REVIEW

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# 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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## DIGITAL FEATURES

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## ABSTRACT

**Objective:** 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:** Thirteen studies met the inclusion criteria, of which 1878 women belonged to the long-acting GnRH-agonist follicular protocol group and 2342 to the GnRH-antagonist protocol group. There was no difference in live birth rate (relative risk (RR)= 1.38; 95% confidence interval (CI): 0.79 - 2.39; *P*= 0.2542) and miscarriage rate (RR=0.97, 95% CI:0.63-1.49, P=0.8833) between the long-acting GnRH-agonist follicular and antagonist protocols. Clinical pregnancy rate (RR= 1.48; 95% CI: 1.37 - 1.59; *P<0.0001*) and implantation rate (RR= 1.39; 95% CI: 1.10 - 1.75; *P=0.0062*) were higher in the long-acting GnRH-agonist follicular protocol compared with the antagonist protocol group. However, OHSS rate (RR= 1.35; 95% CI: 1.06 - 1.72; *P*= 0.015) 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 clinical pregnancy rate and implantation rate whereas the incidence of OHSS was significantly lower in women undergoing the GnRH-antagonist protocol.

**Keywords:** Assisted reproductive technology; Controlled ovarian hyperstimulation; GnRH-agonist; GnRH-antagonist; *in vitro* fertilization; Meta-analysis; Systematic review; Women's Health

**Key Summary Points**

- Gonadotropin-releasing hormone agonist (GnRH-agonist) and the GnRH-antagonist protocols are well-established methods for controlled ovarian hyperstimulation (COH) among patients who are undergoing assisted reproductive technology (ART).
- 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 were searched.
- Thirteen studies met the inclusion criteria, of which 1878 women belonged to the long-acting GnRH-agonist follicular protocol group and 2342 to the antagonist protocol group.
- There was no difference in live birth rate between the long-acting GnRH-agonist follicular and antagonist protocols (RR= 1.38; 95% CI: 0.79 - 2.39; P= 0.2542).
- Ovarian hyperstimulation syndrome (OHSS) rate (RR= 1.35; 95% CI: 1.06 - 1.72; P= 0.015) was lower in the GnRH-antagonist protocol compared to the long-acting GnRH-agonist protocol.

## INTRODUCTION

The gonadotropin-releasing hormone agonist (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 involves sustained treatment of GnRH-agonist for the induction of both the endogenous LH surge and ovulation, and its ability to cause complete refractoriness of the pituitary to GnRH action in the later stage may lead to prevention of premature LH surge [4]. Prolonged down-regulation achieved by 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 treatment of choice with increased ongoing pregnancy rate compared to the GnRH-antagonist protocol [8]. Though the long-acting GnRH-agonist protocol is associated with 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 than frozen transfer cycle. A Cochrane review by Albuquerque et al. highlights the advantages of 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 IVF patients compared to GnRH-antagonist protocol [5]. And long-acting GnRH-agonist follicular protocol, a full single dose of 3.75 mg

long-acting GnRH-agonist was administered on early follicular phase (1~5 day) of menstrual cycle is different from traditional long GnRH-agonist protocol which GnRH-agonist usually starts mid-luteal phase of 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 yielded mixed findings  For example, one systematic review reported no difference in clinical pregnancy rate and live birth rates with the GnRH-antagonist protocol compared to the long-acting GnRH-agonist protocol, however the incidence of OHSS was reported to be lesser 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 due to 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 from internationally published meta-analyses [12] i.e. existing studies are subject to publication bias. To date, no published meta-analysis exists evaluating the effectiveness of the long-acting GnRH-agonist follicular protocol compared with the GnRH-antagonist protocols. 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.

**METHODOLOGY**

This systematic review and meta-analysis followed the "Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA)" guidelines [13]. 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.

**Search Strategy and Participants**

A literature search was performed in PubMed, Embase, Cochrane, CNKI and Wanfang for articles published up to 1st March 2019 using 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 2 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 long-acting GnRH-agonist follicular protocol with GnRH-antagonist protocol and studies reporting live birth rate, clinical pregnancy rate, implantation rate, miscarriage or OHSS. 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 (1~5 day) of the menstrual cycle, ovarian-stimulation was started if pituitary down-regulation was established (most are twenty-eight days after GnRH-agonist administer) until trigger. GnRH-antagonist protocol: ovarian-stimulation was started on early follicular phase (1~5 day) of

menstrual cycle, after few days GnRH-antagonist was administered daily until ovulation was triggered.

