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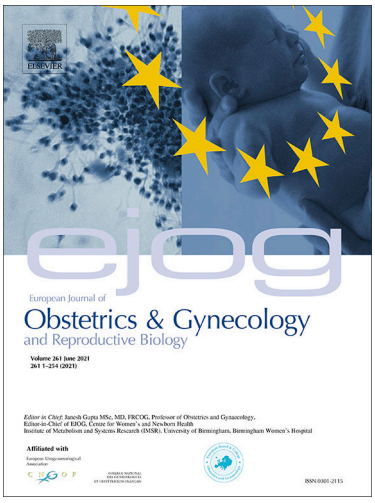

Review article

Recombinant-luteinzing hormone supplementation in women during IVF/ ICSI cycles with GNRH-antagonist protocol: a systematic review and meta-analysis

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RECOMBINANT-LUTEINZING HORMONE SUPPLEMENTATION IN WOMEN DURING IVF/ICSI CYCLES WITH GNRH-ANTAGONIST PROTOCOL: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract

The objective of this meta-analysis is to determine the beneficial effect of recombinant-luteinizing Hormone (r-LH) addition in women undergoing in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) with gonadotropin-releasing hormone (GnRH) antagonist protocol and whether an optimal time of Recombinant-Luteinizing Hormone (r-LH) supplementation exist during the controlled of stimulation (COS). The primary outcomes are clinical Pregnancy rate and the number of oocytes retrieved. Secondary outcomes are the number of metaphase II oocytes, miscarriage rate and live birth rate. Results show that supplementation of LH generated a greater number of oocytes retrieved than patients who did not receive LH supplementation, but it did not help with other pregnancy outcomes. Furthermore, the result of the subgroup analysis revealed no significant difference in the outcomes with different LH addition times.

Keywords:

Recombinant Luteinizing hormone; Assisted reproductive technology; In vitro fertilization; Luteinizing hormone supplementation; Controlled of Stimulation; GnRH-antagonist protocol; Optimal time of r-LH supplementation

Introduction

GnRH antagonist protocol gained popularity in COS due to its advantage of shorter treatment duration, lower OHSS risk, and lack of flare-up effect, with the mechanism that competitive and reverse binding to GnRH receptors in the pituitary gland reduces GnRH action and inhibits LH and FSH that release from the anterior pituitary(1). Numerous studies demonstrated that it prevented Ovarian hyperstimulation syndrome (OHSS). Lambalk's article showed that GnRH antagonists had a similar continued pregnancy rate with reduced OHSS in PCOS patients, poor responders, and normal responders(2). The GnRH antagonist protocol was related to a similar live birth rate, continued pregnancy rate, and a lower incidence of OHSS, according to a 2010 study(3) Thus, ESHRE recommends GnRH antagonists for all populations.

However, GnRH antagonist protocol had limitations. Compared to GnRH agonist, GnRH antagonist had fewer retrieved oocytes and a lower clinical pregnancy and live birth rate(4). It may be due to the GnRH antagonist's effect on endometrial receptivity and reduced serum oestradiol during follicular recruitment(5). Depending on an individual's sensitivity to GnRH antagonist, the LH serum level may be over-suppressed. A low LH level that does not meet the LH threshold might result in several side effects, including the absence of paracrine signaling between granulosa and theca, androgen synthesis, and complete oocyte maturation(6). Low LH (1 mIU/mL) caused fewer viable embryos and a decreased live birth rate, according to Luo's research(7). With research on LH's role in follicular recruitment thriving, it has been shown that exogenous LH increased androgen production for its late aromatization to estrogens and improved oocyte quality and implantation rates(8). Another study suggested that LH stimulates CYP17 to convert progesterone into androgen, which can further develop into estrogens, benefiting the endometrium by decreasing the risk of premature progesterone depletion(9).

Numerous articles proved the importance of recombinant Luteinizing hormone (rLH) in follicular recruitment. However it remained controversial if exogenous LH was advantageous for IVF patients,

GnRH antagonist protocol in particular. In GnRH agonist protocol, a single dose of triptorelin depot can suppress LH for up to eight weeks(10), which could cause LH insufficiency. Exogenous LH was indicated to be supplemented with FSH in women with LH and FSH deficiency(11). Until now, there were two meta-analyze articles on the supplementation of LH in the GnRH-antagonist protocol and one article on the supplementation of LH in patients of advanced ages: Xiong found no significant difference between LH supplementation and r-FSH alone in women undergoing IVF/ICSI with the GnRH antagonist protocol(12). The combination of r-LH and r-FSH may prevent a decline in oestradiol after antagonist delivery and boost the number of metaphase II oocytes(13). Conforti showed that r-LH and r-FSH co-treatment could enhance pregnancy and implantation rates in women ages 35 to 40(14). Neither article compared LH addition time, and there was no consensus for the optimal LH addition time. This paper compares LH addition timing on pregnancy outcome by subgroup analysis.

