods	Randomisation: stated as randomised. Allocation concealment: sealed opaque sequentially numbered, identical envelopes. Blinding: double-blind. Trial Design: Parallel. 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: 14 (seven growth hormone, seven placebo). Inclusion Criteria: IVF previous poor responders defined as E2 < 500 pg/ml on day of human chorionic gonadotropin, < three oocytes retrieved. Normal serum FSH, LH levels. Cause of Subfertility: ovulatory disorders or tubal factor infertility. Age: 30 to 45.
Interventions	Intervention: growth hormone 18 IU SC on days two, four, six, and eight of stimulation. Treatment Protocol: Short GnRHa/FSH/hMG protocol used, SC on cycle days two, four, six, and eight. Dose of human chorionic gonadotropin: 10000 IU when serum oestradiol was >200pg/ml and at least two follicles were > 18mm in diameter.
Outcomes	Pregnancy rate.
Notes	Mannitol chosen as placebo because "no known ovarian effects."

Risk of bias

Bias	Authors' judgement	Support for judgement

Dor 1995 *(Continued)*

Adequate sequence generation?	Unclear risk	Stated as 'randomised' no other details
Allocation concealment?	Low risk	Sealed opaque sequentially numbered, identical envelopes
Blinding? All outcomes	Low risk	Double blinded
Free of selective reporting?	Low risk	There is no indication the study has reported outcomes selectively
Free of other bias?	High risk	No adverse effects reported

Hazout 2003

Methods	Randomisation: stated as randomised. Allocation concealment: unclear. Blinding: double. Intention to treat analysis: not performed. Power calculation: not performed. Study setting: single centre - Paris, France. Withdrawals: none. Cancelled cycles: <10%.
Participants	Number of women n = 35 (12 growth hormone 4IU, 11 growth hormone 8IU, 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.
Interventions	Intervention: four or eight IU sub cutaneous. Induction protocol: unclear. Dose of human chorionic gonadotropin: 1000 IU IM when at least two follicles were >16mm in diameter.
Outcomes	Pregnancy rate.
Notes	Thirty-five women in total were included in Hazout 2003 and they were divided into three groups, placebo, growth hormone four IU and growth hormone eight IU. Since only two groups could be compared for the table of comparisons the two growth hormone 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.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Stated as randomised. No other details
Allocation concealment?	Unclear risk	Not stated within the text
Blinding? All outcomes	Low risk	Double blinded

Hazout 2003 *(Continued)*

Free of selective reporting?	Low risk	There is no indication the study has reported outcomes selectively
Free of other bias?	High risk	No adverse effects reported

Hazout 2003 4 IU

Methods	Randomisation: stated as randomised. Allocation concealment: unclear. Blinding: double. Intention to treat analysis: not performed. Power calculation: not performed. Study setting: single centre - Paris, France. Withdrawals: none. Cancelled cycles: <10%
Participants	Number of women n = 35 (12 growth hormone four IU, 11 growth hormone 8IU, 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.
Interventions	Intervention: four or eight IU sub cutaneous. Induction protocol: unclear. Dose of human chorionic gonadotropin: 1000 IU IM when at least two follicles were >16mm in diameter.
Outcomes	Pregnancy rate.
Notes	Same trial as Hazout 2003 but refers to women randomised to growth hormone four IU treatment arm.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Stated as randomised
Allocation concealment?	Unclear risk	Not stated within the text
Blinding? All outcomes	Low risk	Doubleblinded
Free of selective reporting?	Low risk	There is no indication the study has reported outcomes selectively
Free of other bias?	High risk	No adverse effects reported

Hazout 2003 8 IU

Methods	Randomisation: stated as randomised. Allocation concealment: unclear.

Hazout 2003 8 IU *(Continued)*

	Blinding: double. Intention to treat analysis: not performed. Power calculation: not performed. Study setting: single centre - Paris, France. Withdrawals: none. Cancelled cycles: <10%.
Participants	Number of women n = 35 (12 growth hormone four IU, 11 growth hormone eight 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.
Interventions	Intervention: four or eight IU sub cutaneous. Induction protocol: unclear. Dose of human chorionic gonadotropin: 1000 IU IM when at least two follicles were >16mm in diameter.
Outcomes	Pregnancy rate.
Notes	Same trial as Hazout 2003. but refers to women randomised to growth hormone 8 IU treatment arm.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Stated as randomised
Allocation concealment?	Unclear risk	Not stated within the text
Blinding? All outcomes	Low risk	Double blinded
Free of selective reporting?	Low risk	There is no indication the study has reported outcomes selectively
Free of other bias?	High risk	No adverse effects reported

Kueuk 2008

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 growth hormone, 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	Intervention: growth hormone 12IU sub cutaneous from day 21 of preceding cycle along with GnRHa, until the day of human chorionic gonadotropin. Treatment Protocol: Long GnRHa/FSH/hMG protocol used. Dose of human chorionic gonadotropin: 10000 IU when sat least 1 follicle was > 17mm in diameter.
Outcomes	Clinical pregnancy.

Kueuk 2008 *(Continued)*

Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Computer generated randomisation
Allocation concealment?	Unclear risk	Sealed envelopes. No details as to whether opaque
Blinding? All outcomes	Low risk	Triple blinded
Free of selective reporting?	Low risk	There is no indication the study has reported outcomes selectively
Free of other bias?	High risk	No adverse effects reported

Owen 1991

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 growth hormone, 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. Cause of subfertility: 18 of 25 women found to have polycystic ovaries on ultrasound. Age: <38
Interventions	Intervention: growth hormone 24 IU intramuscular (IM), days 1, 3, 5, 7, 9, and 11 of hMG treatment, during long GnRHa protocol, vs placebo given IM on same cycle days as active treatment groups. 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 growth hormone treatment. The data from Jacobs 1995 is also presented in Owen 1991.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Two randomisation lists were made with 20 women on each list and block randomised into blocks of four
Allocation concealment?	Unclear risk	Not stated within the text
Blinding? All outcomes	Low risk	Double blinded
Free of selective reporting?	Low risk	There is no indication the study has reported outcomes selectively

Owen 1991 *(Continued)*

Free of other bias?	High risk	Nature of placebo not described. Follicular fluid IG1 increased by 27% with growth hormone treatment

