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The influence of different growth hormone addition protocols to poor ovarian responders on clinical outcomes in controlled ovary stimulation cycles

A systematic review and meta-analysis

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Abstract

Background: Growth hormone (GH) is used as an adjuvant therapy in in vitro fertilization and embryo transfer (IVF-ET) for poor ovarian responders, but findings for its effects on outcomes of IVF have been conflicting. The aim of the study was to compare IVF-ET outcomes among women with poor ovarian responders, and find which subgroup can benefit from the GH addition.

Methods: We searched the databases, using the terms "growth hormone," "GH," "IVF," "in vitro fertilization." Randomized controlled trials (RCT) were included if they assessed pregnancy rate, live birth rate, collected oocytes, fertilization rate, and implantation rate. Extracted the data from the corresponding articles, Mantel–Haenszel random-effects model, or fixed-effects model was used. Eleven studies were included.

Results: Clinical pregnancy rate (RR 1.65, 95% CI 1.23–2.22), live birth rate (RR1.73, 1.25–2.40), collected oocytes number (SMD 1.09, 95% CI 0.54–1.64), MII oocytes number (SMD 1.48, 0.84–2.13), and E_2 on human chorionic gonadotropin (HCG) day (SMD 1.03, 0.18–1.89) were significantly increased in the GH group. The cancelled cycles rate (RR 0.65, 0.45–0.94) and the dose of gonadotropin (Gn) (SMD –0.83, –1.47, –0.19) were significantly lower in patients who received GH. Subgroup analysis indicated that the GH addition with Gn significantly increased the clinical pregnancy rate (RR 1.76, 1.25–2.48) and the live birth rate (RR 1.91, 1.29–2.83).

Conclusion: The GH addition can significantly improve the clinical pregnancy rate and live birth rate. Furthermore, the GH addition time and collocation of medications may affect the pregnancy outcome.

Abbreviations: CI = confidence interval, E_2 = estradiol, FSH = follicle-stimulating hormone, GH = growth hormone, HCG = human chorionic gonadotropin, IVF-ET = in vitro fertilization and embryo transfer, POR = poor ovarian responders, RR = risk ratio.

Keywords: clinical outcomes, growth hormone, in vitro fertilization, poor ovarian responders

1. Introduction

Many different studies reported that the incidence of poor ovarian responders (POR) is increasing and vary from 9% to 24%. The problem of POR has been increased following the increasement of later marriage and childbearing in assisted reproductive technology (ART).[1–4] POR has been related to several factors, including advanced female age, high body mass index, and history of ovarian and pelvic surgeries.[5] However, the definition of POR was debatable and not unified for many

years. According to Bologna Criteria[6] in 2011, POR should be diagnosed as the result of the presence of at least 2 of the 3 features: age≥ 40 years or any other risk factor for POR, POR history (3 of fewer oocytes with ovulation induction), and low ovarian reserve test. Although the low successes, there are many intervention protocols that have been suggested to improve the outcome of IVF in poor responders, such as adding growth hormone as an adjuvant treatment to the stimulation protocols.[7] Many studies show that GH plays an important role in granulose cell, which can promote ovarian steroid genesis and follicular development.[8,9] The first report of GH role in POR which published 25 years ago is puzzling.[10] Four meta-analysis assessed the value of GH addition in IVF. A meta-analysis by Kolibianakis et al[11] had reported an increment in the clinical pregnancy rate and the live birth rate with the administration of GH in POR, however, the number of cases studied was too small. Kyrou et al[12] found an improvement on the probability of pregnancy with GH addition on day 2 versus day 3 of embryo transfer. A meta-analysis showed that GH supplement increased serum estradio (E_2) level on HCG day, Metaphase II (MII) oocyte number, 2PN number, and obtained embryo number,[13] however there was no significant difference on clinical pregnancy rate. A 2003 Cochrane review thought that the GH role in IVF needed further research.[14] The aim of this meta-analysis is compare IVF outcomes among women with POR who used GH or not, and find which subgroup can benefit from GH.

