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REVIEW

Comparison of the Long-Acting GnRH Agonist Follicular Protocol with the GnRH Antagonist Protocol in Women Undergoing In Vitro Fertilization: A Systematic Review and Meta-analysis

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ABSTRACT

Introduction: To evaluate the effectiveness and safety of long-acting GnRH agonist follicular and GnRH antagonist protocols among women undergoing in vitro fertilization (IVF) using data published in both English-language and Chinese studies.

Methods: We systematically searched the PubMed, Embase, Cochrane, CNKI, and Wanfang databases up to March 2019 for studies comparing long-acting GnRH agonist follicular and GnRH antagonist protocols in women undergoing IVF. The primary outcome was live birth rate; secondary outcomes were clinical pregnancy rate and implantation rate; safety outcomes were ovarian hyperstimulation syndrome (OHSS) and miscarriage rate in fresh cycle. Statistical analysis was done using R software. The study protocol was registered with PROSPERO (CRD42019139396).

Results: In 11 studies that met the inclusion criteria, 1994 women belonged to the long-acting GnRH agonist follicular protocol group and 1678 to the GnRH antagonist protocol group. Live birth rate (relative risk (RR) 1.61; 95% confidence interval (CI) 1.27, 2.05; $P < 0.001$), clinical pregnancy rate (RR 1.44; 95% CI 1.32, 1.58; $P < 0.001$), and implantation rate (RR 1.58; 95% CI 1.44, 1.73; $P = 0.001$) were higher in the long-acting GnRH agonist follicular protocol compared with the antagonist protocol group. There was no difference in miscarriage rate (RR 0.98; 95% CI 0.58, 1.64; $P = 0.98$) between the long-acting GnRH agonist follicular and antagonist protocols. However, OHSS rate (RR 1.63; 95% CI 1.15, 2.32; $P = 0.0058$) was lower in the GnRH antagonist protocol compared to the long-acting GnRH agonist protocol group.

Conclusion: The long-acting GnRH agonist follicular protocol was beneficial in improving live birth rate, clinical pregnancy rate, and implantation rate whereas the incidence of OHSS was significantly lower in women undergoing the GnRH antagonist protocol.

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Keywords: Assisted reproductive technology; Controlled ovarian hyperstimulation; GnRH antagonist; GnRH agonist; In vitro fertilization; Meta-analysis; Systematic review

Key Summary Points

The best protocol among long-acting GnRH-agonist follicular protocol and GnRH-antagonist protocols for in vitro fertilization is widely debated in the literature, and the optimal protocol remains inconclusive due to several confounders including variation in study population.

In this meta-analysis, we evaluated the effectiveness and safety of long-acting GnRH-agonist follicular and antagonist protocols using the published data from English and Chinese studies.

Live birth rate, clinical pregnancy rate and implantation rate were significantly higher in the long-acting GnRH-agonist follicular protocol compared with the antagonist protocol group.

Ovarian hyperstimulation syndrome rate was significantly lower in the GnRH-antagonist protocol and there was no difference in miscarriage rate.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.12967709.

