REVIEW ARTICLE

Gonadotrophin-releasing hormone antagonist regimen versus agonist regimen among normal ovarian responders: a systematic review and meta-analysis

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Abstract

This systematic review and meta-analysis compared the efficacy and safety of gonadotrophin-releasing hormone antagonist (GnRH-ant) versus GnRH agonist (GnRH-a) regimens in women with a normal ovarian response undergoing controlled ovarian stimulation. PubMed, Embase, Cochrane Library, CNKI, VIP, and Wanfang were searched from inception to April 30, 2024. Randomized controlled trials were independently screened, appraised for risk of bias, and synthesized using meta-analysis. Eight RCTs involving 1,841 participants were included. Compared with GnRH-a, GnRH-ant was associated with fewer retrieved oocytes (WMD −0.77, 95% CI −1.35 to −0.20; P=0.009) and a lower implantation rate (RR 0.75, 95% CI 0.60 to 0.93; P=0.009), but required less total gonadotrophin (WMD −389.65; P<0.001) and a shorter stimulation duration (WMD −2.00 days; P<0.001). GnRH-ant reduced the risk of ovarian hyperstimulation syndrome (OHSS) (RR 0.33, 95% CI 0.11 to 0.94; P=0.037). Clinical pregnancy (RR 0.84, P=0.056) and abortion rates (RR 1.13, P=0.729) were comparable. Taken together, GnRH-ant reduced gonadotrophin exposure, shortened stimulation, and lowered OHSS risk, but produced slightly fewer oocytes and a lower implantation rate; clinical pregnancy and abortion rates did not differ significantly between regimens. *(Afr J Reprod Health 2026; 30 [6]: 125-139).*

Keywords: GnRH antagonist regimen; GnRH agonist regimen; normal ovarian responders; controlled ovarian stimulation; in vitro fertilization

Résumé

Cette revue systématique et méta-analyse a comparé l'efficacité et la sécurité des protocoles antagoniste de l'hormone de libération des gonadotrophines (GnRH-ant) et agoniste de la GnRH (GnRH-a) chez des femmes présentant une réponse ovarienne normale et bénéficiant d'une stimulation ovarienne contrôlée. Les bases de données PubMed, Embase, Cochrane Library, CNKI, VIP et Wanfang ont été consultées depuis leur création jusqu'au 30 avril 2024. Les essais contrôlés randomisés ont été sélectionnés indépendamment, évalués quant au risque de biais et synthétisés par méta-analyse. Huit ECR totalisant 1 841 participantes ont été inclus. Comparé au GnRH-a, le GnRH-ant était associé à un nombre plus faible d'ovocytes recueillis (DMP −0,77 ; IC 95 % −1,35 à −0,20 ; P = 0,009) et à un taux d'implantation inférieur (RR 0,75 ; IC 95 % 0,60 à 0,93 ; P = 0,009), mais nécessitait une dose totale de gonadotrophines plus faible (DMP −389,65 ; P < 0,001) ainsi qu'une durée de stimulation plus courte (DMP −2,00 jours ; P < 0,001). Le GnRH-ant réduisait également le risque de syndrome d'hyperstimulation ovarienne (SHO) (RR 0,33 ; IC 95 % 0,11 à 0,94 ; P = 0,037). Les taux de grossesse clinique (RR 0,84 ; P = 0,056) et de fausse couche (RR 1,13 ; P = 0,729) étaient comparables entre les deux protocoles. En conclusion, le protocole GnRH-ant réduisait l'exposition aux gonadotrophines, raccourcissait la durée de stimulation et diminuait le risque de SHO, mais entraînait un nombre légèrement inférieur d'ovocytes et un taux d'implantation plus faible ; les taux de grossesse clinique et de fausse couche ne différaient pas significativement entre les deux protocoles. *(Afr J Reprod Health 2026; 30 [6]: 125-139).*

Mots-clés: Protocole antagoniste de la GnRH ; protocole agoniste de la GnRH ; réponse ovarienne normale ; stimulation ovarienne contrôlée ; fécondation in vitro

Introduction

Infertility is a state of low fertility, denoting a situation where a couple has regular unprotected sexual intercourse for at least 12 months without achieving clinical pregnancy[1]. Over 186 million individuals globally are affected by infertility, with the majority residing in developing countries[2]. At

the China International Infertility Forum, the "Research Report on the Current Status of Infertility in China" announced that over the past two decades, China has experienced a marked elevation in infertility rates, rising from 2.5-3% to 12.5%-15%[3].