2. Materials and methods

This meta-analysis does not involve patients and, thus, do not require institutional review board approval. Databases including PubMed, Medline, Embase, and Cochrane Library were searched for reports published. The search terms were "growth hormone," "GH," "IVF," "in vitro fertilization." We also divided the included articles into 2 subgroups, 1 group was GH addition with Gn, and the other group was GH addition in the middle luteal phase, and then compared which subgroup could benefit from GH. In addition, the relevant studies were also searched in the references of selected articles and reviews.

Inclusion criteria were as follows: (1) the study population was POR or sub-optimal responders undergoing IVF or intra-cytoplasmic sperm injection (ICSI), with any ovarian stimulation protocol; (2) the selected articles were RCT; and (3) the reported outcomes were pregnancy rates, live birth number, cancelled cycles, collected oocytes number, MII oocytes number, implantation rate, fertilization rate, E_2 on HCG day and dose of gonadotropin.

The abstracts of all studies by keywords search were screened by 2 investigators (XL and FL). The eligible abstracts were evaluated independently by 2 reviewers (XL and XH). Any disagreement between 2 reviewers was resolved through discussion. If the abstract of a study was eligible, then 2 investigators (XL and LW) read and judged the whole article carefully.

Data for methods (type of articles, purpose of intervention, method of allocation, inclusion criteria), participant character-istics (number of participants and age), interventions (dose of GH, and other stimulation protocols), and outcomes (pregnancy rates, live birth number, cancelled cycles, collected oocytes, MII oocytes number, implantation rate, fertilization rate, E_2 on HCG day and dose of gonadotropin) were extracted by 2 reviewers (XZ and KL). Any disagreement between 2 reviewers was also resolved through discussion. Articles were also assessed for potential sources of bias, including the solution of randomiza-tion, allocation concealment, and blinding.

We used Review Manager 5.2 to analyze the results. Data are presented as mean ± standard deviation or number (%). Out-comes were sum up by cumulating risk ratio (RR) and 95% confidence intervals (CIs). χ^2 test and I^2 were used to assess the heterogeneity between studies. If the $I^2 > 50\%$ or $P < 0.10$ indicates significant heterogeneity, the Mantel–Haenszel ran-dom-effects model was used, otherwise, fixed-effects model was used.

3. Results

A total of 16 articles were fully eligible, 2 articles were not RCT, 1 article was no outcome of interest, and 2 articles were no full text, so 11 (663 patients) articles were included in this meta-analysis (Fig. 1, Table 1). The quality assessment of the included studies was presented in Fig. 2.

3.1. Pregnancy rate

All 11 studies, only 10 studies reported clinical pregnancy or clinical pregnancy rate, and were included in this meta-analysis (Fig. 3A). Six[15,16,18,20–22] studies showed an increase of pregnancy rate among women who received GH, whereas the difference did not reach to statistical significance. A pooled result using fixed-effects model showed that clinical pregnancy rate (RR 1.65, 95% CI 1.23–2.22; $p < 0.001$) was significantly increased in the GH group. There was no heterogeneity between studies ($I^2 = 0$).
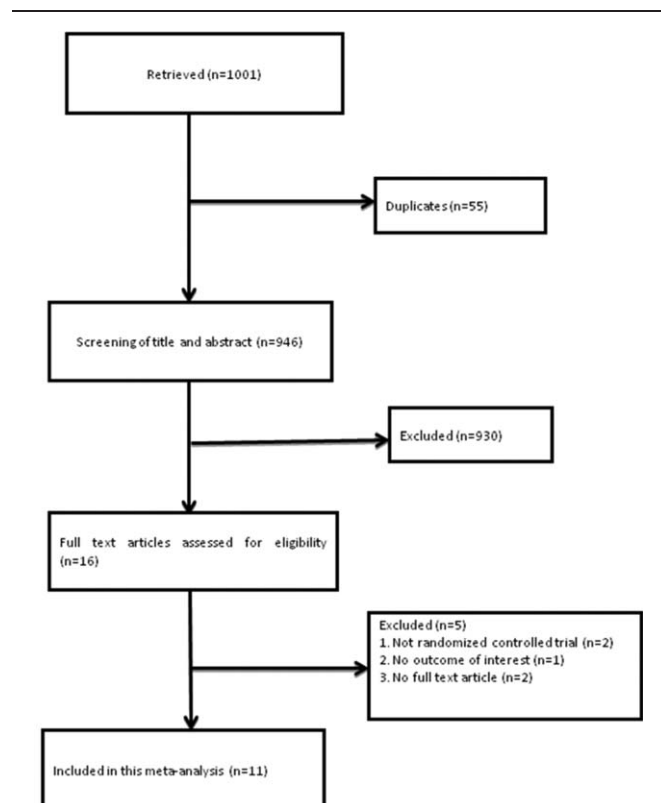

Figure 1. Flowchart of study selection.