This meta-analysis aimed to compare the efficacy of recombinant LH supplementation in women undergoing assisted reproduction with stimulation with recombinant FSH for protocols of ovarian stimulation with antagonists in IVF/intracytoplasmic sperm injection (ICSI) cycles with some critical outcomes: clinical pregnancy rate, number of oocytes retrieved, number of metaphase II oocytes, miscarriage rate and live birth rate. This meta-analysis also determines whether the timing of LH addition affects the final pregnancy outcome.

Method:

Systematic search and strategy

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines(15). This study was exempted from institutional review board approval as it did not involve any human intervention. The study protocol was registered at http://www.crd.york.ac.uk/PROSPERO/ (registration number CRD42022351329) before quantitative analysis.

Search Strategy and Participants

A systemic search of the relevant literature was performed restricted to randomized controlled trials (RCTs) and articles in English. We mainly explored electronic databases (PUBMED, MEDLINE, EMBASE, Web of science and Cochrane Library) and clinical trial registries (ClinicalTrials.gov and the World Health Organization [WHO] international clinical trial registry platform) for the relevant studies about the effect of the combination of r-LH with r-FSH for COH in patients undergoing IVF/ICSI with GnRH-antagonist protocol on IVF/ICSI outcomes, published up to 12nd August 2022. The following search strategy was used: ("luteinizing hormone" or "recombinant luteinizing hormone" or "lh" or "r-LH" or "hlh" or "recombinant lh" or "ovarian stimulation" or "recombinant FSH" or "lutropin alfa" or "recombinant human LH") AND ("GnRH antagonist") AND ("assisted reproductive techniques" or "ART" or "IVF" or "ICSI" or "in vitro fertilization" or "intracytoplasmic sperm injections") AND ("randomized controlled trial" or "clinical trial" or "multicenter study" or "controlled study" or "double blind procedure" or "single blind procedure").

Inclusion and Exclusion Criteria

Inclusion criteria were RCTs that compared the effect of recombinant follicle-stimulating hormone

(r-FSH) alone and in combination with recombinant luteinizing hormone (r-LH) in women undergoing IVF/ICSI with GnRH antagonist protocol on IVF/ICSI outcomes. Exclusion criteria included failure to report appropriate randomization procedures, participants as poor responders, or outcomes unclear or inappropriate. Two authors (HL, ML) conducted data extraction using predefined data fields.

Data Extraction and Quality Assessment

The risk of bias in individual studies was assessed independently by two reviewers (AS and SJ) using the Cochrane risk of bias tool 2.0 for randomized trials(16). The overall quality of the evidence was graded according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group guidelines(17).

Study Outcomes

The primary outcome was the clinical pregnancy rate per started cycle, defined according to the International Glossary on Infertility and Fertility Care as "A pregnancy diagnosed by ultrasonographic visualization of one or more gestational sacs or definitive clinical signs of pregnancy" (18) and the number of oocytes retrieved. Secondary outcomes were the number of metaphase II (MII) oocytes, miscarriage, and live birth rate.

Statistical Analysis

All the data management, relevancy and duplication removal, and eligibility assessment as per PRISMA guidelines were performed using Microsoft Excel. Statistical analysis was conducted using Review Manager 5.4 (The Nordic Cochrane Centre, The Cochrane Collaboration). We calculated the pooled odds ratio (OR) for dichotomous data and weight mean difference (WMD) for continuous data with an associated 95% confidence interval (CI). Given that the studies included in this review differ significantly in terms of dosage used, protocols and ethnicity, we used a random effect model to account for sources of variations among studies because it is a more conservative approach than the fixed effect model(19). Heterogeneity was assessed using the percentage of the total variation in the estimated effect across studies (I^2). A fixed effects (FE) model was used when heterogeneity was low (I^2<50%), and a random effects (RE) model was used when I^2 was greater than 50%. If the P value for heterogeneity was < 0.05 or I^2 is >50%. The heterogeneity was considered statistically significant.

Subgroup and sensitivity analysis

Sensitivity analysis was carried out by measuring the overall effect size of all groups. Expressly, studies judged to be at a high risk of bias for at least one issue or at an unclear risk for at least two issues according to the risk of bias assessment tool were excluded from the analysis. In addition, we performed subgroup analyses of studies in which only r-LH supplementation is either added in D1 or with GnRH-Antagonist. Finally, we performed a subgroup analysis of studies in which vitrification was used as the sole method for the optimal time for r-LH addition.

Results

Our systematic search generated 869 records. Another ten records were added from reference lists. After removing duplications, 493 references were screened by analyzing the titles and abstracts.

After analyzing the full text of 15 studies, we selected ten studies to be included in the review and nine studies to be included in the meta-analysis. The PRISMA flow diagram details our search results shown in supplementation table 1.