INTRODUCTION

The gonadotropin-releasing hormone (GnRH) agonist and the GnRH antagonist protocols are well-established methods for controlled ovarian hyperstimulation among patients who are undergoing assisted reproductive technology (ART) [1]. Since the advent of GnRH agonists in the 1980s to prevent premature luteinizing hormone (LH) outpouring, thereby increasing the number of retrieved oocytes and pregnancy rates, GnRH agonist protocols have become the gold standard for in vitro fertilization (IVF) [2, 3]. The mechanism of action with sustained treatment of GnRH-agonist involves induction of both the endogenous LH surge and ovulation, and cause complete refractoriness of the pituitary to GnRH action in the later stage which may lead to prevention of premature LH surge [4]. Prolonged downregulation achieved by the GnRH agonist protocol may increase the endometrial receptivity of women undergoing IVF treatment leading to better reproductive outcomes [5–7]. A recent systematic review and meta-analysis emphasizes the long-acting GnRH agonist protocol as the first-choice treatment with increased ongoing pregnancy rate compared with the GnRH antagonist protocol [8]. Though the long-acting GnRH agonist protocol is associated with ovarian hyperstimulation syndrome (OHSS) or other side effects, a recent study by Van den Wijngaard et al. evaluating patients' preferences using discrete choice analysis showed that the majority of patients preferred a long-acting GnRH agonist protocol favoring increased pregnancy rate compared to an antagonist protocol [2]. Moreover, it can shorten the time to live birth in fresh transfer cycle relative to frozen transfer cycle. A Cochrane review by Albuquerque et al. highlights the advantages of the long-acting GnRH agonist protocol among the other types of GnRH agonist ovarian-stimulating protocols [9]. In a recent study, Geng et al. demonstrated the positive effect of the long-acting GnRH agonist follicular protocol on reproductive outcome by increasing the endometrial receptivity of patients undergoing IVF compared to results with the GnRH antagonist protocol [5]. Furthermore, in the long-acting GnRH agonist follicular protocol, a full single dose of 3.75 mg long-acting GnRH agonist was administered during early follicular phase (ca. 1–5 days) of the menstrual cycle; which is different from the traditional long-acting GnRH agonist protocol

where GnRH agonist usually starts in the mid-luteal phase of the menstrual cycle.

Randomized controlled trials (RCTs) and meta-analysis comparing long-acting GnRH agonist and GnRH antagonist protocols on pregnancy rate and live birth rate have resulted mixed findings. For example, a systematic review reported no difference in clinical pregnancy rate and live birth rates with the GnRH antagonist protocol compared with the long-acting GnRH agonist protocol; however, the incidence of OHSS was lower in long-acting GnRH agonist protocol [10]. Another study reported equivalent live birth rate with both protocols [11]. The best protocol for IVF is widely debated in the literature and the optimal protocol remains inconclusive because of several confounders including variation in study population, variation in treatment arms apart from agonist and antagonists, and variation in stimulation strategies [1]. In China, different GnRH agonist protocols are used flexibly and long-acting GnRH agonist follicular protocols have been used in increasing number of IVF centers in recent years. Of note, long-acting GnRH agonist follicular protocols are widely used in China but the results of these studies, being published in Chinese, are often excluded in the meta-analyses published in other countries thus leading to publication bias [8]. Moreover, till date, no published meta-analysis exists evaluating the effectiveness of the long-acting GnRH agonist follicular protocol compared with the GnRH antagonist protocols to our knowledge. Hence, in this meta-analysis, we evaluated the effectiveness and safety of long-acting GnRH agonist follicular and antagonist protocols using the published data from English and Chinese studies and hope the result will help with IVF clinical practice.

METHODS

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [12].

This article is based on previously conducted studies and the authors did not conduct any experiments that included human participants or animals.

Search Strategy and Participants

A literature search was performed in PubMed, Embase, Cochrane, CNKI, and Wanfang for articles published up to 1 March 2019 using the following search strings: [(GnRH a or GnRHa or GnRH agonist or gonadotropin-releasing hormone agonist or gonadorelin or triptorelin or goserelin or leuprorelin or nafarelin or alarelin or histrelin) and (agonist protocol) and (GnRH ant or GnRH antagonist or gonadotropin-releasing hormone antagonist or cetrorelix or ganirelix or teverelix) and (antagonist protocol)]. The corresponding Chinese search string is provided in Supplementary Table 1.

Duplicates were removed and all the studies were screened as per the inclusion criteria by two independent reviewers after reaching consensus on the eligibility of the study.