Table 1

Included studies.

Study	RCT	Method of allocation	Intervention	GH/Control	Inclusion criteria	Outcome measures
Bassiouny et al[20]	Yes	Sealed envelopes	GH/HMG/GnRHant vs HMG/GnRHant, 7.5IU GH daily	68/73	Age≥40 years, history of POR, low ovarian reserve.	HMG dose, E2, M II oocytes number, collected oocytes number, clinical pregnancy rate.
Bayoumi et al[15]	Yes	Specific computer system and sealed envelops	GH/ HMG/ GnRHa vs HMG/ GnRHa, 2.5 mg GH daily	72/73	Age ≥40 years, previous POR, abnormal ovarian reserve	Clinical pregnancy rate, HMG dose, estradiol level, collected oocytes number, MII oocytes number, fertilization rates, implantation rates, clinical pregnancy rates.
Eftekhar et al[24]	Yes	Sealed envelopes	GH/HMG/GnRH antagonist vs HMG/GnRHant, 4IU GH daily	40/42	Previous failed IVF-ET cycles and/or E2≤500 pg/mL	HMG dose, E2 levels, collected oocytes number, clinical pregnancy rates, fertilization rate, implantation rate.
Kucuk et al[21]	Yes	Sealed envelopes	GH/FSH/GnRHa vs FSH/GnRHa, 12IU GH daily	31/30	Respond poorly to high dose gonadotropin	FSH dose, E2 level, MII oocyte number, implantation rate, clinical pregnancy number.
Guan et al[17]	Yes	Not stated	GnRHa/rFSH/GH/aspirin vs GnRHa/rFSH 4IU GH on alternate day	20/20	Respond poorly to gonadotropin	Collected oocytes number, MII oocyte number, pregnancy number.
Liu et al[18]	Yes	Not stated	GnRHa/rFSH/GH vs GnRHa/rFSH 4.5IU GH on alternate day	32/56	Poor responders	HMG dose, E2, levels, collected oocytes number, pregnancy rates, fertilization rate, implantation rate.
Suikkari et al[22]	Yes	Not stated	GH/FSH/GnRHa vs placebo, 4IU, 8IU GH daily	16/6	Oocytes retrieved≤2, serum FSH <16 mIU/mL	E2 level, fertilization rate, implantation number, pregnancy number.
Dor et al[25]	Yes	Not stated	GH/HMG/GnRHa vs placebo, 18IU GH on alternate days	7/7	17βoestradiol<501 pg/mL, less follicles, retrieved oocytes ≤3	HMG ampoules, pregnancy number, fertilization rate.
Bergh et al[23]	Yes	Not stated	GH/HMG/GnRHa vs placebo, 5–6IU GH daily	9/9	Poor responders	HMG dose, E2 level, pregnancy number, fertilization rate.
Zhuang et al[16]	Yes	Not stated	GH/ HMG/ GnRHa vs HMG/ GnRHa,2IUGH alternate day	12/15	Respond poorly to gonadotropin	Collected oocytes number, pregnancy number, fertilization rate,
Owen et al[19]	Yes	Not stated	GH/HMG/GnRHa vs placebo,24IU GH alternate day	13/12	Respond suboptimally	HMG dose, pregnancy number

E₂ = estradiol, FSH = follicle-stimulating hormone, GH = growth hormone, GnRHa = GnRH agonist, GnRHant = GnRH antagonist, HMG = human menopausal gonadotropin, IVF-ET = in vitro fertilization and embryo transfer.