Suikkari 1996

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: Withdrawals: < 10% . Cancelled Cycles: >10% (therefore include in meta-analysis but perform sensitivity analysis).
Participants	Number of women: n= 22 (10 growth hormone 4 IU, 6 growth hormone 12 IU, 6 placebo) Inclusion Criteria: previous poor response in more than or equal to two assisted cycles. Definition of poor Response: < or equal to two oocytes retrieved or > or equal to 48 AMP hMG consumed in a stimulation cycle. Cause of subfertility: tubal (n=10), endometriosis (n=1), male factor (n=2), idiopathic (n=9). Age 25-40 years.
Interventions	Intervention: six women received 12 IU growth hormone and 10 women received four IU growth hormone daily SC from day three of spontaneous menstrual cycle. 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 and adverse effects (multiple pregnancy).
Notes	Twenty two women in total were included in Suikkari 1996 and they were divided into three groups, placebo, growth hormone four IU and growth hormone 12IU. Since only two groups could be compared for the table of comparisons the two growth hormone 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.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Stated as randomised
Allocation concealment?	Unclear risk	Not stated within the text
Blinding? All outcomes	Low risk	Double blinded
Free of selective reporting?	Low risk	There is no indication the study has reported outcomes selectively

Suikkari 1996 *(Continued)*

Free of other bias?	High risk	Cancelled Cycles: >10% (therefore include in meta-analysis but perform sensitivity analysis).

Suikkari 1996 12 IU

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: Withdrawals: < 10% . Cancelled Cycles: >10% (therefore include in meta-analysis but perform sensitivity analysis).
Participants	Number of women : n=22 (10 growth hormone four IU, six growth hormone 12 IU, six placebo) Inclusion Criteria: previous poor response in more than or equal to two assisted cycles. Definition of poor Response: < or equal to two oocytes retrieved or > or equal to 48 AMP hMG consumed in a stimulation cycle. Cause of subfertility: tubal (n=10), endometriosis (n=1), male factor (n=2), idiopathic (n=9). Age 25-40 years.
Interventions	Intervention: six women received 12 IU growth hormone and 10 women received 4 IU growth hormone daily SC from day three of spontaneous menstrual cycle. 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 and adverse effects (multiple pregnancy).
Notes	Same trial as Suikkari 1996 but refers to women randomised to growth hormone 12 IU treatment arm.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Stated as randomised
Allocation concealment?	Unclear risk	Not stated within the text
Blinding? All outcomes	Low risk	Double blinded
Free of selective reporting?	Low risk	There is no indication the study has reported outcomes selectively
Free of other bias?	High risk	Cancelled Cycles: >10% (therefore include in meta-analysis but perform sensitivity analysis)

Suikkari 1996 4 IU

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: 2 centres. Analysis: No power calculation or intention to treat analysis performed. Withdrawals: Withdrawals: < 10% . Cancelled Cycles: >10% (therefore include in meta-analysis but perform sensitivity analysis).
Participants	Number of women: 22 (10 growth hormone 4 IU, 6 growth hormone 12 IU, 6 placebo) Inclusion Criteria: previous poor response in more than or equal to 2 assisted cycles. Definition of poor Response: < or equal to 2 oocytes retrieved or > or equal to 48 AMP hMG consumed in a stimulation cycle. Cause of subfertility: tubal (n=10), endometriosis (n=1), male factor (n=2), idiopathic (n=9). Age 25-40 years.
Interventions	Intervention: 6 women received 12 IU growth hormone and 10 women received 4 IU growth hormone daily SC from day 3 of spontaneous menstrual cycle. Study Protocol: A boost "flare-up" protocol was used for ovarian stimulation. On day 2 of spontaneous menstrual cycle leuprolide acetate was administered SC 0.75mg in the morning. On day 3 gonadotrophin Metrodin was started at 300IU SC for 4 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 18-20mm.
Outcomes	Live birth rate, pregnancy rate, embryo transfer and adverse effects (multiple pregnancy).
Notes	Same trial as Suikkari 1996 but refers to women randomised to growth hormone 4 IU treatment arm.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Stated as randomised
Allocation concealment?	Unclear risk	Not stated within the text
Blinding? All outcomes	Low risk	Double blinded
Free of selective reporting?	Low risk	There is no indication the study has reported outcomes selectively
Free of other bias?	High risk	Cancelled Cycles: >10% (therefore include in meta-analysis but perform sensitivity analysis)

Tapanainen 1992

Methods	Randomisation: Stated as randomised, method unclear.

Tapanainen 1992 *(Continued)*

	Allocation concealment: trial codes kept in sealed envelopes until the study was completed. 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 growth hormone, 19 placebo). Cause of Subfertility: normally cycling women with unexplained infertility, tubal infertility or mild to moderate endometriosis. Age: 27-37.
Interventions	Intervention: growth hormone 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, 300µg 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 and 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 growth hormone 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
Adequate sequence generation?	Unclear risk	Stated as randomised
Allocation concealment?	Unclear risk	Trial codes kept in sealed envelopes until the end of the study, no details as to whether centralised or envelopes opaque
Blinding? All outcomes	Low risk	Double blinding
Free of selective reporting?	Low risk	There is no indication the study has reported outcomes selectively
Free of other bias?	Low risk	Report both live birth rate and adverse effects

Tesarik 2005

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

Tesarik 2005 *(Continued)*

	Withdrawals: none. Cancelled cycles: <10%.
Participants	Number of women: 100 (50, growth hormone, 50 placebo). Inclusion criteria: women >40 years old asking for an assisted reproduction attempt by ICSI were assessed for eligibility.
Interventions	Intevention: growth hormone 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
Adequate sequence generation?	Low risk	Computer generated random number tables
Allocation concealment?	Low risk	Opaque envelopes
Blinding? All outcomes	Low risk	Double blinded
Free of selective reporting?	Low risk	There is no indication the study has reported outcomes selectively
Free of other bias?	High risk	No details of adverse effects reported

Younis 1992

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. 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 growth hormone, 22 placebo). Cause of Subfertility: Ovulating women with mechanical factor infertility. Normal serum FSH, LH, PRL, T and DHEAS. Normal semen (WHO criteria). Exclusion Criteria: ? Age: < or equal to 38 years
Interventions	Intervention: growth hormone 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 and adverse effects (multiple pregnancy).