Inclusion and Exclusion Criteria

Eligible studies were RCTs, prospective non-randomized studies, observational, cohort, and retrospective studies comparing the long-acting GnRH agonist follicular protocol with GnRH antagonist protocol and studies reporting live birth rate, clinical pregnancy rate, implantation rate, miscarriage, or OHSS. The long-acting GnRH agonist follicular protocol: a full single dose of 3.75 mg long-acting GnRH agonist was administered in the early follicular phase (ca. 1–5 days) of the menstrual cycle; ovarian stimulation was started if pituitary downregulation was established (mostly 28 days after GnRH agonist administration) until trigger. GnRH antagonist protocol: ovarian stimulation was started in the early follicular phase (ca. 1–-5 days) of the menstrual cycle, a few days after GnRH antagonist was administered daily until ovulation was triggered.

Studies with the following characteristics were excluded: meta-analysis, systematic literature reviews, narrative reviews, case reports, conference proceedings, results not reporting desired objective and outcomes of interest,

studies reporting combination therapy of long-acting GnRH agonist follicular and GnRH antagonist protocols, frozen-thawed embryo transfer study, animal study, and non-English articles (for PubMed, Embase, and Cochrane), articles with calculation errors in the reported results were also excluded. The study protocol was registered in PROSPERO (CRD42019 139396).

Data Extraction and Quality Assessment

Two independent reviewers extracted data such as author, year of publication, title, study design, demographics of the study population and outcomes of interest from included studies into standardized MS Office Excel sheet. The methodological quality of eligible RCTs and observational studies was assessed using the Jadad scale [13] and Newcastle-Ottawa scale respectively. The publication bias was evaluated using funnel plots for live birth rate, clinical pregnancy rate, and implantation rate.

Study Outcomes

The primary outcome of the study was live birth rate (LBR); secondary outcomes were clinical pregnancy rate and implantation rate, presented as incidence. Safety outcomes like miscarriage and OHSS were presented as proportions.

Statistical Analysis

All the data management, relevancy and duplication removal, and assessment of eligibility as per PRISMA guidelines were performed using Microsoft Excel. The statistical data analysis was performed after completion of validation and quality checks using R statistical software. Descriptive statistics were used to analyze the baseline parameters and all continuous variables were presented as means, medians, and standard deviations. For analysis, all comparisons of LBR, pregnancy rate, implantation rate, and OHSS rate were reported as relative risk (RR) with 95% confidence interval (CI) for clinical outcomes and presented as Forest plots. Even though some papers have reported moderate or severe OHSS, some reported total OHSS, all papers were combined for analysis as OHSS rate. RR was calculated by the metaphor package using R software. Heterogeneity among the studies was determined via Cochrane's Q and I^2 statistics. 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.

RESULTS

The search identified 5331 hits. Following screening, 11 articles were included in the comparison of the long-acting GnRH agonist follicular protocol with GnRH antagonist protocol for analysis (Fig. 1). Among 11 studies included, 10 were observational studies (9 retrospective study; 1 prospective study) and one was a RCT (Supplementary table 2). There were nine Chinese and two English articles included in the analysis. The number of women in the agonist and antagonist arms were 1994 and 1678, respectively; the mean age in both the groups was 30.9 years. The proportions of normal ovarian responders, polycystic ovary syndrome (PCOS), and poor responders in each group were 69.2%, 27.1%, and 3.8%, respectively, in the agonist group and 42.5%, 46.5%, and 11.0%, respectively, in the antagonist group.

Quality Assessment and Publication Bias

Publication Bias

Publication bias of LBR, clinical pregnancy rate, and implementation rate depicted by funnel plots showed relatively lesser publication bias among the included studies for the long-acting GnRH agonist follicular protocol compared with the antagonist protocol. The funnel plot asymmetry for LBR ($P = 0.35$), clinical pregnancy rate ($P = 0.49$), and implantation rate ($P = 0.75$) was not statistically significant (Supplementary Fig. 1).