3.2. Live birth rate

Nine studies reported live birth rate, and 9 studies were included in this meta-analysis (Fig. 3B). The meta-analysis showed that GH addition could significantly increase the live birth rate (RR 1.73, 95% CI 1.25–2.40; $P < 0.001$) per transfer cycle. There was no heterogeneity between studies ($I^2 = 0$).

3.3. Cancelled cycles rate

Seven of the 11 studies[15,20–24] reported the cancelled cycles rate in the meta-analysis (Fig. 3C). Pooling their results showed that the cancelled cycles rate (RR 0.65, 95% CI 0.45–0.94; $P = 0.02$) was significantly lower in patients who received GH. There was no heterogeneity among studies ($I^2 = 0$).

3.4. Implantation rate

The implantation rate was reported in 5 studies, which were included in this meta-analysis (Fig. 3D). The pooled analysis demonstrated no significant difference in the implantation rate (RR 1.05, 95% CI 0.56–1.99; $P = 0.87$). There was high heterogeneity between the studies ($I^2 = 73\%$).

3.5. Fertilization rate

A total of 7 studies reported on the fertilization rate and were included in this meta-analysis (Fig. 4A). There was no significant difference between the GH group and the control group in the fertilization rate (RR 0.99, 95% CI 0.85–1.15; $P = 0.89$). High heterogeneity existed between the studies ($I^2 = 73\%$).

Figure 2. Quality assessments of included studies. ? = unclear, + = low risk, − = high risk.

3.6. Collected oocytes number

Six studies reported collected oocytes number and were included in the meta-analysis (Fig. 4B). The pooled results indicated that the GH addition significantly increased collected oocytes number (SMD 1.09, 95% CI 0.54–1.64; $P < 0.001$). There was high heterogeneity between the studies ($I^2 = 87\%$).

3.7. MII oocyte number

Five studies reported MII oocytes number and were included in the meta-analysis (Fig. 4C). The pooled results indicated that the GH addition significantly increased MII oocytes number (SMD 1.48, 95% CI 0.84–2.13; $P < 0.001$). There was high heterogeneity between the studies ($I^2 = 89\%$).

3.8. E_2 on HCG day

Seven studies reported E_2 level on HCG day and were included in the meta-analysis (Fig. 4D). Pooling their results showed that E_2 on HCG day (SMD 1.03, 95% CI 0.18–1.89; $P = 0.02$) was significantly higher in patients who received GH. High heterogeneity existed between the studies ($I^2 = 95\%$).

3.9. Dose of gonadotropin

Eight studies reported dose of gonadotropin but only 4 were included in the meta-analysis (Fig. 4E). Two studies used ampules as measure, which were different from other studies.[22,25] Two studies used median was also excluded.[18,23] The dose of gonadotropin (SMD −0.83, 95% CI −1.47, −0.19; $P = 0.01$) was significantly lower among patients who received GH than among those who was in the control group. There was high heterogeneity between the studies ($I^2 = 90\%$).

3.10. Subgroup analysis

Seven articles[15,16,18,19,20,22,23] were included in the GH addition with Gn group, clinical pregnancy rate (RR 1.76, 95% CI 1.25–2.48; $P = 0.001$) and live birth rate (RR 1.91, 95% CI 1.29–2.83; $P = 0.001$) was significantly increased in this group (Fig. 5A). There was no heterogeneity among studies ($I^2 = 0$). Three articles[17,21,24] were included in the GH addition in the middle luteal phase group, there were no significant differences for clinical pregnancy rate (RR 1.37, 95% CI 0.76–2.47; $P = 0.30$) (Fig. 5B) and live birth rate (RR 1.37, 95% CI 0.76–2.47; $P = 0.30$) (Fig. 5B) in the GH addition in the middle luteal phase group, there was no heterogeneity among studies ($I^2 = 0$).

3.11. Adverse events

Only 1 study reported slight edema in 2 patients for a short period during treatment. Six studies reported no adverse effects during the process of studies, while the other 4 studies had no related information about the effect of GH addition.