Younis 1992 *(Continued)*

Notes	Mannitol chosen as placebo.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Stated as randomised
Allocation concealment?	Unclear risk	Allocation not revealed until all outcomes calculated and comparisons between groups performed
Blinding? All outcomes	Low risk	Double blinded
Free of selective reporting?	Low risk	There is no indication the study has reported outcomes selectively
Free of other bias?	Low risk	

Zhuang 1994

Methods	Randomisation: stated as randomised, method unclear. Allocation concealment: unclear of method Blinding: Outcome assessors were blind to treatment allocation. Study Design: Parallel. Study Setting: unclear. Analysis; Power calculation done. Withdrawals; none. Cancelled Cycles; none.
Participants	Number of women randomised: n=27 (12 growth hormone, 15 control). Definition of poor response: not provided Inclusion Criteria: previous sub-optimal response to hyperstimulation cycles in IVF. Exclusion Criteria: Cause of subfertility: tubal factor or unexplained. Age: growth hormone 33.2 +/-3.9, Placebo 32.3 +/-3.9.
Interventions	Intervention: growth hormone 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 growth hormone). Dose of human chorionic gonadotropin: 10000 iu.
Outcomes	Live birth rate and 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

Zhuang 1994 *(Continued)*

Adequate sequence generation?	Unclear risk	Stated as randomised
Allocation concealment?	Unclear risk	Not stated within the text
Blinding? All outcomes	Low risk	Single
Free of selective reporting?	Low risk	There is no indication the study has reported outcomes selectively
Free of other bias?	High risk	No details of adverse effects reported

BA: Buserelin Acetate
E2: Oestrogen
Only outcomes relevant to the review were stated in the table of included studies
GnRH-a: Gonadotrophin releasing hormone agonist

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

Study	Reason for exclusion
Blumenfeld 1994	During the 2009 update additional data was sort to clarify which women included in the trial received which method of assisted conception and the definition of poor responder used.
Busacca 1996	Method of assisted conception used was not IVF but artificial insemination-husband or GIFT.
Homburg 1990	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 growth hormone releasing factor not growth hormone.
Hughes 1994	Any women who failed to produce 3 follicles greater than 20mm were cancelled. These women were not included in the analysis. This unpublished information could not be obtained from the author. Hughes 1992 and Huang 1993 are the same trial as Hughes 1994.
Jacobs 1995	Only concerns ovulation induction, not IVF.
Landolfi 1994	Only concerns ovulation induction, not IVF.
Owen 1991b	There are two publications for this trial. The analysis used women randomised to receive growth hormone in the trial and retrospective cases of women who had also received growth hormone in the past.
Rinehart 1999	Allocation was stated as "alternating randomisation", suggesting allocation to groups by alternation, not randomisation.
Schoolcraft 1997	Both treatment groups received the same dose of growth hormone, the intervention was oral contraceptive.

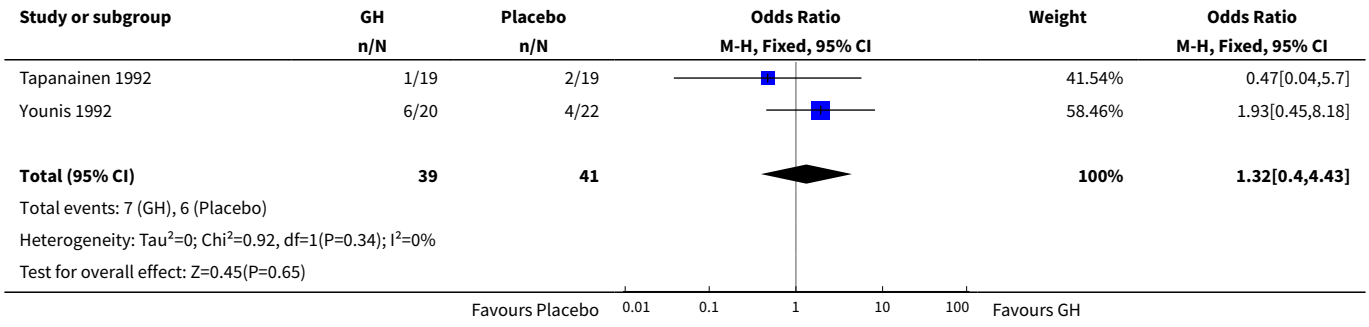
Study	Reason for exclusion
Tulandi 1993	Method of assisted conception was intra uterine insemination not IVF.

DATA AND ANALYSES

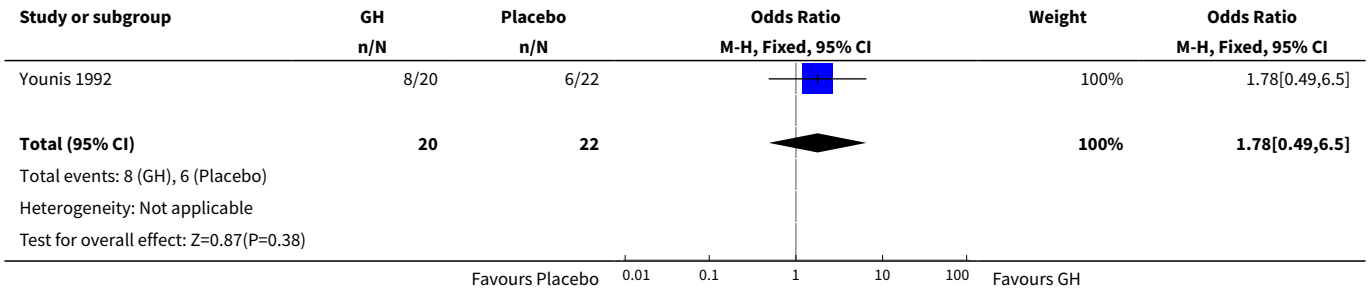
Comparison 1. Growth hormone versus placebo: Routine use

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth rate per woman randomised	2	80	Odds Ratio (M-H, Fixed, 95% CI)	1.32 [0.40, 4.43]
2 Pregnancy rate per woman randomised	1	42	Odds Ratio (M-H, Fixed, 95% CI)	1.78 [0.49, 6.50]
3 Number of women with at least one oocyte retrieved per woman randomised	1	42	Odds Ratio (M-H, Fixed, 95% CI)	2.86 [0.11, 74.31]
4 Embryo transfer per woman randomised	1	42	Odds Ratio (M-H, Fixed, 95% CI)	7.36 [0.36, 151.91]
5 Mean number of ampoules of gonadotrophin used per woman	2	80	Mean Difference (IV, Fixed, 95% CI)	0.18 [-1.51, 1.87]
6 Adverse Events	2	80	Odds Ratio (M-H, Fixed, 95% CI)	0.62 [0.18, 2.15]