Studies with 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 and animal study, and non-English articles (for PubMed, Embase and Cochrane). The study protocol was registered in PROSPERO (CRD42019139396).

**Data Extraction and Quality Assessment**

Two independent reviewers extracted data into standardized MS Office Excel based data extraction sheets from included studies regarding author, year of publication, title, study design, demographics of the study population and outcomes of interest. The methodological quality of eligible RCTs was determined using the Jaded scale [14], and publication bias was evaluated using funnel plots for live birth rate, clinical pregnancy rate and implatation 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 incidents. Safety outcomes like miscarriage and OHSS were presented as proportions.

**Statistical Analysis**

All the data management, relevancy and duplication removal, assessment of eligibility as per PRISMA guidelines was 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 analyse 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 are presented as Forest plots. RR was calculated by 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 when $I^2$ was >50% a random-effects (RE) model was used. If the *P* value for heterogeneity is <0.05 or $I^2$ is >50%, the heterogeneity was statistically significant.

**RESULTS**

The search identified 5331 hits. Following screening, 13 articles were included in comparison of long-acting GnRH-agonist follicular protocol with GnRH-antagonist protocol for analysis (Figure 1). Among these, 10 had a retrospective study design, two were RCTs and one had prospective observational study design (Supplementary table 2). There were 11 Chinese and two English articles included in the analysis. The number of women in the agonist and antagonist arms were 2342 and 1878, respectively. The mean age was 30 years in both the groups. The proportion of normal ovarian responders, PCOS and poor responders in each group were 72.2%, 24.5% and 3.2%, respectively, in agonist group and, and 46.9%, 43.4% and 9.8%, respectively, in antagonist group.

**Quality Assessment and Publication Bias**

***Publication Bias***

Publication bias of LBR, clinical pregnancy rate and implementation rate depicted by funnel plots show relatively lesser publication bias in the included studies for long-acting GnRH-agonist follicular protocol comparing with antagonist protocol. The funnel plot asymmetry for LBR (*P=0.56)*, clinical pregnancy rate (*P*=0.46) and implantation rate (*P*=0.29) was not statistically significant (Supplementary figure 1).

**Primary Outcomes**

***Live Birth Rate***

Of the 13 studies, only 3 reported outcomes on live birth rate with a range of 46.5 to 46.9% in the agonist group and 20.5 to 56.4% in antagonist group. There was no significant difference in live birth rate between the long follicular agonist and the antagonist groups (RR, 1.38, 95% CI: 0.79,2.39) with RE model, $I^2$=82.08%, *P*=0.2542 (Figure 2).

**Secondary Outcomes**

***Clinical Pregnancy Rate***

All 13 studies [5,15–26] provided data on clinical pregnancy rate, which varied from 39.3-67.7% in the long follicular agonist and 33.3-67.2% in the antagonist protocols. Clinical pregnancy rate was significantly higher in the long follicular agonist group compared to antagonist (RR 1.48, 95% CI 1.37-1.59), *P*<0.001 with RE model, $I^2$=56.12% Figure 3).

***Implantation Rate***

Seven studies [5,15,16,21,22,25,26] reported implantation rate, which varied from 36.4-79.3% in the long-acting GnRH-agonist follicular group and 22.0-83.1% in antagonist group. Analysis (RE model, $I^2$=81.51%, P<.0001) showed significantly higher implantation rate among the women using long follicular agonist protocol compared to the antagonist protocol (RR=1.39, 95% CI 1.10-1.75, *P=0.0062*) (Supplementary figure 2).

***Miscarriage Rate***

Among the nine [15–17,19,20,22–24,26] 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 compared to the long-acting follicular agonist group in the miscarriage rate with fixed effect model, ($I^2$=0%, no. of studies: 9) (RR 0.97, 95% CI 0.63-1.49), *P*=0.8833 (Supplementary figure 3).