4. Discussion

The present systematic review and meta-analysis of RCT demonstrated that co-treatment with GH in controlled ovary stimulation cycles significantly improved clinical pregnancy rate, live birth rate, collected oocytes number, MII oocytes number and E_2 on HCG day in POR. Besides, cancelled cycles rate and dose of gonadotropin were significantly lower in patients who received the treatment of GH. There were no significant differences between the GH and control groups on the implantation rate and the fertilization rate. The subgroup analysis indicated that the GH addition with Gn group significantly increased the clinical pregnancy rate and the live birth rate, however, as for the clinical pregnancy rate and live birth rate at the GH addition in the middle luteal phase group, no significant differences were found.

GH plays an essential role in the function of ovarian, as it can stimulate the growth and function of granulose cells by increasing intraovarian production of insulin-like growth factor-1 (IGF-1).[9] Research on animal and human have shown that GH is important for ovarian steroidogenesis and follicular development. Co-treatment with GH improves the Gn effects on granulose cells. Regarding the use of GH, a study showed that mouse oocyte maturation was significantly affected by treating
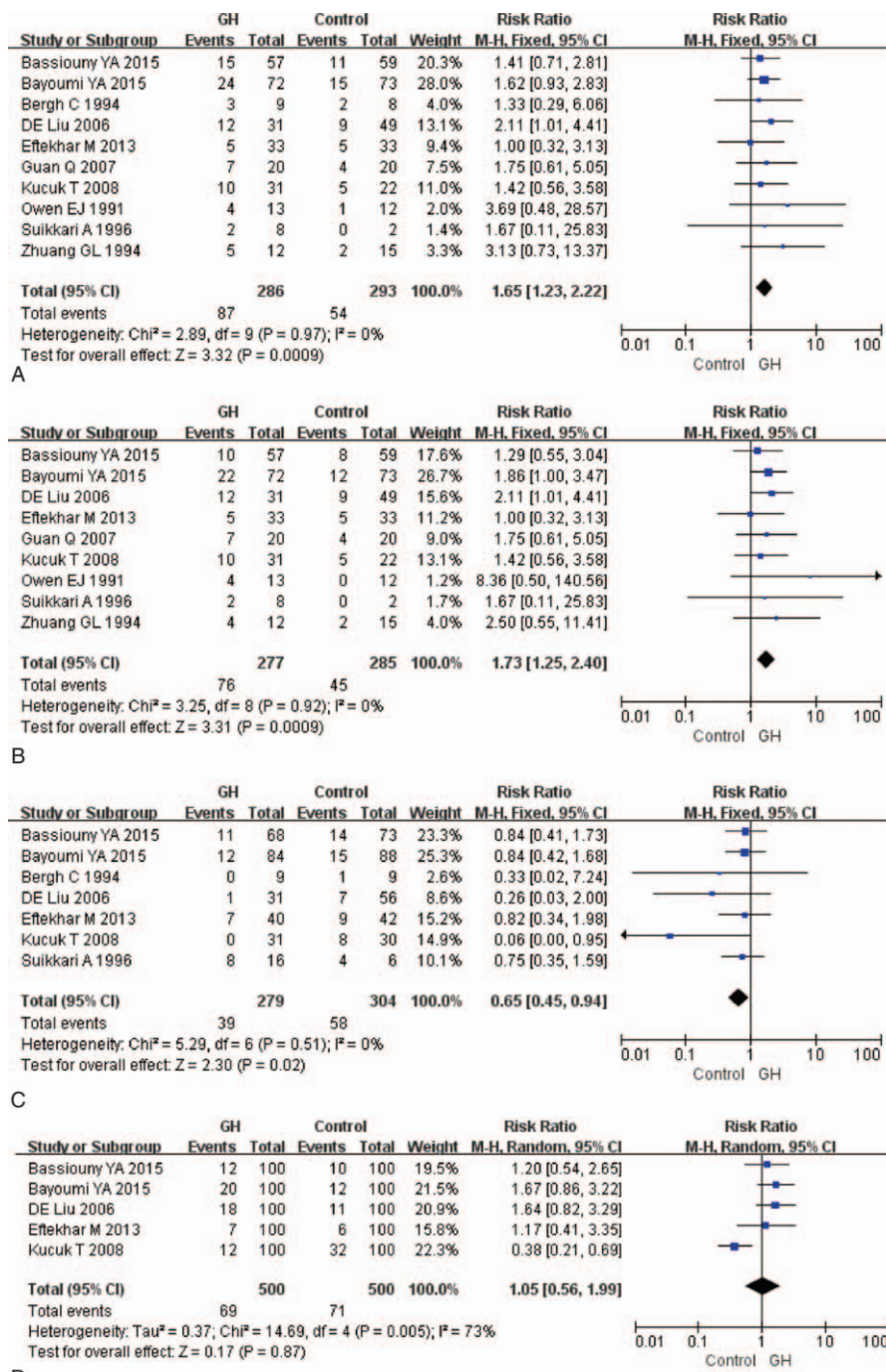
Figure 3. Forest plots for (A) clinical pregnancy rate, (B) live birth rate, (C) cancelled cycles rate, and (D) implantation rate. CI = confidence interval, GH = growth hormone.