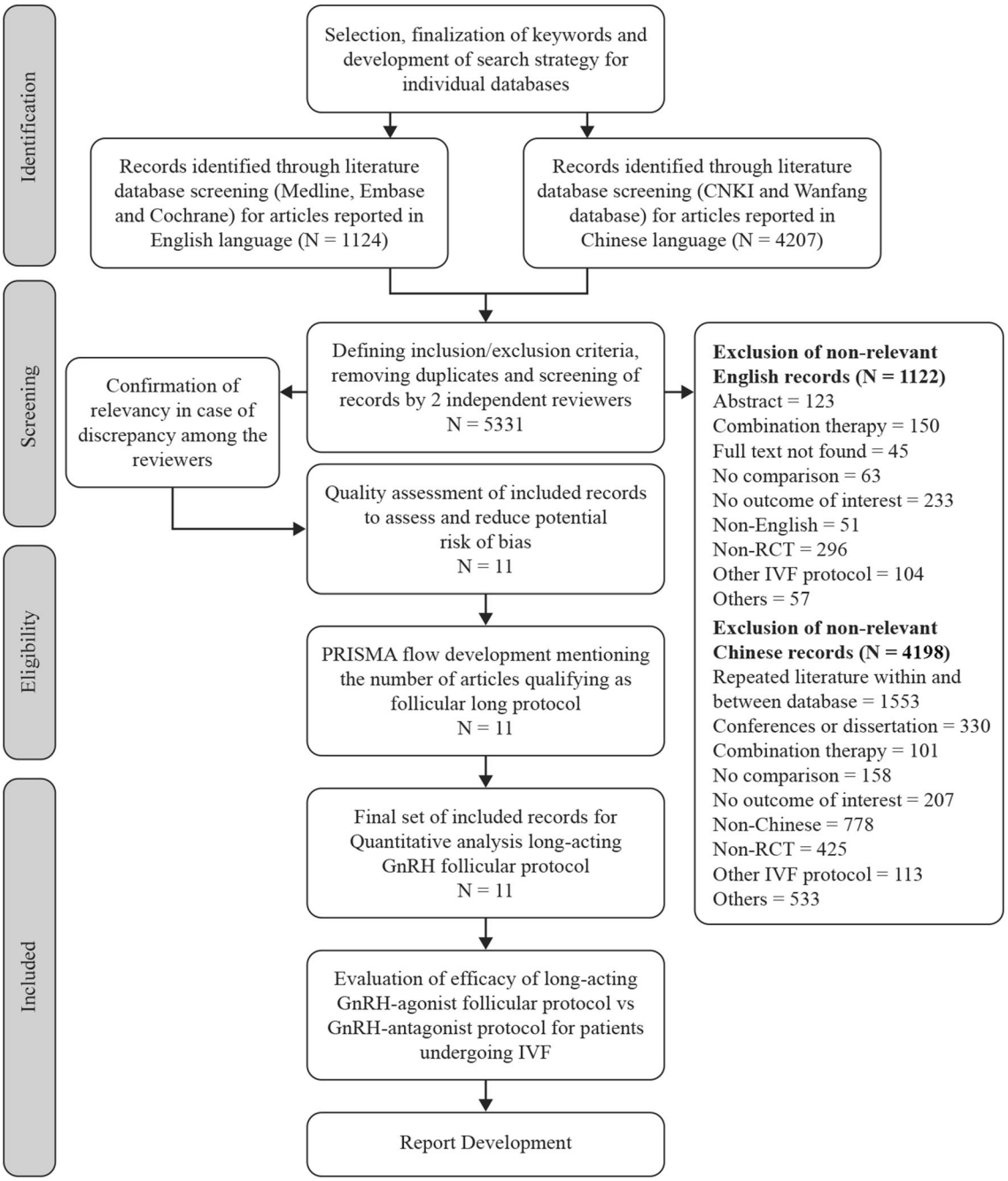

Fig. 1 PRISMA flow chart for article selection. Abbreviations: CNKI, China National Knowledge Infrastructure; IVF, In vitro fertilization; GnRH, gonadotropin-releasing hormone; RCT, Randomized controlled trial