Assisted reproductive technology (ART) is extensively employed and swiftly advancing in infertility treatment[4]. In recent decades, ART has made significant progress, markedly increasing the delivery rate from 26% in the 1990s to around 40% today[5]. Since its implementation in 1970, controlled ovarian stimulation (COS) acts a pivotal stage in ART[6]. Gonadotrophin-releasing hormone agonist (GnRH-a) and gonadotrophin-releasing hormone antagonist (GnRH-ant) regimens are the common COS regimens used. The GnRH-a regimen has always been regarded as a classic approach for COS. The treatment outcome of this regimen is superior to other conventional ovulation induction and microstimulation regimens in normal responders. The benefits of the GnRH-a regimen include suppressing premature luteinizing hormone (LH) peak, decreasing the number of cancelled cycles, improving follicular synchrony, obtaining an increased number of oocytes, improving endometrial receptivity (ER), stabilizing clinical pregnancy rates, and avoiding weekend oocyte retrieval by adjusting the starting time. In contrast, the disadvantage of the GnRH-a regimen is that the low estrogen levels after pituitary down-regulation lead to perimenopausal changes and insufficient luteal function. This can increase the likelihood of developing ovarian hyperstimulation syndrome (OHSS) and necessitate higher dosages, longer duration, and greater consumption of gonadotrophins (Gn). Consequently, the overall treatment duration is prolonged. The stimulating effect of agonists may also lead to the occurrence of corpus luteum cyst[7,8].

GnRH-ant regimen is among the frequently utilized COS regimens. In normal responders, the quantity of high-quality embryos is comparable between the two regimens. Additionally, the odds of implantation, clinical pregnancy, overall live birth, sustained pregnancy, and abortion exhibit no marked variations. Moreover, their pregnancy outcomes are similar. The occurrence of OHSS is decreased[9,10]. Based on the recommendations from the European Society of Human Reproduction and Embryology (ESHRE) regarding ovarian stimulation for in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI), the GnRH-ant regimen is endorsed as the optimal ovulation induction regimen for normal responders[11].

However, there has been controversy over whether the GnRH-ant regimen can serve as the primary COS regimen for individuals with normal response. In 2017, a meta-analysis was carried out for assessing the GnRH-ant against the GnRH-a across individuals with normal ovarian reserve. Findings indicated that among individuals exhibiting normal ovarian reserve, the GnRH-ant notably decreased the likelihood of OHSS in contrast to the GnRH-a, while keeping comparable pregnancy and live birth rates[12]. No recent pertinent meta-analyses have been released to date. A primary goal of this research was to explore the efficacy and safety of GnRH-ant versus GnRH-a in individuals exhibiting a normal response, offering valuable insights for clinical decision-making and updating current theoretical knowledge.

Methods

The study regimen has been registered in PROSPERO (CRD42024543932).

Research retrieval

A retrieval was performed across various databases, including PubMed, Embase, Cochrane Library, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (VIP), and Wanfang, up to April 30, 2024. Subject headings and text words were applied in the research process. The Chinese search terms (in English) included “normal ovarian function, normal ovarian reserve, normal ovarian response, antagonist protocol, GnRH antagonist, GnRH agonist, long-acting GnRH agonist, and long protocol”. The English search terms included “Ovarian Reserve, Ovarian Reserves, Reserve, Ovarian, Reserves, Ovarian, Normal ovarian function, normal ovarian reserve, normal ovarian response, GnRH antagonist, GnRH-ant, GnRHA, gonadotropin-releasing hormone agonist, gonadotrophin releasing hormone agonist, GnRH

agonist, GnRH-a, and GnRHa". During the selection process, Endnote software was used to independently remove the duplicates to limit false duplicates, which were mistakenly identified as duplicates. Literature filtering and data extraction were carried out via two authors who had received relevant methodological training.

Two independent reviewers (J.L. and R.L.) separately conducted searches, reviewed titles and abstracts for potential inclusion, and acquired full-text versions of relevant articles. The subsequent phase involved a detailed examination of abstracts and full texts by both the primary and the secondary based on predefined inclusion criteria. Any differences were resolved through consensus or by consulting a third reviewer (X.W.), who also ensured the review process's integrity.

Inclusive and exclusive criteria

The inclusive criteria were: articles based on randomized controlled trials (RCTs); and research subjects being individuals exhibiting a normal ovarian response. The criteria for normal ovarian response were as follows: subjects aged<35 years; subjects with normal ovarian reserve function (1 ng/ml<anti-mullerian hormone [AMH] <4.0 ng/ml; 6<antral follicle count [AFC] <15; follicle-stimulating hormone [FSH] <10U/L); and subjects without previous history of cancellation of an IVF cycle with ovarian hyporesponsiveness or hyperresponsiveness[13]; The intervention measure was GnRH-ant, while the control was GnRH-a. Primary outcome measures for assessing effectiveness comprised the counts of retrieved oocytes and the clinical pregnancy observed in fresh cycles, while the secondary outcome measures comprised course of Gn stimulation, overall Gn consumption, E2 levels, LH values, and endometrial thickness at the time of HCG application, yields of high-quality embryos, high-quality embryo rate, quantity of available embryos, and implantation rate. The outcome measures for safety evaluation included abortion rate and the occurrence rate of OHSS.The exclusive criteria included the following: Studies that lack control or are self-controlled, studies with a cross-over design, studies on frozen-thawed embryo transfer, and animal studies; conference abstracts, research plan; and articles containing calculation errors in the results.