*OHSS rate*

Eight studies[5,15,16,18–23,26] reported OHSS rate. In long-acting GnRH-agonist follicular protocol group, OHSS rate varied from 3.58-30.0%, whereas in antagonist protocol the rate varied from 2.6-23.4%. The antagonist treatment showed a significantly lower OHSS rate compared to long-acting follicular agonist protocol in analysis with FE model ($I^2$=0, RR=1.35, 95% CI 1.06-1.72, *P*= 0.015) (Figure 4).

**DISCUSSION**

In this study, we compared the efficacy and safety of the long-acting GnRH-agonist follicular protocol with the GnRH-ant protocols among patients undergoing ART. With regards to effectiveness, the main outcome of our study, LBR, showed no differences in the reproductive outcomes between the long-acting GnRH-agonist follicular and the GnRH-antagonist protocol. Clinical pregnancy rate and the implantation rate were higher in long-acting GnRH-agonist follicular protocol compared to GnRH-antagonist protocol and this association was found to be statistically significant. Regarding safety, the incidence of OHSS was lower in GnRH-antagonist protocol compared to long-acting GnRH-agonist follicular protocol.

Long-acting GnRH-agonist protocols, which enables maximum ovarian-stimulation, have been the standard IVF protocol for decades [27]. 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 [28–30]. In our study, the potential benefits of long-acting GnRH-agonist follicular protocol with regard to clinical pregnancy rate and implantation rate was observed, especially for normal ovarian responders, because of the high proportion of this type of patients involved (72.2%) , In addition, the antagonist protocol is more likely to be suitable for patients with PCOS with regard to lower OHSS rate and higher proportion of this type of patient involved (43.4%).

The fact that in literature the GnRH-antagonist protocol demonstrated similar pregnancy outcome could be explained by several factors. Firstly, a greater number of studies used GnRH-antagonist protocol by large , due to relatively less complexity and desirable outcomes offered by antagonist protocol which includes mild ovarian-stimulation, patient-compatible regimen and lower risk of OHSS [31]. .

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 published in Chinese, are excluded from majority of meta-analysis 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 agonist protocol remains to be superior treatment of choice by resulting in better ongoing pregnancy rate compared to antagonist protocol. However, among PCOS and poor ovarian response population, GnRH-antagonist protocol seems to be standard choice of treatment because it is associated with lesser rate of OHSS [8]. Other studies have shown no difference in live birth rate between the long-acting GnRH-agonist and antagonist protocol [31–35]. However, a study conducted by Lambalk et al.[8] suggested that considering ongoing pregnancy as a good proxy to live birth rate,[36]

although discrepancy exist 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.

In our study, compared to 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 In-Inany et al.[37] showed results in favor of long-acting GnRH-agonist protocol. In contrast, no statistically significant difference in clinical pregnancy rate between both the protocols were observed in other studies [38]. 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 long luteal protocol and not 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 [39]. A substantial amount of evidence suggests that the GnRH-antagonist protocol decreases the risk of OHSS in IVF patients [27,32]. Likewise, in our study, the GnRH-antagonist protocol has shown lower rates of OHSS. A recent Cochrane systematic review shows the similar findings [40]. In our meta-analysis it is been evident that IVF women receiving GnRH-antagonist protocol showed lower incidence of moderate or severe OHSS compared to those who received long-acting GnRH-agonist follicular protocol. Additionally, our results show that the follicular long acting protocol is more widely used in China than in Western population, the results 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

limitations. First, 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, 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 study design, small sample sizes in the studies and various study populations with variation in ovarian responses were included in the analysis.

In conclusion, our results reveal significantly higher clinical pregnancy and implantation rates with the GnRH-agonist protocol than with the GnRH antagonists protocol. With regard to safety, especially for hyper-responsible patients, the GnRH-antagonist protocol substantially reduces the risk of OHSS rate.


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### Authorship

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

## Disclosures

Rui Yang, Yichun Guan and Rong Li have nothing to disclose. Valerie Perrot and Juan Ma are employees of Ipsen.