Primary Outcomes

Live Birth Rate

Of the 11 studies, only two reported live birth rate with a range of 45.8–46.6% in the agonist group and 21.2–29.7% in the antagonist group. Live birth rate was significantly higher in the long-acting follicular agonist group compared to the antagonist group (RR 1.61; 95% CI 1.27,

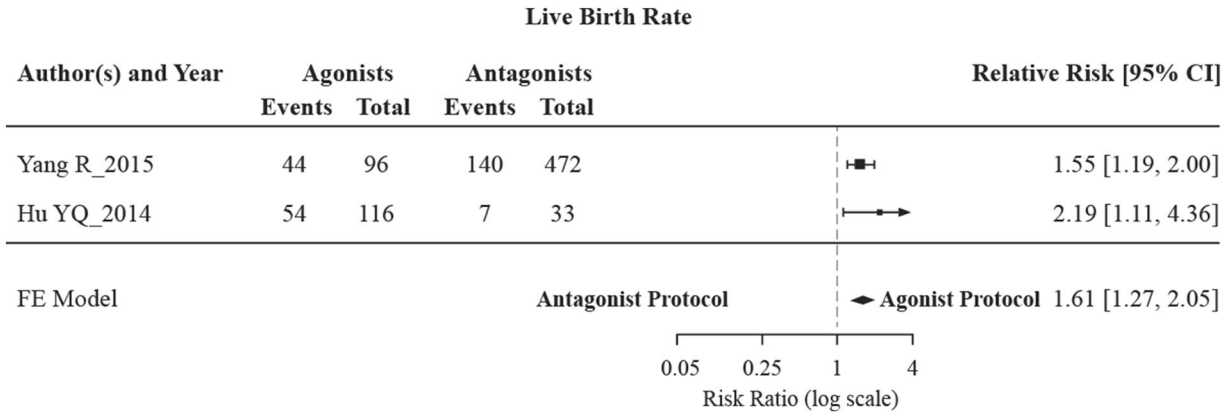

Fig. 2 Forest plot comparing the live birth rate of patients between the long-acting GnRH agonist follicular group and the GnRH antagonist protocol groups. Abbreviations: CI, confidence interval; FE, fixed effect; GnRH, gonadotropin-releasing hormone