with GH and IGF-1, respectively or collectively [26]. A recent meta-analysis about different therapeutic protocols for ovarian stimulation of POR found that GH addition could improve clinical pregnancy rate and live birth rate, however the total numbers in the meta-analysis were small (251 patients) to draw any definitive conclusions.[27] A review of 2009 about several interventions for patients with POR reported that GH addition appeared to improve the probability of pregnancy. In another meta-analysis,[11] which included 6 RCT examined addition of GH to Gn in ovarian stimulation of POR and found that GH

addition significantly increased the clinical pregnancy rate and live birth rate, as in the present study (11RCT). However, a meta-analysis by Yu et al reported that no significant difference was found for clinical pregnancy rate between the GH and control groups, which was not consistent with the present meta-analysis, the author speculate that it may be associated with the quality of the included articles (6 RCTs and 5 CCTs) or the difference of analysis methods.

A study which compared 4 stimulation protocols in POR with GH addition showed that number of retrieved and fertilized
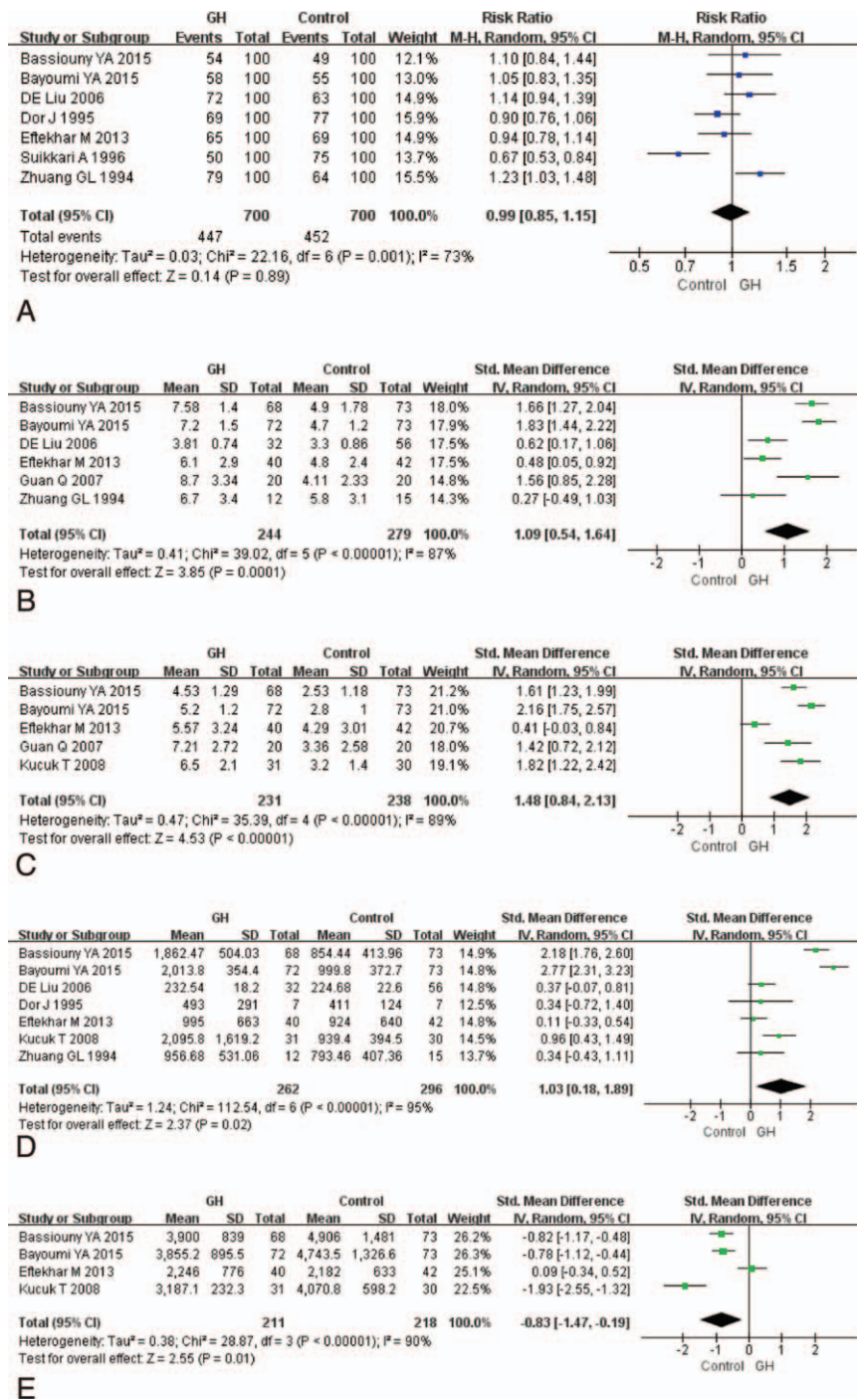
Figure 4. Forest plots for (A) fertilization rate, (B) collected oocytes number, (C) metaphase II oocyte number, (D) E_2 on HCG day, and (E) dose of gonadotropin. CI = confidence interval, GH = growth hormone.