Those nine studies included patients undergoing IVF/ICSI with GnRH-antagonist protocol. Experiment groups are patients who receive r-FSH/r-LH co-treatment in either D1 or D5/6 with GnRH antagonists. The LH addition time is included in supplementation table 2. The control group are patients who only receive r-FSH monotherapy. Our systematic search yielded 1 study in which the r-FSH/HMG group was the experiment group and the r-FSH/r-LH group was the control group, and therefore excluded from the review. Table 1 presents the characteristics of the selected studies and the quality of evidence using GRADE.

Primary outcome

Clinical Pregnancy per ET

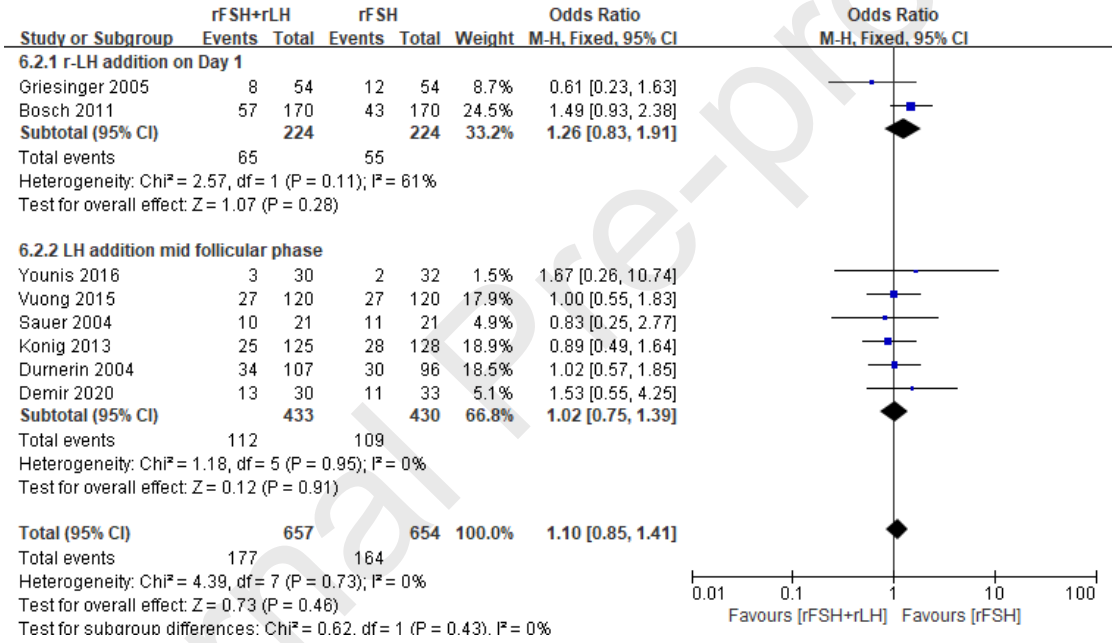

Figure 1: Forest plot of clinical pregnancy per ET with or without r-LH supplementation for COS in patients undergoing IVF or ICSI-ET with GnRH antagonist protocol, and the subgroup analysis in different r-LH supplementation day.

Figure 1 demonstrates the effect of r-LH supplementation on the clinical pregnancy rate. 8 trials with 1311 patients provided data on the clinical trial per ET. The pooled analysis with these 8 trials did not show differences between the r-LH supplementation group and the r-FSH monotherapy group (8 trials: OR 1.10; 95% CI 0.85 to 1.41), and there was no indication of statistical heterogeneity(I^2=0%)

In the subgroup of patients receiving r-LH at different time points (Fig.1), two studies (8, 20) in which r-LH is administrated on Day 1 and r-FSH. In contrast, the rest of the studies have r-LH addition during mid to late follicular recruitment. Results show no significant difference in clinical pregnancy per ET between LH addition time points.

