Addition of growth hormone to gonadotrophins in ovarian stimulation of poor responders treated by in-vitro fertilization: a systematic review and meta-analysis

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BACKGROUND: Whether the addition of growth hormone (GH) can improve the probability of pregnancy in poor responders undergoing ovarian stimulation for in-vitro fertilization (IVF) has been examined to date by several underpowered studies, which have not provided solid conclusions.

METHODS: A computerized literature search in MEDLINE, EMBASE, CENTRAL and randomized controlled trial (RCT) registries was performed independently by two reviewers, aiming to identify RCTs that evaluated the following research question: does GH addition increase the probability of pregnancy in poor responders undergoing ovarian stimulation with gonadotrophin releasing hormone (GnRH) analogues and gonadotrophins for IVF?

RESULTS: Six relevant RCTs were identified, including a total of 169 patients. GH addition significantly increased clinical pregnancy (rate difference: +16%, 95% CI: +4 to +28; fixed effects model) (number-needed-to-treat (NNT) = 6, 95% CI: 4–25) and live birth rates (rate difference: +17%, 95% CI: +5 to +30; fixed effects model) (NNT = 6; 95% CI: 3–20). Furthermore, GH addition was associated with a significantly higher proportion of patients reaching embryo transfer (rate difference: +22%, 95% CI: +7 to +36; fixed effects model).
CONCLUSIONS: The present meta-analysis provides evidence that GH addition increases the probability of clinical pregnancy and live birth in poor responders undergoing ovarian stimulation with GnRH analogues and gonadotrophins for IVF. However, the total number of patients analyzed is small and thus further RCTs are warranted to prove or disprove this finding.

Key words: growth hormone / in-vitro fertilization / live birth / poor ovarian response

Introduction

Poor response to ovarian stimulation, the incidence of which has been estimated to range from 9 to 24% (Ben-Rafael et al., 1991; Jenkins et al., 1991; Surrey and Schoolcraft, 2000), represents a significant therapeutic challenge in assisted reproductive technologies. Poor ovarian response has been associated with several factors, including female age (Akande et al., 2002), previous ovarian surgery (Nargund and Bromham, 1995) and high body mass index (Ragni et al., 2000; Loh et al., 2002). However, not infrequently, poor ovarian response occurs unexpectedly (Keay et al., 1997).

Numerous interventions have been proposed for the management of poor ovarian response. In this respect, several comparisons between stimulation protocols have been performed, recently reviewed in Kyrou et al. (2009), such as short versus long gonadotrophin releasing hormone (GnRH) agonist protocol, GnRH antagonist protocol versus short/long GnRH agonist protocols, combination of clomiphene citrate with recombinant follicle stimulating hormone (FSH) in a flexible GnRH antagonist protocol versus a long GnRH agonist protocol, stop versus non-stop long GnRH agonist protocol, short GnRH agonist protocol versus natural cycle/in-vitro fertilization (IVF) and recombinant FSH versus urinary FSH. Furthermore, addition of pyridostigmine, oral L-arginine, transdermal testosterone, letrozole and growth hormone (GH) or GH-releasing factor (GHRF) have also been proposed (Kyrou et al., 2009).

The rationale for adding GH for the improvement of pregnancy rates in poor responders undergoing IVF has been based on both animal and human data, which suggest that GH plays an important role in ovarian steroidogenesis and follicular development. In mice lacking GH receptor and GH-binding protein, follicular development is significantly reduced in response to gonadotrophin stimulation (Bachelot et al., 2002). Moreover, GH may increase the intra-ovarian production of insulin-like growth factor 1 (Hsu and Hammond, 1987; Yoshimura et al., 1996), which is considered to play an important role in ovarian function (Adashi et al., 1985; Erickson et al., 1989), stimulating follicular development, estrogen production and oocyte maturation (Yoshimura et al., 1996).

To date, a limited number of studies have been performed in order to assess whether the addition of GH can improve the probability of pregnancy in poor responders undergoing ovarian stimulation for IVF. Moreover, the existing studies are underpowered and, thus, inconclusive. Although a relevant Cochrane systematic review, published in 2003, showed that a beneficial effect with GH addition was present in poor responders, the use of GH in routine clinical practice was discouraged by the authors of that meta-analysis (Harper et al., 2003). It should be noted, however, that evidence of a beneficial effect does not exist for any of the other stimulation protocols that have been proposed so far for the management of poor ovarian response (Kyrou et al., 2009).