oocytes were highest in the long/GH protocol when compared in the rest of the protocols, while considering the clinical pregnancy rate, there was a difference for the long/GH protocol but the difference did not reach statistical significance.[28] Some investigators had been confirmed low-dose GH supplementation increased clinical pregnancy rate in POR undergoing IVF.[29] Another study showed the pregnancy rate was higher in the GH group than in the control group in patients with repeated IVF failures.[30] In a sequential crossover study, GH supplementation

improved implantation rate[31] in poor-prognosis patients which is different from our result, we speculate that it may be connected with the different expression of rate. One study demonstrated GH addition significantly increased in the fertilization rate for those patients who had ICSI in GH deficiency patients.[32] There was evidence that GH addition significantly lower cycle cancellations in POR with micro dose gonadotropin releasing hormone (GnRH) agonist protocol[33] which was consistent with the present meta-analysis. However, retrospective matched case-
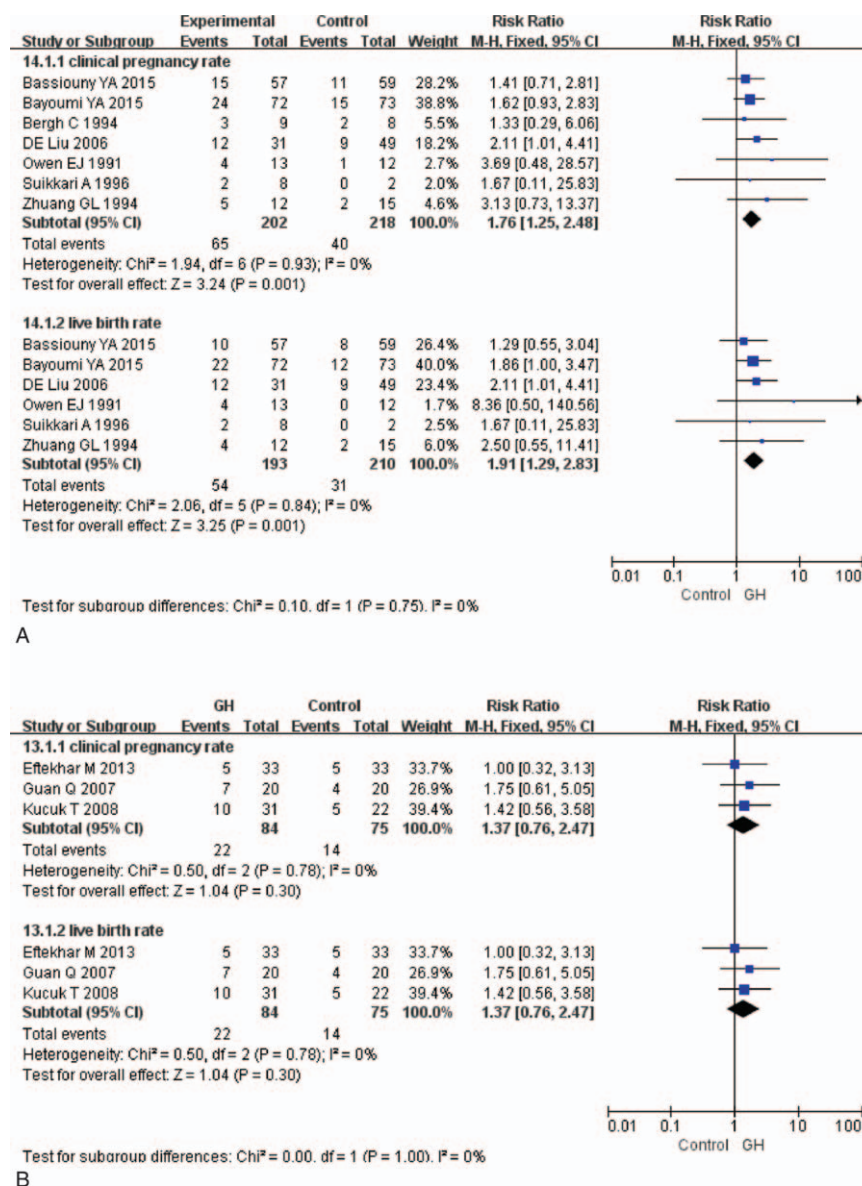
Figure 5. Forest plots for subgroup analysis (A) GH addition with Gn subgroup, and (B) GH addition in the middle luteal phase subgroup. CI = confidence interval, GH = growth hormone, Gn = Gonadotropin.