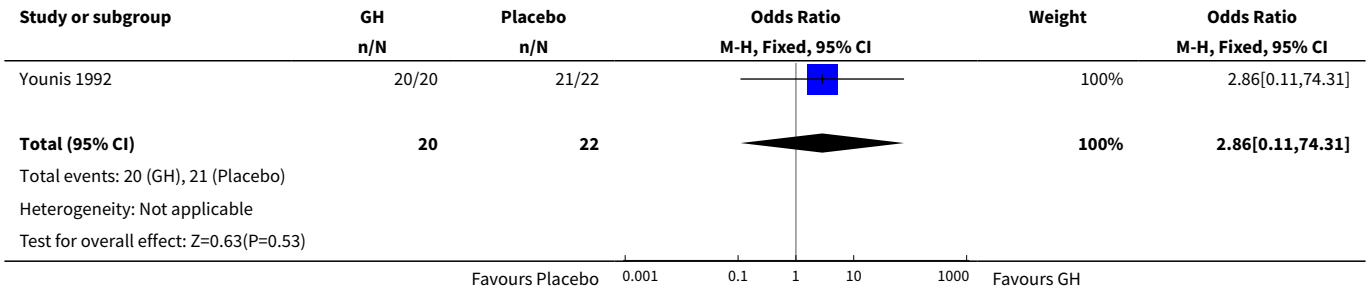
Analysis 1.1. Comparison 1 Growth hormone versus placebo: Routine use, Outcome 1 Live birth rate per woman randomised.



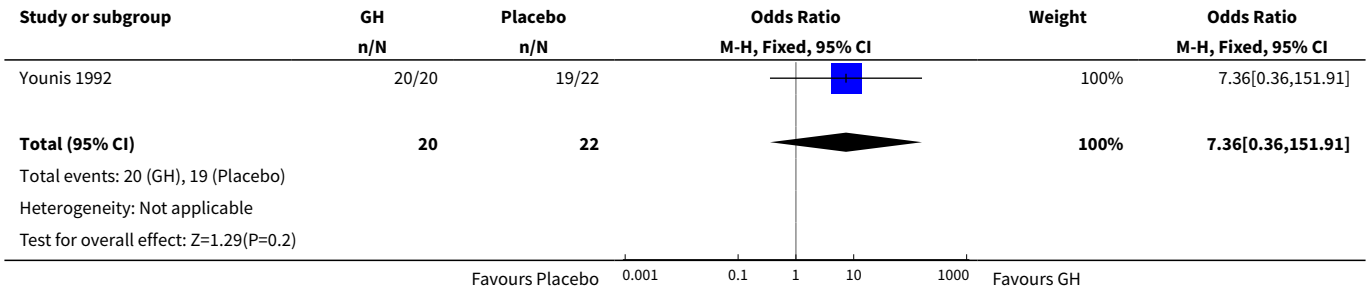
Analysis 1.2. Comparison 1 Growth hormone versus placebo: Routine use, Outcome 2 Pregnancy rate per woman randomised.



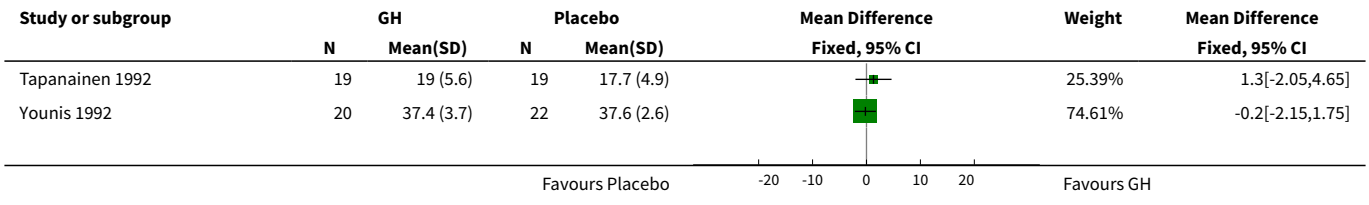
Analysis 1.3. Comparison 1 Growth hormone versus placebo: Routine use, Outcome 3 Number of women with at least one oocyte retrieved per woman randomised.

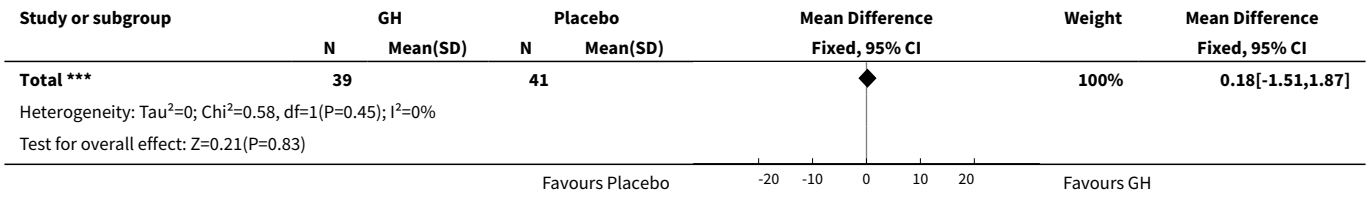


Analysis 1.4. Comparison 1 Growth hormone versus placebo: Routine use, Outcome 4 Embryo transfer per woman randomised.