The purpose of this systematic review and meta-analysis was to update the existing evidence from randomized controlled trials (RCTs) regarding the effect of GH addition on the probability of pregnancy in poor responders undergoing ovarian stimulation with GnRH analogues and gonadotrophins for IVF.

Methods

A computerized literature search in MEDLINE, EMBASE, CENTRAL and RCT registries covering the period until May 2008 was performed independently by two reviewers (E.M.K. and C.A.V.) aiming to identify RCTs that evaluated the following research question: does GH addition increase the probability of pregnancy in poor responders undergoing ovarian stimulation with GnRH analogues and gonadotrophins for IVF? For this purpose, the free-text search terms [‘Growth hormone’ or ‘GH’] and [‘[‘poor’ or ‘low’ or ‘slow’ or ‘inadequate’ or ‘suboptimal’] and (‘response’ or ‘responder’ or ‘ovarian reserve’) were used. Additionally, the citation lists of all relevant publications and review articles were hand-searched. Meeting proceedings of the European Society of Human Reproduction and Embryology and the American Society for Reproductive Medicine were also hand-searched for the identification of relevant studies. No language limitations were applied.

Selection of studies

Criteria for inclusion/exclusion of studies were established prior to the literature search. Studies had to fulfill the following criteria for eligibility: (a) randomization should have been used to allocate patients in groups, (b) women should have been subjected to IVF using gonadotrophins and GnRH analogues for ovarian stimulation (c) women should have been characterized as poor responders.

All RCTs that evaluated the addition of GH were included in the current systematic review and meta-analysis, irrespective of the definition of poor ovarian response, the dose and protocol of GH administered, the type of gonadotrophin injected, or the type and protocol of GnRH analogue used. Selection of the studies was performed independently by two of the reviewers (E.M.K. and C.A.V.). Any disagreement was resolved unanimously by discussion.

Data extraction

Data extraction was performed independently by two of the reviewers (E.M.K. and C.A.V.). The following data were recorded from each of the eligible studies: demographic (citation data, country, study period, number of patients included), methodological (method of randomization, allocation concealment), procedural (whether financial support was declared, type of GnRH analogue and protocol used for luteinizing hormone (LH) surge inhibition, dose and protocol of GH administration, type and starting dose of gonadotrophin administered for ovarian stimulation, type and dose of medication used for triggering final oocyte maturation, criteria used for triggering final oocyte maturation, type of fertilization, day of embryo transfer, type of luteal support, adverse events associated with the use of GH). Any disagreement between the
two reviewers responsible for data extraction was solved unanimously by discussion.

**Outcomes**

The main outcome measure chosen for the current meta-analysis was achievement of pregnancy per patient randomized, expressed as clinical pregnancy (evidence of intrauterine sac with fetal heart activity at 6–8 weeks of gestation) or as live birth. Secondary outcome measures included duration of gonadotrophin stimulation, total dose of gonadotrophins required for ovarian stimulation, number of cumulus oocyte complexes (COCs) retrieved, number of embryos transferred and proportion of women who achieved embryo transfer. In case of missing information, the study authors were contacted in order to retrieve relevant data.

**Quantitative data synthesis**

The dichotomous data results for each of the eligible for meta-analysis studies were expressed as an odds ratio (OR) or risk difference (RD) with 95% confidence intervals (CI). These results were combined for meta-analysis using the Mantel-Haenszel model, when using the fixed effects method, and the DerSimonian and Laird model (DerSimonian and Laird, 1986), when using the random effects method. When the outcome of interest was of a continuous nature, the differences were pooled across the studies, which provided information on this outcome, resulting in a weighted mean difference (WMD) with 95% CI. The inverse variance method and the DerSimonian and Laird method were used when the fixed or random effects method were applied, respectively. All results were combined for meta-analysis with Revman Software (Version 5, Copenhagen: the Nordic Cochrane Centre, The Cochrane Collaboration, 2003). Study-to-study variation was assessed by using the Chi² statistic (the hypothesis tested was that the studies are all drawn from the same population, i.e. from a population with the same effect size). A fixed effects model was used where no statistically significant heterogeneity was present, whereas in the presence of statistically significant heterogeneity, a random effects model was applied. Statistical significance was set at a \( P \) level of 0.05. The presence of publication bias was tested by using the Harbord–Egger’s test (Harbord et al., 2006). Moreover, subgroup analysis was a priori planned to be performed based on the protocol of GH used.