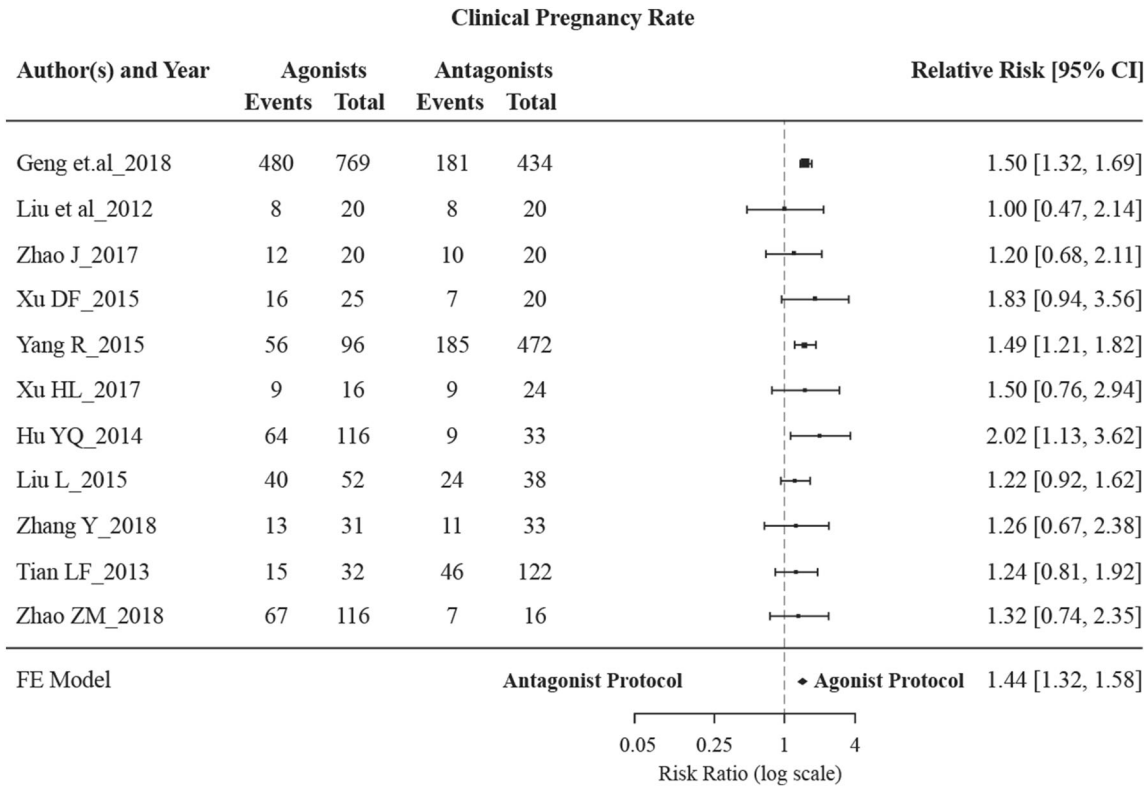

Fig. 3 Forest plot comparing the clinical pregnancy rate of patients between the long-acting GnRH agonist follicular group and the GnRH antagonist protocol groups. Abbreviations: CI, confidence interval; FE, fixed effect; GnRH, gonadotropin-releasing hormone

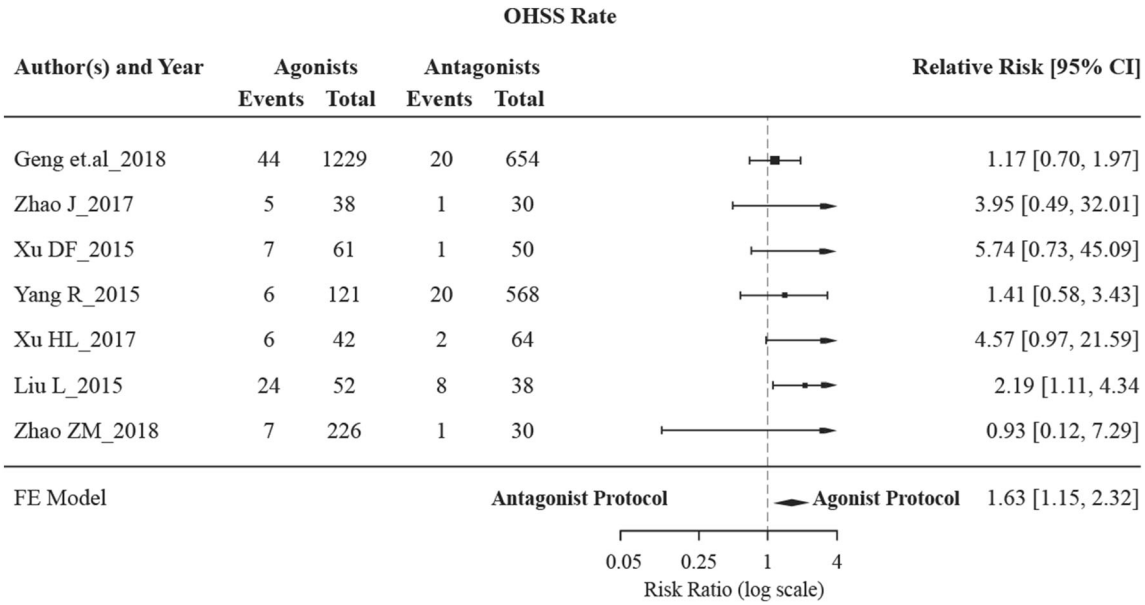

Fig. 4 Forest plot comparing the OHSS rate of patients between the long-acting GnRH agonist follicular group and the GnRH antagonist protocol groups. Abbreviations: CI, confidence interval; FE, fixed effect; GnRH, gonadotropin-releasing hormone; OHSS, ovarian hyperstimulation syndrome

2.05) with the FE model, $I^2 = 0\%$, $P = < 0.001$ (Fig. 2).