Number of retrieved oocytes

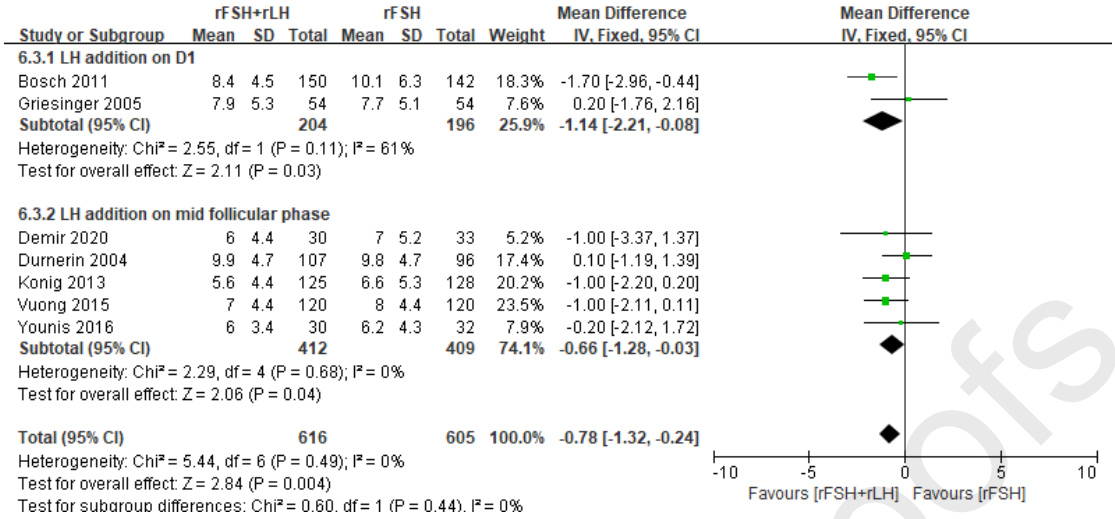

Figure 2. Forest plot of number of retrieved oocytes with or without r-LH supplementation for COS in patients undergoing IVF or ICSI-ET with GnRH antagonist protocol, and the subgroup analysis in different r-LH supplementation day.

Figure 2 demonstrates the effect of LH supplementation on the number of oocytes retrieved. 7 trials with a total of 1221 patients provided data on the number of oocytes retrieved. The pooled analysis with these 7 trials did not show differences between the r-LH supplementation group and the r-FSH monotherapy group (7 trials: WMD -0.78; 95% CI -1.32 to -0.03), and there was no indication of statistical heterogeneity(I^2=0%)

In addition, according to Figure 2, the subgroup analysis demonstrates that patients receiving r-LH supplementation on D1 and during the COS have a more significant number of oocytes retrieved. There is no indication of statistical heterogeneity (I^2=0%).

Secondary Outcome

Number of metaphase II oocytes

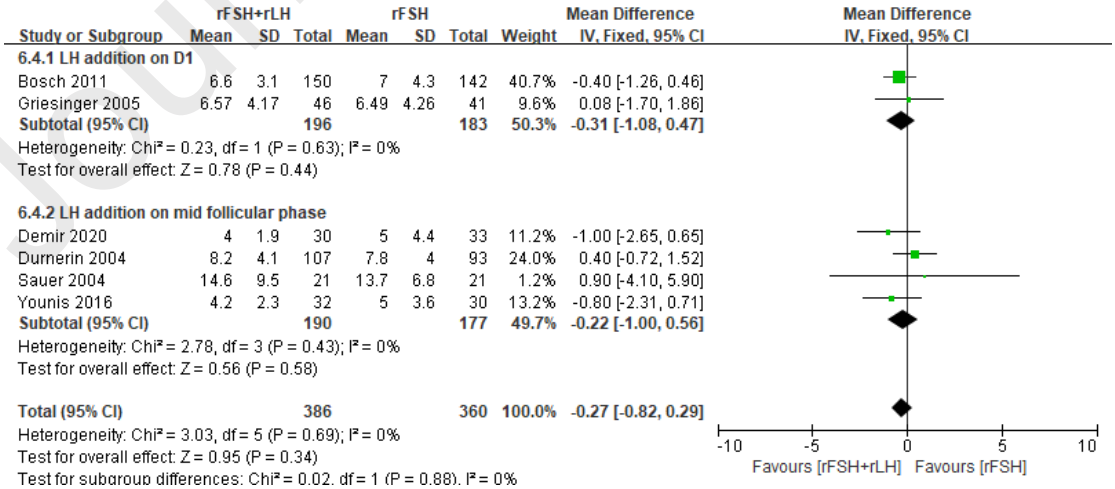

Figure 3. Forest plot of number of metaphase II oocytes with or without r-LH supplementation for COS in patients undergoing IVF or ICSI-ET with GnRH antagonist protocol, and the

subgroup analysis in different r-LH supplementation day.

Figure 3 displays 6 trials with a total of 746 patients provided data on the number of metaphase II oocytes. The pooled analysis with these 6 trials did not show differences between the r-LH supplementation group and the r-FSH monotherapy group (6 trials: WMD -0.27; 95% CI -0.82 to 0.29), and there was no indication of statistical heterogeneity(I^2=0%)

The subgroup analysis supported the argument that the time of LH addition does not significantly affect the metaphase II oocytes, according to figure 3.