**Results**

The literature search yielded 305 potentially relevant trials (Fig. 1). Subsequently, the titles of these manuscripts were examined to exclude irrelevant studies, resulting in 62 potentially eligible publications. The abstracts of these studies were examined and eventually

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**Figure 1** QUOROM statement flow diagram.
29 manuscripts that could provide data to answer the research question were identified. The full text of these studies was examined thoroughly, resulting in the exclusion of 23 publications (Supplementary Table). Eventually, six studies were considered eligible for inclusion in the meta-analysis (Owen et al., 1991; Bergh et al., 1994; Zhuang et al., 1994; Dor et al., 1995; Suikkari et al., 1996; Kucuk et al., 2008). Characteristics of the studies included in the systematic review appear in Tables I and II. Eligible studies were published between 1991 and 2008. Randomization method was reported in three of the studies, while information regarding allocation concealment was present in two of the studies included (Table I). All of the studies were underpowered to detect a difference of 5% in pregnancy rates (usually considered as clinically important), since the number of participants ranged from 14 to 61 (median 23.5). Definition of poor ovarian response varied between studies, while financial support was declared in three out of six eligible studies (Table I). The largest study published so far on this issue is the most recent by Kucuk et al. (2008).

Ovarian reserve testing by assessing basal FSH was performed in four out of six eligible trials. GnRH agonists were used in all eligible trials for premature LH surge inhibition (long protocol in four out of six trials and short agonist protocol in the remaining two studies) (Table II). Urinary gonadotrophins were used in all studies with the exception of the study by Kucuk et al. (2008), in which recombinant FSH was used. The dose and the protocol of GH administration varied between studies, as was the case with the dose of human chorionic gonadotrophin (hCG) used to trigger final oocyte maturation (ranging from 5000 to 10 000 IU) and the criteria used for this purpose (Table II). No cycle cancellation policy was reported in any of the eligible studies. Embryo transfer policy appears in Table III. The policy of transferring all available embryos in both groups was applied in two out of six studies, while in one study up to four embryos with evidence of normal cleavage were transferred (Table III). In the remaining three studies, no relevant information was available or could be obtained by the authors. Embryos were transferred on day two or day three of embryo culture, while the type of luteal support was unclear in four out of six studies and was performed with hCG or i.m. progesterone in the remaining two studies (Table II).

Meta-analysis

Primary outcome measures

Clinical pregnancy

In four out of the six eligible studies, a non-significant improvement in the probability of clinical pregnancy was observed with GH addition. However, when these data were pooled, it was shown that the probability of clinical pregnancy was significantly increased (OR: 2.82, 95% CI: 1.24–6.38; fixed effects model). GH addition led to an absolute increase of clinical pregnancy rate by 16% (95% CI: +4 to +28; fixed effects model) (number-needed-to-treat (NNT) = 6, 95% CI: 4–25) (Fig. 2). No publication bias could be detected by using the Harbord–Egger’s test ($P = 0.46$) It should be noted, that one of the eligible studies (Suikkari et al., 1996) was a three-armed RCT comparing two different doses of GH, 4 and 12 IU, using the same control group (Table I). In order to avoid a unit-of-analysis error, the two intervention groups were combined in one group and thus a single comparison was entered in the main analysis. This methodology is recommended for such cases by the Cochrane Collaboration (Higgins and Green, 2008). Furthermore, a sensitivity analysis by including both intervention arms from that study (4 and 12 IU) and splitting the control group into two groups, as alternatively proposed by the Cochrane Collaboration, was also performed (Higgins and Green, 2008). This analysis did not materially change the results obtained (RD for clinical pregnancy: +16%, 95% CI: +4 to +28).