control study reported there was no difference between the groups in clinical pregnancy rate and cycle cancellation rate in POR patients,[34] which is different from our analysis. Result of Gregoraszczuk et al[35] demonstrated that the influence of exogenous GH on steroid secretion by granulose cells and theca cells recovered from different follicles, GH addition stimulated both estradiol and progesterone secretion from large preovulatory follicles. However, Tapanainen et al[36] suggested that serum E_2 concentration was lower in the GH group than in the placebo group of HCG day for normally cycling women in vitro fertilization, which was not a finding of the present meta-analysis.

Potential limitation of the present study includes the inclusion of different dose of GH addition, and the different definition of POR. Furthermore, 2 articles are different from the other articles. One article had 4 groups, but only group I and group II were included, because group I is about GH use with standard protocol

and group II is about standard treatment, Groups III and IV about GH preprocessing were eliminated. Another study included 3 groups, placebo, GH4 IU and GH 12 IU, as only 2 groups could be compared for the software, the 2 GH groups were merged and compared with placebo group in this meta-analysis. These 2 studies were analyzed separately and no significant difference in the overall result was recorded, so it was decided to add these 2 studies and analyze all 11 studies together.

Regarding to the heterogeneity of the included studies, there was high heterogeneity in the analysis except the pregnancy rate, live birth rate, and cancelled cycles rate. The sources of heterogeneity between the studies may be related to the different timings and doses of GH.

In summary, GH administration can improve the ovarian response in the patients with POR.[37] The addition of GH significantly improved the clinical pregnancy rate, live birth rate,

number of oocytes collected, MII oocyte number, and E_2 on HCG day in POR. Besides, the cancelled cycles rate and dose of Gn were significantly lower in patients who received GH. No significant differences were found between the GH and control groups for the implantation rate and the fertilization rate. The subgroup analysis showed GH addition with the Gn group significantly increased the clinical pregnancy rate and the live birth rate. Furthermore, for the GH addition in the middle luteal phase group, no significant differences were found for the clinical pregnancy rate and the live birth rate. As the total number of patients analyzed in the GH addition with Gn group and the GH addition in the middle luteal phase group is small and further larger RCT with adequate simple sizes are needed to reach more definitive verdict.

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