## 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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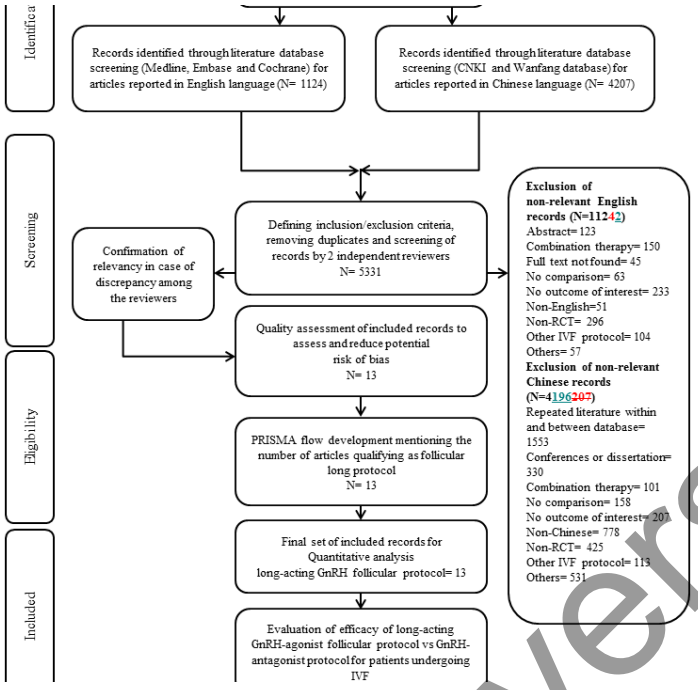


**Figure 1.** Preferred Reporting Items for Systematic reviews and Meta-Analyses flow chart for article selection

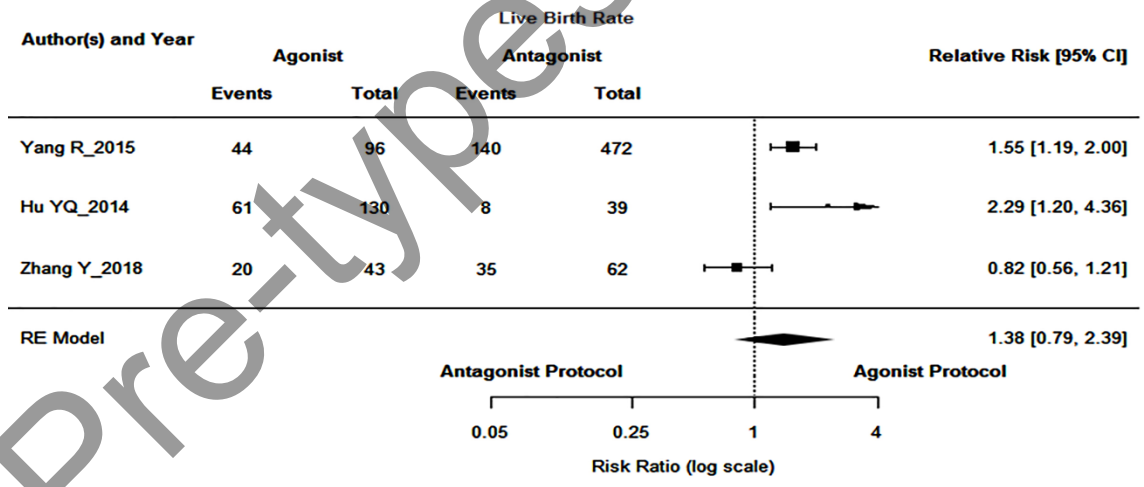


**Figure 2.** Forest plot comparing the live birth rate per patients between the long-acting GnRH-agonist follicular group and the GnRH-ant protocol groups