Live birth

In four out of five studies providing data on live birth, a non-significant improvement in the probability of live birth was observed with GH addition. However, when these data were pooled [by combining the two interventions groups of the Suikkari et al. (1996) study in one group as proposed by the Cochrane Collaboration], it was shown that live birth rate was significantly increased with GH addition (OR: 3.15 95% CI: 1.26–7.85; fixed effects model). GH addition led to an absolute increase of live birth rate by 17% (95% CI: +5 to +30, fixed effects model) (NNT = 6, 95% CI: 3–20) (Fig. 3). No publication bias could be detected by using the Harbord–Egger’s test ($P = 0.31$). Sensitivity analysis performed by including both intervention arms from the study by Suikkari et al. (1996) and splitting the control group into two groups [as alternatively proposed by the Cochrane Collaboration (Higgins and Green, 2008)] did not change the direction or the significance of the results obtained (RD: +17%, 95% CI: +4 to +30; fixed effects model).

An additional sensitivity analysis was also performed, by excluding the study by Zhuang et al. (1994), in which important information such as definition of poor ovarian response and randomization method were not reported. In this case, both clinical pregnancy rate per patient randomized (RD: +14%, 95% CI: +1 to +27; fixed effects model) as well as live birth rate per patient randomized (RD: +16%, 95% CI: +3 to +30; fixed effects model) remained significantly increased in patients treated with GH as compared with those who were not.

Furthermore, when only those studies in which the embryo transfer policy was explicitly stated were considered (Table III) (Owen et al., 1991; Bergh et al., 1994; Kucuk et al., 2008), the direction or the significance of the results obtained remained unaltered, for both clinical (RD: 16%, 95% CI: +0.2 to +32; $P = 0.04$; fixed effects model) and live birth rate (RD: +20%, 95% CI: +3 to +37; $P = 0.02$; fixed effects model).

Finally, the potential moderating effect of the protocol used for down-regulation on the association between GH addition and pregnancy outcome was evaluated with the use of a categorical meta-analysis. No statistically significant difference in the rate difference for clinical pregnancy was shown between studies using the long or the short GnRH agonist protocol (heterogeneity between groups: $q = 1.51$; $P = 0.22$). The same was true regarding the rate difference for live birth (heterogeneity between groups: $q = 1.59$; $P = 0.21$).

Secondary outcome measures

Duration of stimulation

No pooling of data was feasible for duration of stimulation due to the fact that most studies reported medians with corresponding interquartile ranges (Owen et al., 1991; Bergh et al., 1994; Dor et al., 1995;
### Table I Characteristics of the RCTs included in the meta-analysis