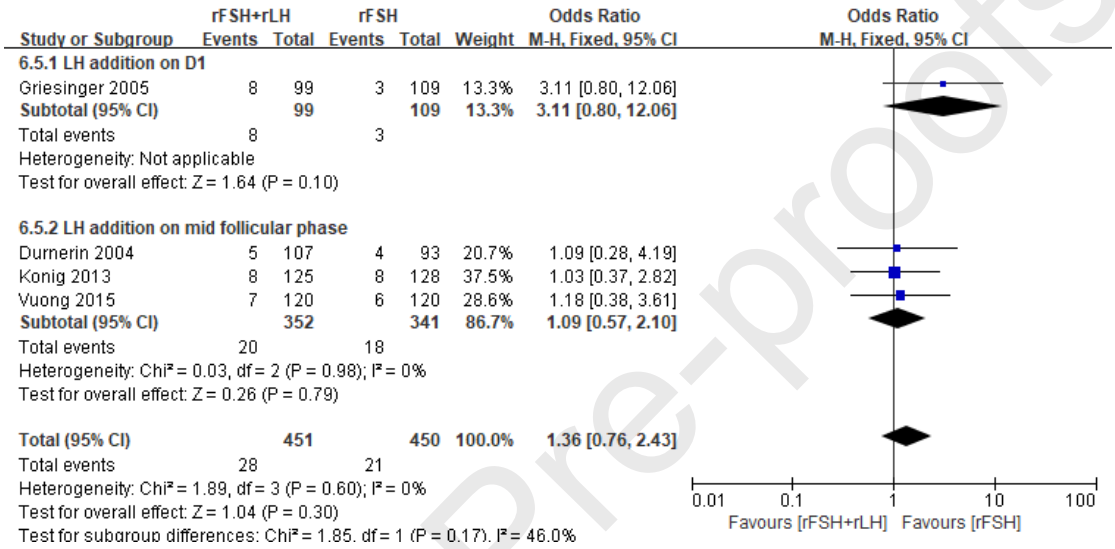

Figure 4. Forest plot of miscarriage rate with or without r-LH supplementation for COS in patients undergoing IVF or ICSI-ET with GnRH antagonist protocol, and the subgroup analysis in different r-LH supplementation day.

4 trials with a total of 901 patients provided data on the miscarriage rate (Fig.4). The pooled analysis with these 4 trials did not show differences between the r-LH supplementation group and the r-FSH monotherapy group (6 trials: OR 1.36; 95% CI 0.76 to 2.43), and there was no indication of statistical heterogeneity(I^2=0%)

Moreover, the subgroup analysis that Figure 4 displays shows no significant difference in miscarriage rate despite the r-LH being supplied at different time points.

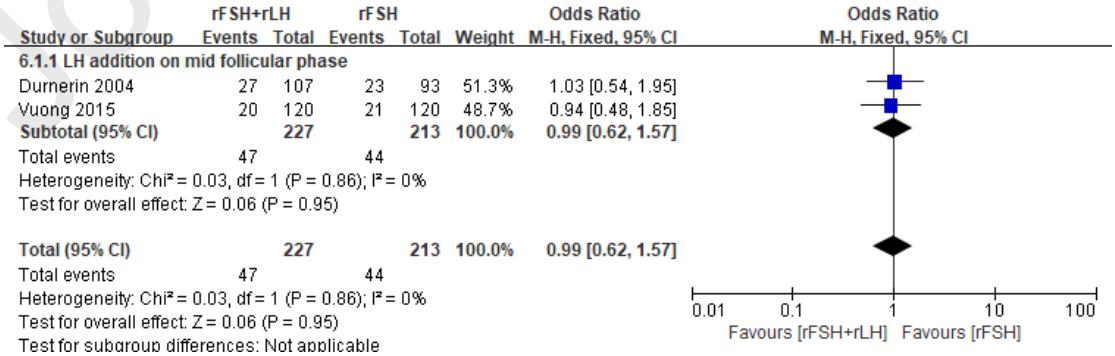

Figure5. Forest plot of live birth rate with or without r-LH supplementation for COS in patients undergoing IVF or ICSI-ET with GnRH antagonist protocol

2 trials with a total of 440 patients provided data on the live birth rate (Fig.5). The pooled analysis with these 2 trials did not show differences between the r-LH supplementation group and the r-FSH monotherapy group (2 trials: OR 0.99; 95% CI 0.62 to 1.57), and there was no indication of statistical heterogeneity(I^2=0%)

Sensitivity analysis

Sensitivity analysis conducted excluding studies with a high risk of bias revealed that the pooled effect sizes were not affected by any outcome addressed (Supplementary Figure 2). studies judged to be at a high risk of bias for at least one issue or at an unclear risk for at least two issues according to the risk of bias assessment tool were excluded from the analysis.

The quality of evidence

We access the quality of the evidence on the primary outcomes (Clinical Pregnancy rate and Number of Oocytes and secondary outcomes(number of metaphase II, miscarriage rate and live birth rate) using the five GRADE considerations: risk of bias, consistency, imprecision, indirectness and publication bias. The result of GRADE has illustrated according to Supplementary Table 1.

Discussion

This systematic review investigated the efficacy of r-LH supplementation in patients undergoing IVF/ICSI with a GnRH-antagonist protocol. The overview of all literature included in this meta-analysis is presented in Supplement Table2. We discovered that r-LH treatment had no effect on clinical pregnancy rate, number of metaphases II, miscarriage rate, or live birth rate; however, it did increase the number of oocytes recovered. In addition, subgroup analysis revealed that the time of r-LH supplementation did not affect the pregnancy outcomes. There is no significant correlation between receiving r-LH on day 1 and during the COS on these outcomes.