Secondary Outcomes

Clinical Pregnancy Rate

All 11 studies [5, 14–23] provided data on clinical pregnancy rate, which varied from 40.0% to 76.9% in the long-acting follicular agonist and 27.3% to 63.2% in the antagonist protocols. Clinical pregnancy rate was significantly higher in the long-acting follicular agonist group compared to antagonist (RR 1.44; 95% CI 1.32, 1.58), $P < 0.001$ with the FE model, $I^2 = 0\%$ (Fig. 3).

Implantation Rate

Six studies [5, 15, 19, 20, 22, 23] reported implantation rate, which varied from 33.33% to 61.4% in the long-acting GnRH agonist follicular group and 20.76% to 38.6% in the antagonist group. Analysis (FE model, $I^2 = 0\%$, $P < 0.001$) showed significantly a higher implantation rate among the women using the long-acting follicular agonist protocol compared to the antagonist protocol (RR 1.58; 95% CI 1.44, 1.73; $P < 0.001$) (Supplementary Fig. 2).

Miscarriage Rate

Among the eight [14–16, 18, 20–23] studies reporting miscarriage rate, the range in the long-acting GnRH agonist follicular was 5.0–22.2% and 0.00–18% in the antagonist protocol. There was no significant difference between the antagonist treatment group and long-acting follicular agonist group in the miscarriage rate with the FE model, ($I^2 = 0\%$, $n = 8$ studies) (RR 0.98; 95% CI 0.58, 1.64), $P = 0.98$ (Supplementary Fig. 3).

OHSS Rate

Among the seven studies [5, 14, 18–21, 23] that reported OHSS rate, three [5, 18, 21] reported total OHSS rate, three [19, 20, 23] reported moderate and severe OHSS rate, and one [14] reported severe OHSS rate. We combined them to analyze the OHSS rate, so the result was just a trend. In the long-acting GnRH agonist follicular protocol group, OHSS rate varied from 3.1% to 46.2%, whereas in the antagonist protocol

the rate varied from 2.0% to 21.1%. The antagonist treatment showed a significantly lower OHSS rate compared to the long-acting follicular agonist protocol in analysis with the FE model (I^2 = 0%, RR 1.63; 95% CI 1.15, 2.32; P = 0.0058) (Fig. 4).

DISCUSSION

In this study, we compared the efficacy and safety of the long-acting GnRH agonist follicular protocol with the GnRH antagonist protocols among patients undergoing ART. With regards to effectiveness, the main outcome of our study (LBR) and secondary outcomes (clinical pregnancy rate and the implantation rate) were higher in the long-acting GnRH agonist follicular protocol compared with GnRH antagonist protocol, and this association was found to be statistically significant. Regarding safety, the incidence of OHSS was lower in the GnRH antagonist protocol compared to the long-acting GnRH agonist follicular protocol.

Long-acting GnRH agonist protocols, which enable maximum ovarian stimulation, have been the standard IVF protocol since decades [24]. The long-acting GnRH agonist protocol has advantages over the GnRH antagonist, primarily by complete elimination of the fluctuation in preovulatory LH levels during the course of ovarian hyperstimulation [1]. A decreased probability of pregnancy due to the increased incidence of LH instability in the GnRH antagonist cycles has been evaluated by many studies [25–27]. In our study, the potential benefits of the long-acting GnRH agonist follicular protocol with regard to live birth rate, clinical pregnancy rate, and implantation rate were observed, especially for normal ovarian responders, as our study had 69.2% of normal ovarian responders. In addition, the antagonist protocol was more likely to be suitable for patients with PCOS with regard to lower OHSS rate and higher proportion of this type of patient involved (46.6%).