<table>
<thead>
<tr>
<th>Study, country of origin (number of centers)</th>
<th>Journal</th>
<th>Study period</th>
<th>Randomization method/blinding/allocation concealment</th>
<th>Sample size calculation</th>
<th>No. of participants</th>
<th>Definition of poor ovarian response</th>
<th>Financial support by pharmaceutical company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Owen et al. (1991), UK (single centre)</td>
<td>Fertility and Sterility</td>
<td>January 1989–December 1989</td>
<td>Randomization list/double blind/not reported</td>
<td>No</td>
<td>ITT population: 25 GH: 13 Control: 12</td>
<td>&lt;6 COCs with &lt;4 embryos developed in a previous cycle</td>
<td>Yes</td>
</tr>
<tr>
<td>Bergh et al. (1994), Sweden (multicentre)</td>
<td>Fertility and Sterility</td>
<td>Not reported</td>
<td>Randomization list/double blind/central pharmacy</td>
<td>No</td>
<td>ITT population: 20 GH: 10 Control: 10</td>
<td>&lt;5 COCs with adequate stimulation in two previous failed attempts</td>
<td>Yes</td>
</tr>
<tr>
<td>Dor et al. (1995), Israel (single centre)</td>
<td>Human Reproduction</td>
<td>Not reported</td>
<td>Not reported/double blind/not reported</td>
<td>No</td>
<td>ITT population: 14 GH: 7 Control: 7</td>
<td>E2 on the day of hCG &lt; 501 pg/ml, &lt;4 follicles &gt;14 mm, &lt;3 COCs retrieved</td>
<td>Not reported</td>
</tr>
<tr>
<td>Suikkari et al. (1996), Australia (single centre)</td>
<td>Fertility and Sterility</td>
<td>Not reported</td>
<td>Not reported/double blind/not reported</td>
<td>No</td>
<td>ITT population: 22 GH 4 IU: 10 GH 12 IU: 6 Control: 6</td>
<td>&lt;2 COCs retrieved or requirement of &gt;48 ampoules of hMG</td>
<td>Yes</td>
</tr>
<tr>
<td>Kucuk et al. (2008), Turkey (single centre)</td>
<td>Journal of Assisted Reproduction and Genetics</td>
<td>January 2005–June 2007</td>
<td>Computer-generated randomization table/not blind/yes (sealed envelopes)</td>
<td>No</td>
<td>ITT population: 61 GH: 31 Control: 30</td>
<td>&lt;4 follicles to a high rFSH dose (450 IU) in the first cycle at the same center</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Baseline ovarian reserve testing</th>
<th>GnRH analogue protocol/analogue (dose)</th>
<th>FSH type /starting dose/dose adjustments</th>
<th>hCG</th>
<th>Criteria for hCG administration</th>
<th>Fertilization</th>
<th>Embryo transfer day</th>
<th>LPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Owen et al. (1991)</td>
<td>Not reported</td>
<td>Long follicular/buserelin acetate (200 μg/day sc)</td>
<td>hMG/225 IU/yes, from day 7 onwards</td>
<td>5000 IU hCG</td>
<td>3 follicles of &gt;14 mm with at least 1 follicle &gt;17 mm in the presence of E2 &gt; 1500 pmol/l</td>
<td>IVF</td>
<td>Day 2</td>
<td>hCG</td>
</tr>
<tr>
<td>Zhuang et al. (1994)</td>
<td>All patients had basal FSH &lt; 20 IU/l</td>
<td>Long luteal/buserelin acetate (1.2 mg/day nas)</td>
<td>hMG/150 IU/not reported</td>
<td>10 000 IU hCG</td>
<td>Unclear</td>
<td>IVF</td>
<td>Unclear</td>
<td>Unclear</td>
</tr>
<tr>
<td>Bergh et al. (1994)</td>
<td>Not reported</td>
<td>Long follicular/buserelin acetate (1.2 mg/day nas)</td>
<td>hMG/225–300 IU and/or human FSH 75–300 IU/ not reported</td>
<td>10 000 IU hCG</td>
<td>At least one follicle ≥18 mm and 7–8 days of continuous E2 rise</td>
<td>IVF</td>
<td>Day 2, 3</td>
<td>impregnosterone or hCG</td>
</tr>
<tr>
<td>Dor et al. (1995)</td>
<td>All patients had basal FSH &lt; 10 IU/l</td>
<td>Short agonist/triptorelin (0.1 mg/day sc)</td>
<td>Urofollitropin/ 300 IU from cycle day 2 for 5 days, followed by hMG 300 IU</td>
<td>10 000 IU hCG</td>
<td>At least two follicles &gt;18 mm, and serum E2 &gt; 200 pg/ml</td>
<td>IVF</td>
<td>Day 2</td>
<td>Not reported</td>
</tr>
<tr>
<td>Suikkari et al. (1996)</td>
<td>All patients had basal FSH &lt; 16 IU/L</td>
<td>Short agonist/leuprolide acetate (0.75 mg/day sc)</td>
<td>Urofollitropin/300 IU, from day 7 onwards</td>
<td>5000 IU hCG</td>
<td>When the largest follicle reached 18–20 mm</td>
<td>IVF</td>
<td>Day 2</td>
<td>Not reported</td>
</tr>
<tr>
<td>Kucuk et al. (2008)</td>
<td>All patients had basal FSH ≤ 20 IU/L</td>
<td>Long luteal/triptorelin (0.1 /0.05 mg/day sc)</td>
<td>Follicotropin-a/450 IU/yes, from day 6 onwards</td>
<td>10 000 IU hCG</td>
<td>At least one follicle &gt;17 mm</td>
<td>ICSI</td>
<td>Day 3</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

Suikkari et al., 1996). In all of the eligible studies no significant difference in the duration of stimulation was observed in patients who received GH as compared with those who did not.

**Gonadotrophin requirement**

No pooling of data was feasible for gonadotrophin requirement due to the fact that most studies reported medians with corresponding interquartile ranges (Owen et al., 1991; Bergh et al., 1994; Dor et al., 1995; Suikkari et al., 1996). However, it should be noted, that in the largest study by Kucuk et al. (2008), a significantly lower requirement for gonadotrophins was observed in the GH group (mean + SD: 3187 + 232 IUs of FSH) as compared with the control group (mean + SD: 4070 + 598 IUs of FSH) (P = 0.001).