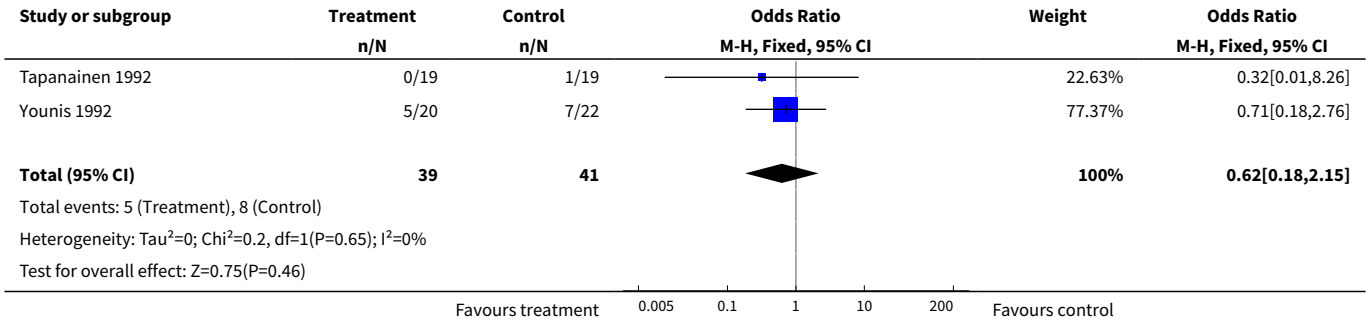


Analysis 1.5. Comparison 1 Growth hormone versus placebo: Routine use, Outcome 5 Mean number of ampoules of gonadotrophin used per woman.





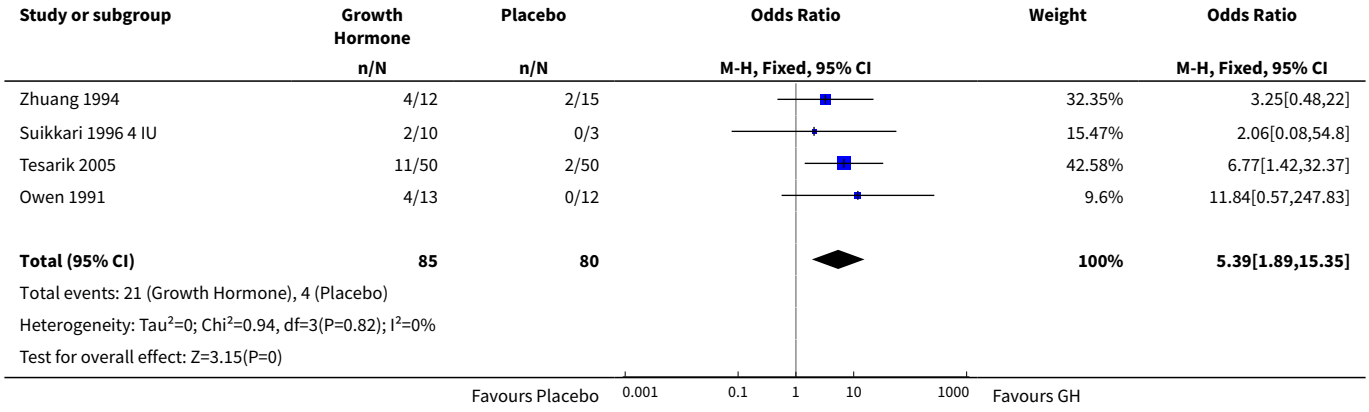
Analysis 1.6. Comparison 1 Growth hormone versus placebo: Routine use, Outcome 6 Adverse Events.



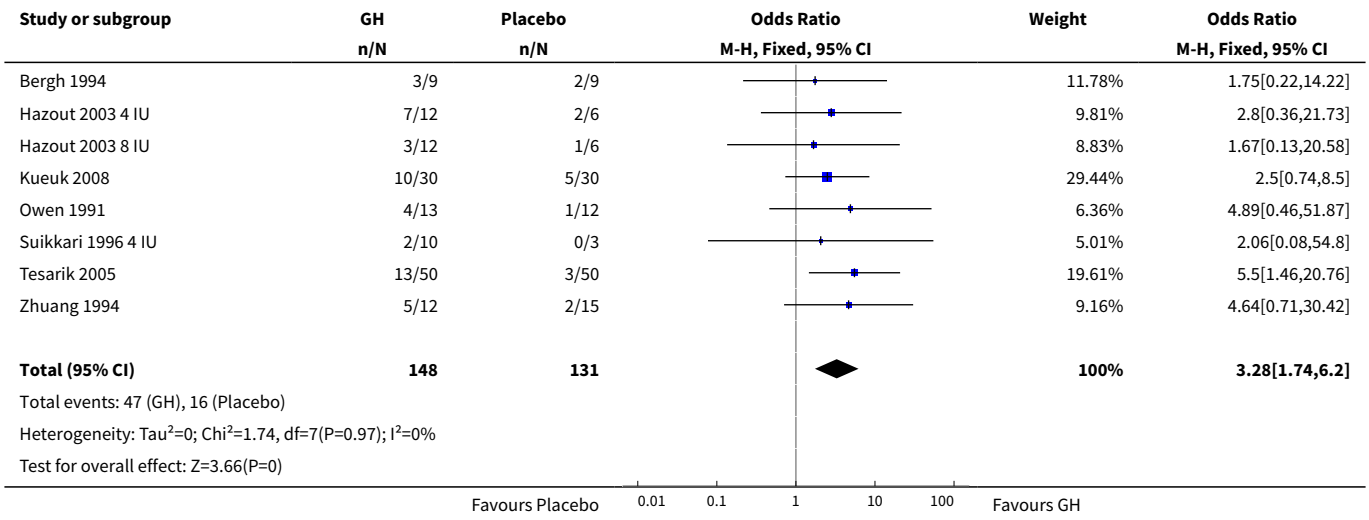
Comparison 2. Growth hormone versus placebo: Poor responder as defined by the study

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Live birth rate per woman randomised	4	165	Odds Ratio (M-H, Fixed, 95% CI)	5.39 [1.89, 15.35]
2 Pregnancy rate per woman randomised	8	279	Odds Ratio (M-H, Fixed, 95% CI)	3.28 [1.74, 6.20]

Analysis 2.1. Comparison 2 Growth hormone versus placebo: Poor responder as defined by the study, Outcome 1 Live birth rate per woman randomised.



Analysis 2.2. Comparison 2 Growth hormone versus placebo: Poor responder as defined by the study, Outcome 2 Pregnancy rate per woman randomised.