Many animal and cell experiments affirmed the luteinizing hormone's role in follicular recruitment and maturation. According to the two-cell two-gonadotropin theory, the luteinizing hormone promotes thecal cells to generate androgens and the follicle-stimulating hormone-stimulated granulosa cells to produce estrogens from androgens(20). Moreover, adding exogenous LH significantly stimulated aromatase activity, increased serum E2 and amplified FSH responsibility in follicular recruitment and growth (21).

r-LH was usually administered on Day 1 of stimulation because of the suppression caused by GnRH-a suppression. There were several arguments in favour of r-LH supplementation. First, adding GnRH antagonist influenced endometrial receptivity, diminishing the pregnancy outcome. The conversion of progesterone produced by the theca and granulosa cells into androgen was stimulated by exogenous LH. As r-LH supplementation decreased serum progesterone levels during the COS, the two-cells and two-gonadotropin theory predicted that endometrial receptivity and pregnancy success would increase. An additional theory that justified the addition of r-LH to the GnRH antagonist treatment: 33 per cent of patients had an increased LH level during stimulation, which was at risk for hyper-response to the antagonist. Rising LH during the first five days of stimulation may predispose patients to a sharp LH drop following the first GnRH antagonist dose and the need for additional LH addition (22). However, a series of research, including Merviel(23), did not

demonstrate an improvement in the pregnancy outcome of GnRH-antagonist patients when r-LH was administered during the COS. Our research supported this assertion.

It was highly contentious whether r-LH should be addressed during the COS, as indicated by the inconsistent results of numerous RCTs. There were many LH supplementation strategies, including the delivery of r-LH to patients with an LH level < 1.2IU/mL: Patients with a serum LH level below 1.2 IU/L are considered to have hypogonadotropic hypogonadism, according to one study(24), when they received HMG following luteal GnRHa downregulation, their clinical pregnancy rate and delivery rates were significantly higher than those of the control group. In addition, a second study(7) discovered that a low endogenous LH level (LH<1.5mIU/mL) on day 1 is related to adverse ART outcomes, including fewer oocytes, a lower clinical pregnancy rate, and a lower live birth rate. On the first day of COS, patients with low endogenous LH levels may benefit from r-LH supplementation. However, more randomized controlled trials are required to determine the effect of r-LH in GnRH antagonists.

Our investigation found that exogenous Luteinizing hormone did not affect the pregnancy outcome. We assessed five distinct pregnancy outcomes, including two primary and three secondary outcomes. In four of the outcomes, subgroup analysis of the various supplementation timings has also been done. We did not undertake a subgroup analysis for the live birth rate since the studies included in this meta-analysis did not provide sufficient information regarding this pregnancy outcome. Our findings implied that adding the luteinizing hormone to a GnRH-antagonist protocol can only increase the number of oocytes retrieved (Fig.2). It did not improve other pregnancy outcomes (Fig.1,3,4,5). Although animal experiments confirmed the role of luteinizing hormones in follicular recruitment, we hypothesize that endogenous luteinizing hormones were sufficient for follicular development and that the GnRH-antagonist suppresses low LH levels could not reflect the LH levels required by the follicular recruitment process. Therefore, supplementation of LH can significantly increase the number of oocytes retrieved. However, it did not help with other pregnancy outcomes such as miscarriage rate, oocyte quality and clinical pregnancy rate.

Meanwhile, the timing of r-LH supplementation was the subject of considerable controversy. Some studies imply that including r-LH on day 1 (D1) was advantageous, while other studies suggested that injection on days 5/6 of stimulation was more effective for GnRH-antagonist patients. A retrospective study in 2014(25) suggested that different timing of r-LH supplementation did not affect the cycle outcome in COS with GnRH-antagonist protocol, Wong recommended r-LH to be subjected to day 6-8 stimulation(11), and Gizzo (26) was in line with this statement, in which mid to late follicular phase was the optimal timing of r-LH supplementation to improve pregnancy outcomes. Our subgroup analysis supported the contention that the pregnancy outcome was not significantly affected by the timing of r-LH dosage. Figure 2 displayed that the number of oocytes can significantly increase in patients receiving r-LH on both day 1 and during the COS.

Limitations

As far as we know, this is the first meta-analysis to establish the effect of r-LH supplementation in the GnRH-antagonist protocol and the optimal time for r-LH addition. However, there are a few limitations to our study. First, LH deficiency strongly correlates with age; a meta-analysis from

2021 demonstrates that patients over the age of 35 benefit more from r-LH supplementation than those under the age of 35. Future meta-studies should address age to clarify the significance of r-LH in patients of various ages.