**Number of COCs**

Combinable data were offered by two studies (Bergh et al., 1994; Kucuk et al., 2008). No statistically significant difference was observed in the number of COCs retrieved, which was higher in the group of patients who received GH (WMD: +0.56, 95% CI: −0.06 to +6.17; random effects model).

**Proportion of patients reaching embryo transfer**

Three studies offered data for this outcome (Bergh et al., 1994; Suikkari et al., 1996; Kucuk et al., 2008). A significantly higher proportion of patients treated by GH reached embryo transfer as compared with those treated by gonadotrophins only (OR: 5.06, 95% CI: 1.44–17.70; RD +22%, 95% CI: +7 to +36).

**Number of embryos transferred**

No pooling of data was feasible for number of embryos transferred due to the fact that most studies reported medians with corresponding interquartile ranges (Owen et al., 1991; Bergh et al., 1994; Dor et al., 1995). However, it should be noted, that in the largest study by Kucuk et al. (2008), significantly more embryos were transferred

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### Table III Characteristics of the RCTs included in the meta-analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Embryo transfer policy</th>
<th>GH protocol</th>
<th>Use of placebo in the control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Owen et al. (1991)</td>
<td>Up to four embryos with evidence of normal cleavage were transferred. Remaining embryos of sufficient quality were cryopreserved</td>
<td>24 IU im/day on alternate days, starting simultaneously with hMG until the day of hCG administration</td>
<td>Yes</td>
</tr>
<tr>
<td>Zhuang et al. (1994)</td>
<td>Not reported</td>
<td>12 IU im/day on alternate days</td>
<td>Not reported</td>
</tr>
<tr>
<td>Bergh et al. (1994)</td>
<td>All embryos of good quality were transferred in both groups. No embryos were cryopreserved</td>
<td>0.1 IU/kg body weight/day sc, starting simultaneously with FSH until the day of hCG administration</td>
<td>Yes</td>
</tr>
<tr>
<td>Dor et al. (1995)</td>
<td>Not reported</td>
<td>18 IU sc on cycle day 2, 4, 6, 8</td>
<td>Yes</td>
</tr>
<tr>
<td>Suikkari et al. (1996)</td>
<td>Not reported</td>
<td>4 or 12 IU, starting on cycle day 3</td>
<td>Yes</td>
</tr>
<tr>
<td>Kucuk et al. (2008)</td>
<td>All embryos were transferred</td>
<td>4 mg (12 IU) sc, from day 21 of the preceding cycle and until the day of hCG administration</td>
<td>No</td>
</tr>
</tbody>
</table>

IU: international units, im: intramuscularly, hMG: human menopausal gonadotrophins, sc: subcutaneously, FSH: follicle stimulating hormone.

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**Figure 2** RD for clinical pregnancy rate in RCTs testing the addition of GH in ovarian stimulation for IVF.

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Suikkari et al., 1996). In all of the eligible studies no significant difference in the duration of stimulation was observed in patients who received GH as compared with those who did not.

**Gonadotrophin requirement**

No pooling of data was feasible for gonadotrophin requirement due to the fact that most studies reported medians with corresponding interquartile ranges (Owen et al., 1991; Bergh et al., 1994; Dor et al., 1995; Suikkari et al., 1996). However, it should be noted, that in the largest study by Kucuk et al. (2008), a significantly lower requirement for gonadotrophins was observed in the GH group (mean ± SD: 3187 ± 232 IUs of FSH) as compared with the control group (mean ± SD: 4070 ± 598 IUs of FSH) (P < 0.001).

**Number of COCs**

Combinable data were offered by two studies (Bergh et al., 1994; Kucuk et al., 2008). No statistically significant difference was observed in the number of COCs retrieved, which was higher in the group of patients who received GH (WMD: +0.56, 95% CI: −5.06 to +6.17; random effects model).

**Proportion of patients reaching embryo transfer**

Three studies offered data for this outcome (Bergh et al., 1994; Suikkari et al., 1996; Kucuk et al., 2008). A significantly higher proportion of patients treated by GH reached embryo transfer as compared with those treated by gonadotrophins only (OR: 5.06, 95% CI: 1.44–17.70; RD +22%, 95% CI: +7 to +36).