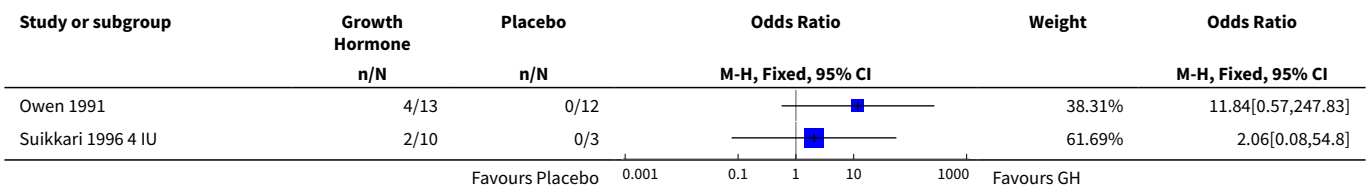


Study or subgroup	GH n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Bergh 1994	3/9	2/9		11.78%	1.75[0.22,14.22]
Hazout 2003 4 IU	7/12	2/6		9.81%	2.8[0.36,21.73]
Hazout 2003 8 IU	3/12	1/6		8.83%	1.67[0.13,20.58]
Kueuk 2008	10/30	5/30		29.44%	2.5[0.74,8.5]
Owen 1991	4/13	1/12		6.36%	4.89[0.46,51.87]
Suikkari 1996 4 IU	2/10	0/3		5.01%	2.06[0.08,54.8]
Tesarik 2005	13/50	3/50		19.61%	5.5[1.46,20.76]
Zhuang 1994	5/12	2/15		9.16%	4.64[0.71,30.42]
Total (95% CI)	**148**	**131**		**100%**	**3.28[1.74,6.2]**
Total events: 47 (GH), 16 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.74, df=7(P=0.97); I^2=0%					
Test for overall effect: Z=3.66(P=0)					

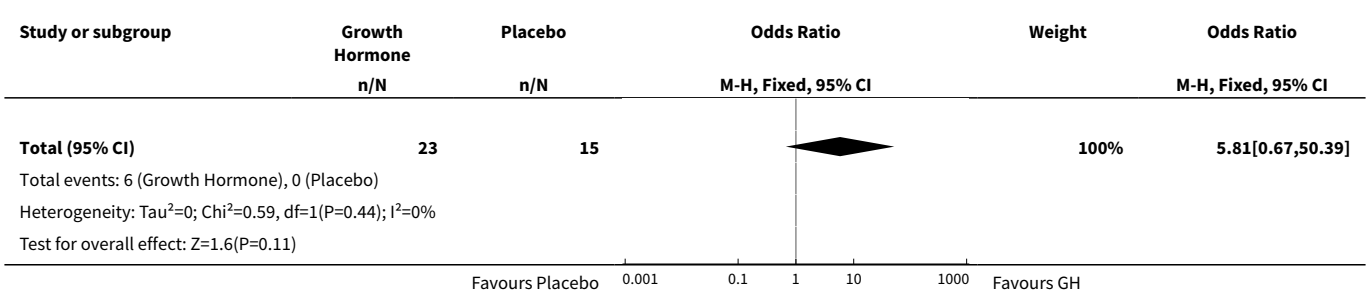
Comparison 3. Growth hormone versus placebo: Poor responder as demonstrated by previous sub-optimal response following controlled ovarian stimulation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth rate per woman randomised	2	38	Odds Ratio (M-H, Fixed, 95% CI)	5.81 [0.67, 50.39]
2 Pregnancy rate per woman randomised	4	116	Odds Ratio (M-H, Fixed, 95% CI)	2.58 [1.03, 6.46]
3 Number of women with at least one oocyte retrieved per woman randomised	1	18	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Embryo transfer per woman randomised	3	40	Odds Ratio (M-H, Fixed, 95% CI)	2.01 [0.38, 10.78]
5 Adverse Events	2	38	Odds Ratio (M-H, Fixed, 95% CI)	1.63 [0.21, 12.59]

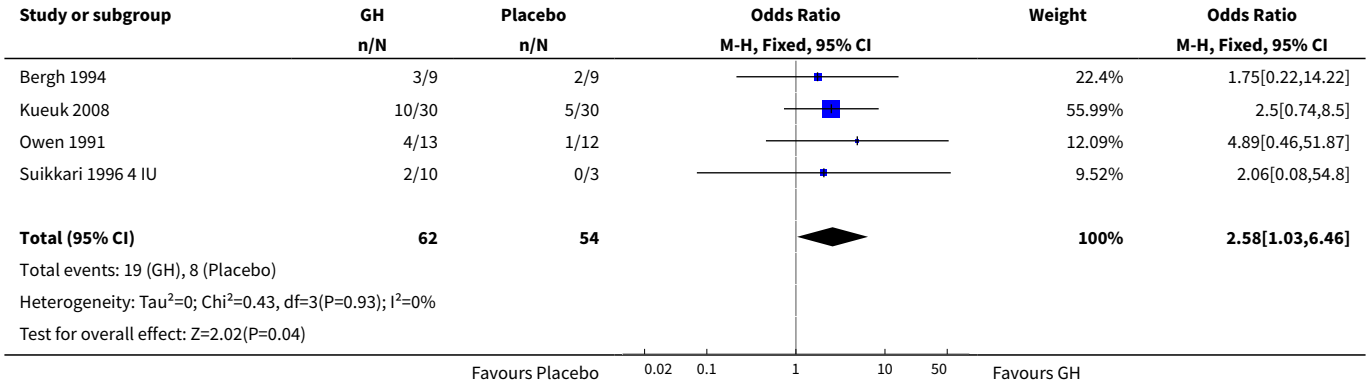
Analysis 3.1. Comparison 3 Growth hormone versus placebo: Poor responder as demonstrated by previous sub-optimal response following controlled ovarian stimulation, Outcome 1 Live birth rate per woman randomised.



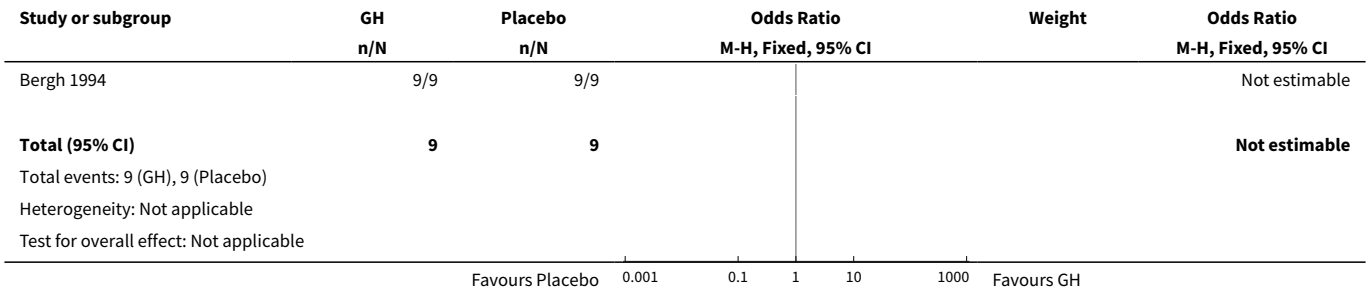
Study or subgroup	Growth Hormone n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Owen 1991	4/13	0/12		38.31%	11.84[0.57,247.83]
Suikkari 1996 4 IU	2/10	0/3		61.69%	2.06[0.08,54.8]