Another limitation of this meta-analysis is that only five outcomes were included (clinical pregnancy rate, number of oocytes retrieved, metaphase II oocytes, live birth rate, miscarriage rate). Future research should include further outcomes such as serum progesterone level on hCG day, rFSH dose, and multiple pregnancy rates to gain complete knowledge of the impact of r-LH.

In addition, although pre-treatment before COS is still debatable, some research has utilized the oral contraceptive pill (OCP) prior to stimulation. However, other studies do not specify the pre-treatment, which may diminish the precision of the outcome—a novel subgroup analysis based on whether patients had been pre-treated with OCP. Although the author was contacted, if necessary, not all trial data were available for the meta-analysis, resulting in the subgroup analysis of a lower number of studies.

Conclusion

The present meta-analysis revealed that r-LH supplementation might increase the number of retrieved oocytes in patients undergoing IVF/ICSI with GnRH antagonist protocol; however, there is no significant relationship between r-LH supplementation and clinical outcomes such as clinical pregnancy rate, the number of metaphases II, miscarriage rate, and live birth rate. Furthermore, the timing of LH addition had little effect on the results. Therefore, it can be assumed that additional of recombinant Luteinzing Hormone does not produce a beneficial effect to patients receiving a GnRH antagonist protocol. The reason might be endogenous luteinizing hormones are sufficient for follicular development, and exogenous luteinizing hormone will not produce its desire effect to improve critical clinical outcomes such as Live Birth Rate and Clinical pregnancy rate along with oocytes number. To further understand the efficacy of r-LH supplementation in patients getting a GnRH antagonist protocol, additional research is required on the employment of the pre-treatment protocol, the age of the patient, and various outcomes.

Competing Interest

The authors declare that they have no conflict of interest.

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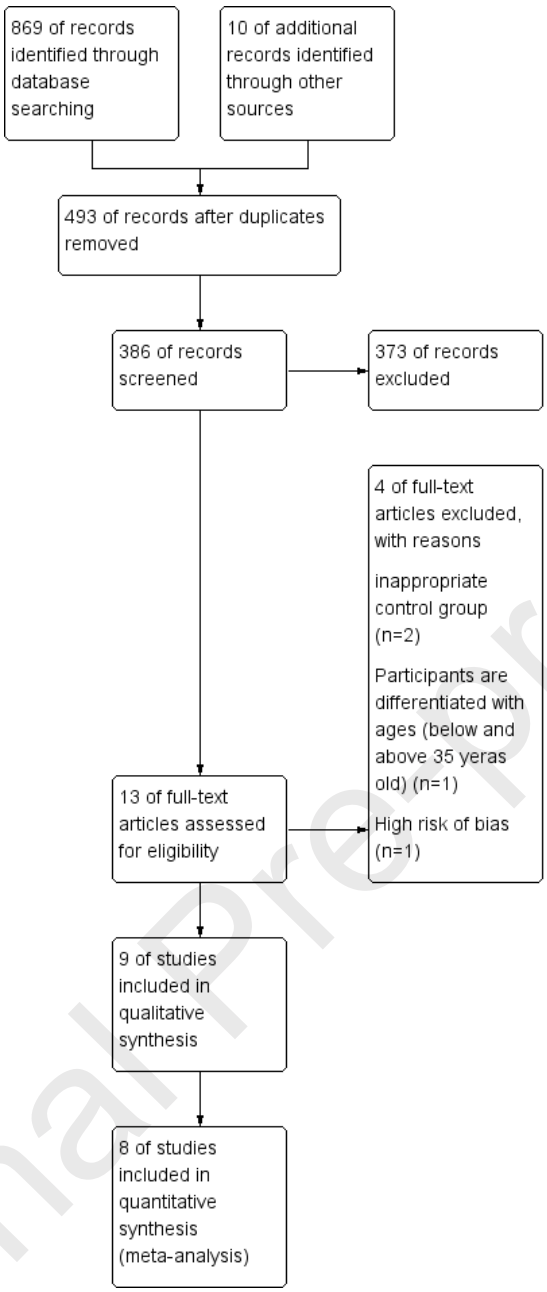
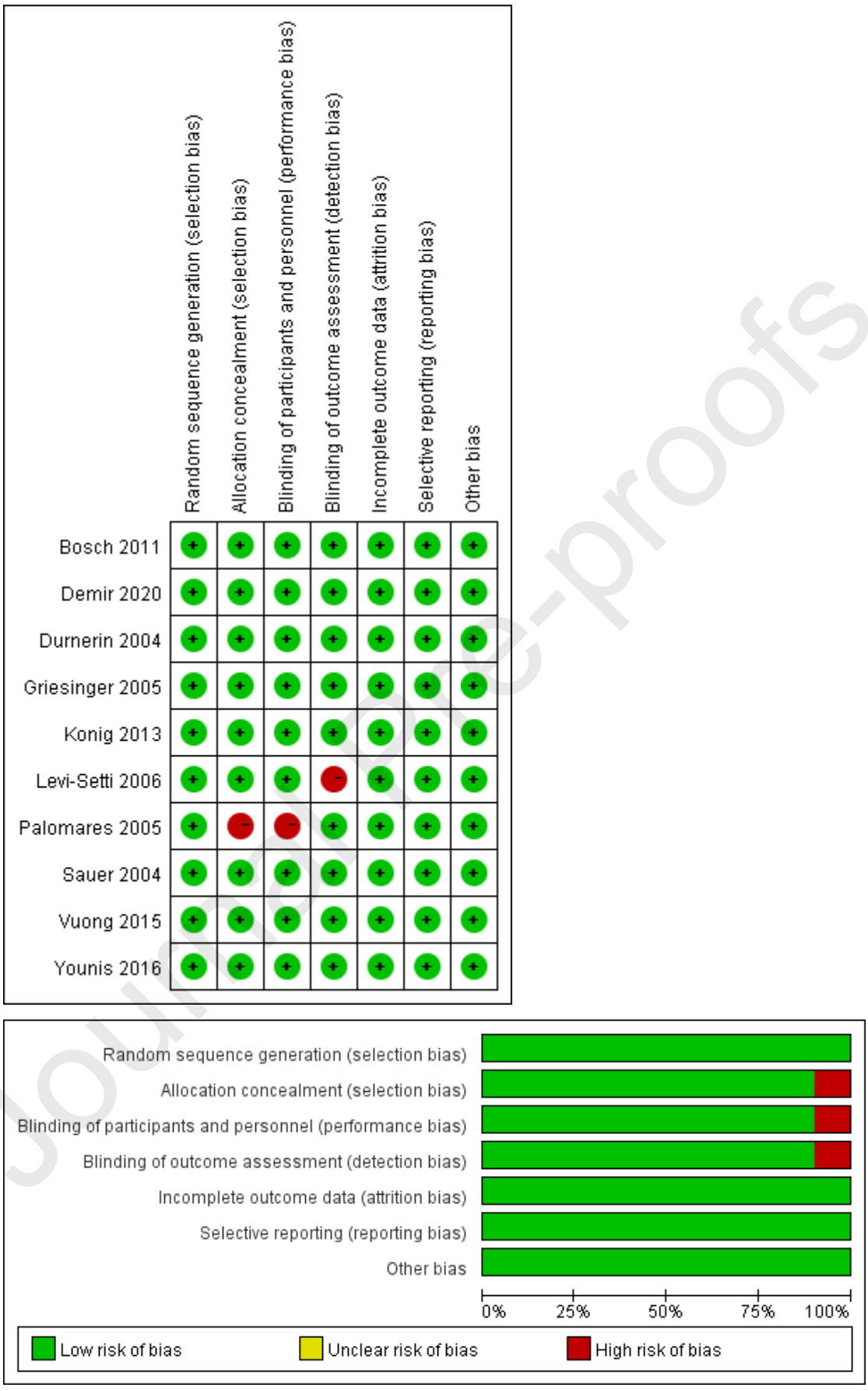
Author's contribution