**Number of embryos transferred**

No pooling of data was feasible for number of embryos transferred due to the fact that most studies reported medians with corresponding interquartile ranges (Owen et al., 1991; Bergh et al., 1994; Dor et al., 1995). However, it should be noted, that in the largest study by Kucuk et al. (2008), significantly more embryos were transferred
in the GH group (mean ± SD: 3.3 ± 1.2) as compared with the control group (mean ± SD: 0.9 ± 0.7) (P < 0.001). In that study, all available embryos were transferred in both groups (Table III).

**Adverse events**
Slight oedema in two patients was reported in one study. Two studies reported no adverse events, while in the remaining three studies no information was available regarding the occurrence of adverse events associated with the use of GH.

**Subgroup analysis based on GH protocol**
Such an analysis was not feasible due to the limited number of RCTs available and the variability of the GH protocols used.

**Discussion**
Although several interventions have been tested for the management of poor responders, the probability of pregnancy in these patients remains disappointingly low (Kyrou et al., 2009). Despite the fact the present meta-analysis evaluates only six small trials, including 169 patients in total, the existing data provide evidence that addition of GH in poor responders undergoing ovarian stimulation with GnRH analogues and gonadotrophins for IVF increases the probability of clinically pregnancy and live birth. This finding persisted in all the sensitivity analyses performed.

It should be noted, that although no significant statistical heterogeneity was observed in the eligible studies, considerable clinical variability was present regarding (a) the definition of poor ovarian response, which raises concerns regarding the homogeneity of population analyzed in the eligible studies, (b) the protocol of GH administration, (c) the protocol used for inhibition of premature LH surge and (d) the protocol used for ovarian stimulation and luteal support. Accumulation of data originating from further well designed RCTs might allow the exploration of clinical heterogeneity and thus increase the robustness of the results obtained. Further trials might also make it possible to assess the optimal dose and scheme of GH administration, as well as its safety. In addition, they might also allow the proper evaluation of GH addition relative to the GnRH analogue protocol used during ovarian stimulation, which, however, based on the limited data analyzed in this review does not seem to have a moderating effect on the association between GH addition and pregnancy rates.

Furthermore, the eligible RCTs are characterized by methodological issues that deserve commenting and that should be addressed in future trials. A uniform definition of poor ovarian response, which was not present among the six eligible trials included in this meta-analysis, would have enhanced its external validity. True methods of randomization for allocation of patients to each treatment (reported only in three out of six studies included in this review) along with allocation concealment (which was clearly stated in only two of six eligible trials) would have enhanced the methodological integrity of the meta-analysis and, thus, the validity of the results obtained. Last but not least, in none of the studies included was a sample size calculation performed, and no individual study was properly powered to detect a clinically relevant difference in pregnancy rates. However, for binary outcomes such as pregnancy, in order to detect a clinically important difference, for instance 10%, a large number of patients would be required (approximately 430 patients to detect an increase in pregnancy rates of 10%, from 10 to 20%). Such figures are probably not feasible for a single RCT, especially considering that poor responders represent only a small proportion of patients undergoing IVF. For this reason, it is likely that combining results from RCTs on poor responders with the use of meta-analytical statistical models is the most realistic way of estimating the true effect of an intervention regarding the probability of pregnancy in this population, not disregarding the inherent limitations of meta-analysis.

The improvement in clinical pregnancy and live birth rates, observed in the current meta-analysis had already been demonstrated in a meta-analysis published by the Cochrane group six years ago (Harper et al., 2003) and confirmed in a recent meta-analysis, which was part of a systematic review of several interventions for the management of poor responders (Kyrou et al., 2009). The current meta-analysis adds a further RCT, with an adequate randomization procedure and a clear definition of poor ovarian response and embryo transfer policy (Tables I and III). This results in a 78% increase in sample size (addition of 61 patients). Although the total number of patients analyzed in the current meta-analysis remains small (n = 169), no change in the direction or the significance of the results obtained is present, while the width of the confidence interval of the estimates is