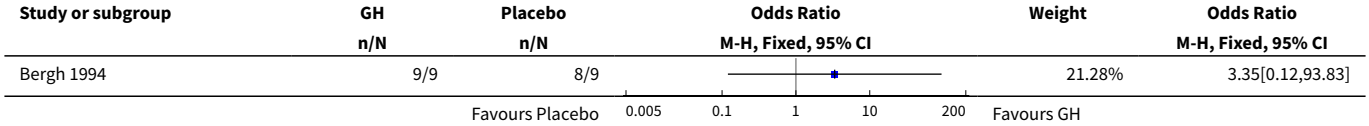
Analysis 3.2. Comparison 3 Growth hormone versus placebo: Poor responder as demonstrated by previous sub-optimal response following controlled ovarian stimulation, Outcome 2 Pregnancy rate per woman randomised.

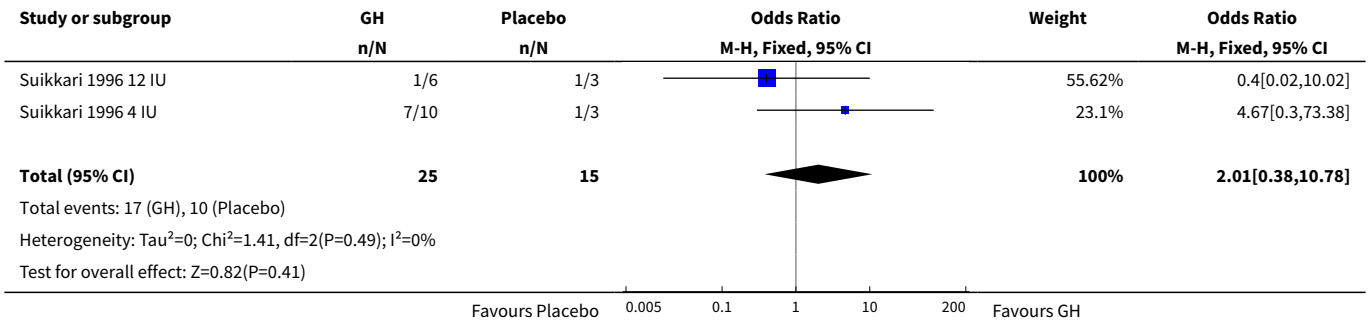


Analysis 3.3. Comparison 3 Growth hormone versus placebo: Poor responder as demonstrated by previous sub-optimal response following controlled ovarian stimulation, Outcome 3 Number of women with at least one oocyte retrieved per woman randomised.

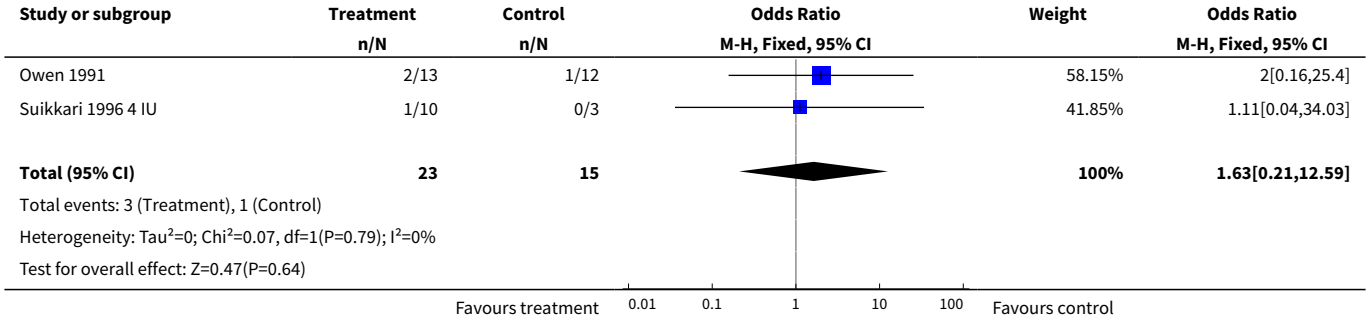


Analysis 3.4. Comparison 3 Growth hormone versus placebo: Poor responder as demonstrated by previous sub-optimal response following controlled ovarian stimulation, Outcome 4 Embryo transfer per woman randomised.





Analysis 3.5. Comparison 3 Growth hormone versus placebo: Poor responder as demonstrated by previous sub-optimal response following controlled ovarian stimulation, Outcome 5 Adverse Events.



APPENDICES

Appendix 1. MDSG search terms

Search string for KH291 MDSG database 28.06.09

Keywords CONTAINS "growth hormone" or "growth hormone derivative" or "human growth hormone" or "growth hormone releasing factor" or "grf" or Title CONTAINS "growth hormone" or "growth hormone derivative" or "human growth hormone" or "growth hormone releasing factor" or "grf"

AND

Keywords CONTAINS "IVF" or "in vitro fertilization" or "IVF" or "ICSI" or "intracytoplasmic sperm injection" or "Embryo" or "in-vitro fertilization" or Title CONTAINS "IVF" or "in vitro fertilization" or "IVF" or "ICSI" or"intracytoplasmic sperm injection" or "Embryo" or "in-vitro fertilization"

Appendix 2. MEDLINE search strategy

Database: Ovid MEDLINE(R) <1950 to June Week 3 2009>
Search Strategy:
---
1 growth hormone/ or human growth hormone/ (47027)
2 somatotrop$.tw. (5778)
3 (somatrop$ or norditropin).tw. (184)
4 (growth adj5 hormone$).tw. (48524)
5 or/1-4 (64412)
6 fertilization in vitro/ or sperm injections, intracytoplasmic/ (22271)