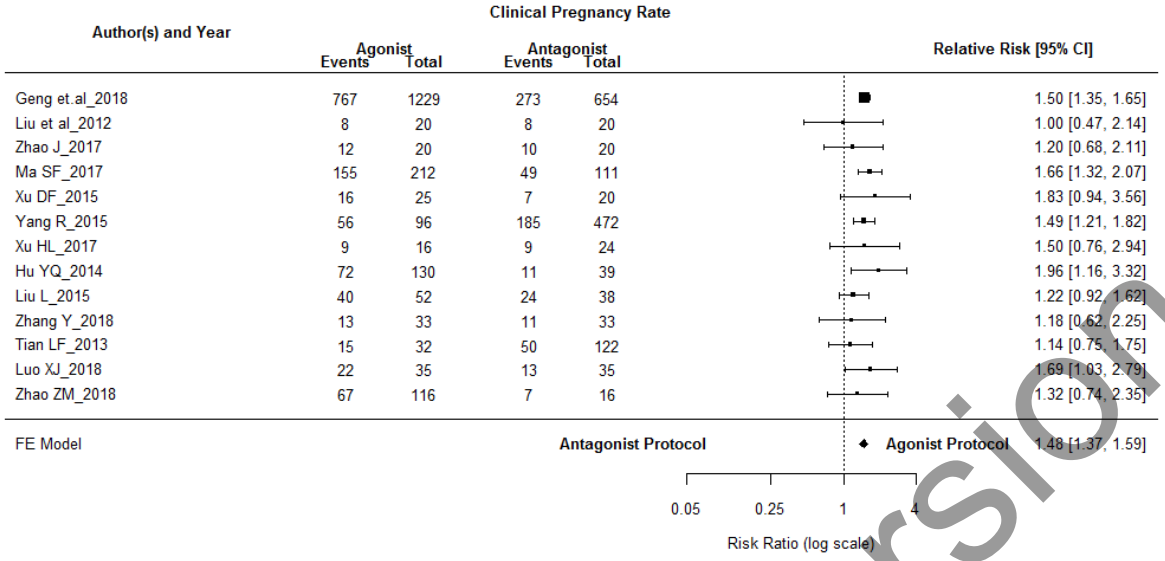


**Figure 3.** Forest plot comparing the clinical pregnancy rate per patients between the long-acting GnRH-agonist follicular group and the GnRH-ant protocol groups

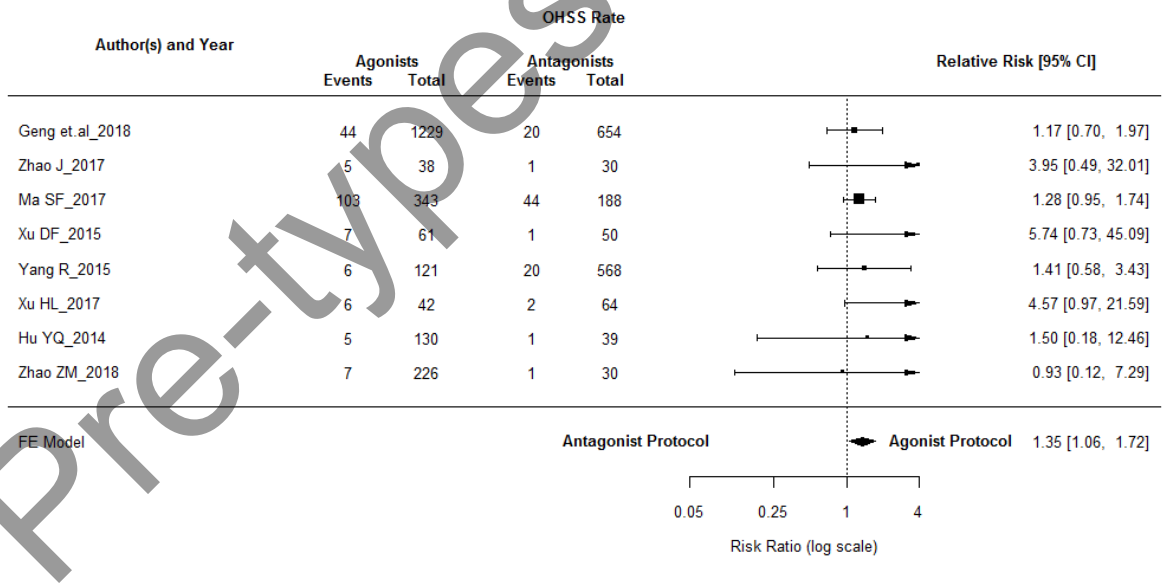


**Figure 4.** Forest plot comparing the OHSS rate per patients between the long-acting GnRH-agonist follicular group and the GnRH-ant protocol groups