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>GH Events</th>
<th>Total</th>
<th>Control Events</th>
<th>Total</th>
<th>Risk Difference</th>
<th>M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dor et al., 1995</td>
<td>0</td>
<td>7</td>
<td>0</td>
<td>7</td>
<td>9.7%</td>
<td>0.00 [−0.24, 0.24]</td>
</tr>
<tr>
<td>Kucuk et al., 2007</td>
<td>10</td>
<td>31</td>
<td>5</td>
<td>30</td>
<td>42.3%</td>
<td>0.16 [−0.06, 0.37]</td>
</tr>
<tr>
<td>Owen et al., 1991</td>
<td>4</td>
<td>13</td>
<td>0</td>
<td>12</td>
<td>17.3%</td>
<td>0.31 [0.04, 0.57]</td>
</tr>
<tr>
<td>Sulkkari et al., 1996</td>
<td>2</td>
<td>16</td>
<td>0</td>
<td>6</td>
<td>12.1%</td>
<td>0.13 [−0.13, 0.38]</td>
</tr>
<tr>
<td>Zhuang et al., 1994</td>
<td>4</td>
<td>12</td>
<td>2</td>
<td>15</td>
<td>18.5%</td>
<td>0.20 [−0.12, 0.52]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>79</td>
<td></td>
<td>70</td>
<td>100.0%</td>
<td>0.17 [0.05, 0.30]</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>20</td>
<td></td>
<td>7</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: \( \chi^2 = 3.19, df = 4 (P = 0.53); I^2 = 0\%

Test for overall effect: \( Z = 2.67 (P = 0.008) \)

**Figure 3** RD for live birth rate in RCTs testing the addition of GH in ovarian stimulation for IVF.
reduced. Moreover, the present systematic review and meta-analysis focuses only on the addition of GH, and not GHRF. This approach, compared with the previous meta-analysis by Harper et al. (2003), reduces heterogeneity in terms of the intervention protocols used.

It is not clear by what mechanism GH addition increases the probability of pregnancy. However, a plausible explanation might be that GH addition is associated with an increased proportion of patients (+22%) who reach embryo transfer and thus are exposed to the chance of pregnancy. In the current meta-analysis, evidence supporting the proposed physiological mechanism of increased FSH responsiveness induced by GH was offered only by the largest study by Kucuk et al. (2008), in which a decreased requirement for gonadotrophins in patients receiving GH was observed.

It might be supported that the policy of transferring up to four or all available embryos is a realistic option for poor responders. This is due to the significantly decreased probability of pregnancy in these patients, who are usually at the end of their reproductive life. However, even for poor responders, the probability of multiple pregnancy and thus the associated risks should not be overlooked.

For a complete evaluation of the effectiveness of GH addition in ovarian stimulation for IVF in women with poor ovarian response, further parameters should be taken into consideration. Among these, the safety of GH addition should while be evaluated both for the patients as well as for their offsprings. Side effects have been reported with the use of GH (Liu et al., 2007). In the current systematic review and meta-analysis, due to the small number of studies analyzed and the unavailability of relevant information in three out of six studies, data on patient safety, although reassuring, could not be properly evaluated. More importantly, data on the health of the children born after ovarian stimulation with GH addition are not available. Furthermore, an increase in the cost of treatment with GH addition was reported in the study by Kucuk et al. (2008). In that study, the mean cost of treatment (±SD) in the group receiving GH was 4652.5 ± 229.1 USD, the mean cost of treatment in the group not receiving GH was 2272 ± 333.3 USD (P < 0.001). However, a thorough cost-effectiveness analysis evaluating GH addition in poor responders is currently lacking.

Poor ovarian response remains an unsolved problem in IVF until today and often leads couples to abandon treatment or seek oocyte donation. Currently, no single pharmacological intervention that could reliably increase the probability of pregnancy in poor responders is available. Thus, the fact that the addition of GH during ovarian stimulation enhances the probability of pregnancy needs to be urgently evaluated in further adequately-powered trials.

In conclusion, the present meta-analysis provides evidence that GH addition increases the probability of live birth in poor responders undergoing ovarian stimulation with GnRH analogues and gonadotrophins for IVF. However, the total number of patients analyzed is small and thus further RCTs are warranted to prove or disprove this finding.

Supplementary data

Supplementary data are available at http://humupd.oxfordjournals.org/.

References


Loh S, Wang JX, Matthews CD. The influence of body mass index, basal FSH and age on the response to gonadotrophin stimulation in


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