The fact that in the literature the GnRH antagonist protocol demonstrated a similar pregnancy outcome could be explained by several factors. Firstly, a greater number of studies used the GnRH antagonist protocol owing to relatively less complexity and desirable outcomes offered by the antagonist protocol, which includes mild ovarian stimulation, patient-compatible regimen, and lower risk of OHSS [25]. Secondly, there could be publication bias in the inclusion of larger studies. As a fact, long-acting GnRH agonist follicular protocols are extensively used in China and studies published in Chinese are excluded from the majority of meta-analyses published internationally [8].

A recent systematic review and meta-analysis by Lambalk et al. [8] compared ovarian stimulation protocols involving various patients, such as couples undergoing IVF in the general population, women with PCOS and poor ovarian response. Our meta-analysis revealed that, in the general IVF population, the long-acting agonist protocol remains the superior treatment of choice by resulting in better ongoing pregnancy rate compared with antagonist protocol. However, among PCOS and poor ovarian responders, the GnRH antagonist protocol seems to be the standard choice of treatment as it is associated with a lesser rate of OHSS [8]. Other studies have shown no difference in live birth rate between the long-acting GnRH agonist and antagonist protocols [23, 25–28]. However, a study conducted by Lambalk et al. [8] suggested that ongoing pregnancy can be considered as a good proxy for live birth rate, although a discrepancy exists between the live birth rate and ongoing pregnancy rate, and reporting of ongoing pregnancy rate is sufficiently powered to detect the ideal differences of the effectiveness of treatments [29].

In our study, compared with the GnRH antagonist protocol, the long-acting GnRH agonist follicular protocol resulted in higher clinical pregnancy rate and implantation rate. Similarly, a Cochrane review conducted by Al-Inany et al. [30] showed results in favor of the long-acting GnRH agonist protocol. In contrast, no statistically significant differences in clinical pregnancy rate between both the protocols were observed in other studies [31]. This difference in results could plausibly be attributed to the number of studies and patients included in these analyses, as well as the inclusion of studies

using the long luteal protocol and not the long agonist follicular protocol.

It is well documented that administration of exogeneous GnRH agonists or GnRH antagonist for ovarian stimulation in IVF can lead to OHSS [1]. A substantial amount of evidence suggests that the GnRH antagonist protocol decreases the risk of OHSS in patients undergoing [21]. Likewise, in our study, the GnRH antagonist protocol has shown lower rates of OHSS. A Cochrane systematic review also reported similar findings [32]. In our meta-analysis women undergoing IVF with the GnRH antagonist protocol showed lower incidence of OHSS compared to those who received the long-acting GnRH agonist follicular protocol. Additionally, our results showed that the follicular long-acting protocol is more widely used in China than in Western population. Hence, our findings highlight the advantages of the follicular long-acting protocol over the antagonist protocol in IVF.

Strength and Limitations of the Study

To the best of our knowledge, this is the first meta-analysis comparing the long-acting GnRH agonist follicular and GnRH antagonist protocols by undertaking a comprehensive literature search that includes English-language and Chinese articles. However, our study has few limitations. First, a limited number of studies published in English were included, which could lead to bias as the results cannot be generalized to the wider population. Second, a limited number of studies assessing live birth rate could also create bias in the analysis and interpretation of the results. Third, owing to the limited number of studies, non-RCTs, retrospective studies, studies with small sample size and various study populations with variation in ovarian responses were included in the analysis.

In conclusion, our results revealed significantly higher live birth, clinical pregnancy, and implantation rates with the GnRH agonist protocol than with the GnRH antagonists protocol. With regard to safety, especially for hyperresponsive patients, the GnRH antagonist protocol substantially reduced the risk of OHSS.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

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