7 IVF.tw. (11335)
8 (in Vitro adj5 fertili$).tw. (14828)
9 icsi.tw. (3589)
10 (intracytoplas$ adj5 sperm).tw. (3510)
11 exp Ovulation Induction/ (8201)
12 ((ovar$ or ovulat$) adj5 (induct$ or stimulat$)).tw. (9654)
13 or/6-12 (37952)
14 exp growth hormone-releasing hormone/ or exp sermorelin/ (4583)
15 (growth hormone adj5 releasing factor).tw. (1341)
16 grf.tw. (1855)
17 or/14-16 (5630)
18 or/5,17 (65464)
19 18 and 13 (460)
20 randomized controlled trial.pt. (273632)
21 controlled clinical trial.pt. (79523)
22 randomized.ab. (183258)
23 placebo.tw. (116263)
24 clinical trials as topic.sh. (144111)
25 randomly.ab. (132970)
26 trial.ti. (79814)
27 (crossover or cross-over or cross over).tw. (43128)
28 or/20-27 (648343)
29 (animals not (humans and animals)).sh. (3296848)
30 28 not 29 (600179)
31 30 and 19 (71)

Appendix 3. EMBASE search strategy

Database: EMBASE <1980 to 2009 Week 26>
Search Strategy:
---
1 growth hormone/ or growth hormone derivative/ or human growth hormone/ (37552)
2 somatotrop$.tw. (3622)
3 (somatrop$ or norditropin).tw. (653)
4 (growth adj5 hormone$).tw. (39350)
5 or/1-4 (52850)
6 fertilization in vitro/ or intracytoplasmic sperm injection/ (23933)
7 IVF.tw. (11213)
8 (in Vitro adj5 fertili$).tw. (12921)
9 icsi.tw. (3793)
10 (intracytoplas$ adj5 sperm).tw. (3461)
11 ovary hyperstimulation/ or ovulation induction/ (9384)
12 ((ovar$ or ovulat$) adj5 (induct$ or stimulat$)).tw. (8632)
13 or/6-12 (35212)
14 5 and 13 (468)
15 exp growth hormone releasing factor/ or exp "growth hormone releasing factor[1-29]"/ (4982)
16 (growth hormone adj5 releasing factor).tw. (1135)
17 grf.tw. (1494)
18 or/15-17 (5770)
19 or/5,18 (53914)
20 19 and 13 (479)
21 Clinical Trial/ (545660)
22 Randomized Controlled Trial/ (170304)
23 exp randomization/ (26900)
24 Single Blind Procedure/ (8278)
25 Double Blind Procedure/ (72902)
26 Crossover Procedure/ (21458)
27 Placebo/ (128084)
28 Randomi?ed controlled trial$.tw. (33843)
29 randomised controlled trials.tw. (2814)
30 random allocation.tw. (641)
31 randomly allocated.tw. (10334)

32 allocated randomly.tw. (1359)
33 (allocated adj2 random).tw. (562)
34 Single blind$.tw. (7573)
35 Double blind$.tw. (85680)
36 ((treble or triple) adj blind$).tw. (140)
37 placebo$.tw. (111457)
38 prospective study/ (83224)
39 or/21-38 (716803)
40 case study/ (6169)
41 case report.tw. (120958)
42 abstract report/ or letter/ (502683)
43 or/40-42 (627435)
44 39 not 43 (691822)
45 44 and 20 (92)

Appendix 4. CENTRAL search Strategy

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <2nd Quarter 2009>
Search Strategy:
---
1 growth hormone/ or human growth hormone/ (2525)
2 somatotrop$.tw. (157)
3 (somatrop$ or norditropin).tw. (43)
4 (growth adj5 hormone$).tw. (3238)
5 or/1-4 (3704)
6 fertilization in vitro/ or sperm injections, intracytoplasmic/ (1223)
7 ivf.tw. (1610)
8 (in Vitro adj5 fertili$).tw. (1203)
9 icsi.tw. (547)
10 (intracytoplas$ adj5 sperm).tw. (339)
11 exp Ovulation Induction/ (717)
12 ((ovar$ or ovulat$) adj5 (induct$ or stimulat$)).tw. (1076)
13 or/6-12 (3192)
14 exp growth hormone-releasing hormone/ or exp sermorelin/ (300)
15 (growth hormone adj5 releasing factor).tw. (43)
16 grf.tw. (71)
17 or/14-16 (344)
18 or/5,17 (3736)
19 18 and 13 (64)
20 limit 19 to yr="2007 -Current" (2)
21 from 20 keep 1-2 (2)

Appendix 5. psycINFO search strategy

Database: PsycINFO <1806 to June Week 1 2009>
Search Strategy:
---
1 growth hormone/ or human growth hormone/ (969)
2 somatotrop$.tw. (151)
3 (somatrop$ or norditropin).tw. (5)
4 (growth adj5 hormone$).tw. (1777)
5 or/1-4 (1922)
6 fertilization in vitro/ or sperm injections, intracytoplasmic/ (0)
7 ivf.tw. (239)
8 (in Vitro adj5 fertili$).tw. (353)
9 icsi.tw. (24)
10 (intracytoplas$ adj5 sperm).tw. (16)
11 exp Ovulation Induction/ (0)
12 ((ovar$ or ovulat$) adj5 (induct$ or stimulat$)).tw. (177)
13 or/6-12 (581)
14 exp growth hormone-releasing hormone/ or exp sermorelin/ (0)
15 (growth hormone adj5 releasing factor).tw. (41)
16 grf.tw. (45)

17 or/14-16 (63)
18 or/5,17 (1943)
19 18 and 13 (3)
20 from 19 keep 1-3 (3)

WHAT'S NEW

Date	Event	Description
20 September 2010	Amended	Contact details updated.

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, I Salim and AJ Watson

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- Dept of Obstetrics and Gynaecology, University of Auckland, New Zealand.

External sources

- Department of Health, UK.

  $5,000 initiative fund.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The authors of the protocol were different from the review, additional authors were included in the 2009 update: G Ahmad, J Brown, JMN Duffy, L Nardo, I Salim and AJ Watson.

INDEX TERMS

Medical Subject Headings (MeSH)

*Ovulation Induction; Chemotherapy, Adjuvant; Fertilization in Vitro [*methods]; Growth Hormone-Releasing Hormone [*therapeutic use]; Human Growth Hormone [*therapeutic use]; Infertility, Female [drug therapy]; Live Birth; Pregnancy Rate; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans; Pregnancy