Lan Hua and Cong Wang were the main contributors to writing the manuscript and designing the work.



Supplementation figure 1. Flow chart



Supplementation Figure 2: Risk of bias per study

Systematic review

Study	**Design**	**LH addition protocol**	**Population**	**Primary outcomes**	**Quality of the Evidence GRADE**
(Demir, 2020)	RCT	r-LH D5 administration r-LH dosage:75IU	Experiment group: n=30 Control group: N=33	Ongoing pregnancy rate	Moderate
(Cedrin-Durnerin et al., 2004)	RCT	r-LH administration with GnRH-A r-LH dosage:75IU	Experiment group: N=107 Control group: N=96	number of total embryos per patient	High
(Griesinger et al., 2005)	RCT	r-LH administration D1 r-LH dosage:75IU	Experiment group: N=54 Control group: N=54	treatment duration until administration of HCG	High
(Konig et al., 2013)	RCT	r-LH D6 administration r-LH dosage:150IU	Experiment group: N=128 Control group: N=125	Clinical pregnancy rate	High
(Sauer et al., 2004)	RCT	r-LH administration D6 r-LH dosage:150IU	Experiment group: N=21 Control group: N=21	number of metaphase II oocytes	High
(Vuong et al., 2015)	RCT	r-LH administration with GnRH-A r-LH dosage:75/150IU	Experiment group: N=120 Control group: N=20	Live birth rate	Moderate
(Younis et al., 2016)	RCT	r-LH administration with GnRH-A r-LH dosage:150IU	Experiment group N=32 Control group N=30	serum E2 level on the day of hCG administration	High
(Bosch et al., 2011)	RCT	r-LH administration D1 r-LH	Experiment group N=292 Control group N=142	number of oocytes retrieved	High

		dosage:75IU			

Supplementation Table 1: Study summary and GRADE analysis

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