Data extraction

The data extraction included: Research characteristics, including author, publication year, country, research design, and sample capacity; Baseline characteristics of the research participants, namely age; Intervention measures and control measures, including drug name and dosage; Outcome measures, including the quantity of events and participants in each group. Two trained and qualified reviewers independently extracted data from the literature, followed by cross-verification. Any discrepancies were resolved with the third reviewer (X.W.).

Quality evaluation

Two reviewers autonomously evaluated the risk of bias in the incorporated RCTs utilizing the evaluation instrument outlined in the Cochrane Handbook (V5.1.0)[14]. After the evaluation was completed, the evaluation results were checked. If the results were inconsistent, they were discussed for resolution, or a third party (X.W.) was consulted to assist in judgment. The evaluation items incorporated the generation of random sequence, allocation masking, blinding of the research subjects and investigators, blinding of outcome evaluation, completeness of outcome findings, selective reporting of study results, and alternative biases.

Statistical analysis

A meta-analysis was carried out utilizing Stata/MP (V17.0). Weighted mean difference (WMD) and 95% confidence interval (95%CI) were employed for continuous variables; relative risk (RR) and its 95%CI were employed for binary variables, with a significance level of $\alpha = 0.05$. Heterogeneity among the enrolled articles was appraised utilizing Q-test and I^2. If I^2 exceeded 50%, demonstrating marked heterogeneity among the articles, a random-effects model (REM) was utilized. Conversely, when I^2 was below 50%, signifying low heterogeneity, a

fixed-effects model (FEM) was employed, with a significance level of α = 0.1. A *P*-value exceeding 0.1 indicated an absence of significant heterogeneity. Conversely, a *P*-value of 0.1 or less indicated statistical heterogeneity among the research outcomes. A sensitivity analysis was carried out utilizing Stata/MP (V17.0), and publication bias was explored utilizing Egger's test conducted within the same software environment. A *P*-value below 0.05 suggested marked publication bias among the included studies. The evaluation of bias risk was performed with the Review Manager (V5.3).

Results

Article search procedure and results

Altogether, 916 articles were initially included in our research. After removing 283 duplicates, 623 articles were excluded because they either failed to meet the inclusive criteria or were identified as duplicates during title and abstract screening. After a full-text review, 2 articles were removed, resulting in a final inclusion of 8 published articles[15-22]. The selection procedure and results are depicted in Figure 1.

Fundamental characteristics of the enrolled articles

This analysis finally included 8 RCTs[15,16], involving a total of 1,841 patients. Among them, 2 articles were published in English[15,16] and 6 articles in Chinese[17-22]. These articles contained 100 to 546 patients, with an average age of 27.96 to 38.97 years. Table 1 presents the key characteristics of the enrolled articles[15-22].

Risk of bias assessment figure

Review Manager (V5.3) software was adopted to evaluate bias risk of the 8 incorporated RCTs utilizing the recommended evaluation tool from the Cochrane Collaboration. Among the 8 RCTs included, 2 studies applied random sequence generation[16,19], 1 studyperformed allocation concealment[16], and 0 studies performed blinding for clinicians and embryologists involved in the study. All studies did not implement blinding for subjects and outcome evaluators, while all studies reported complete data. One study did not report the outcome indicators specified in the regimen[18], and other biases in all studies were unclear. It was depicted in Figures 2 and 3.

Meta-analysis findings

Primary outcome measures of effectiveness

Number of retrieved oocytes

The meta-analysis incorporated 6 articles[16,17,19-22] (1,507 cases) investigating the number of retrieved oocytes. Due to heterogeneity among experiments (*P*=0.063, I^2=52.1%), an REM was employed for meta-analysis. The research findings demonstrated that the GnRH-ant yielded a markedly decreased counts of retrieved oocytes in comparison to the GnRH-a, with a statistically marked difference (WMD [95%CI] =-0.77 [-1.35, -0.20], *P*=0.009). It was depicted in Figure 4.

Clinical pregnancy rate

The meta-analysis incorporated 8 articles[15-22] investigating the clinical pregnancy rate. Due to heterogeneity among experiments (*P*=0.005, I^2=65.7%), an REM was employed for meta-analysis. The research findings demonstrated that the clinical pregnancy rates did not show a notable discrepancy between the GnRH-ant and the GnRH-a groups (RR [95%CI]=0.84 [0.71, 1.00], *P*=0.056). It was depicted in Figure 5.

Secondary outcome measures of effectiveness

Total Gn usage

The meta-analysis incorporated 5 articles[15,17,19,21,22] (993 cases) investigating total Gn usage. Due to heterogeneity among experiments (*P*<0.001, I^2=89.1%), an REM was employed for the meta-analysis.

Table 1: Baseline features of enrolled articles

Author	Year	Country	Study design	Sample size GnRH-ant	GnRh-a	Mean Age GnRH-ant	GnRh-a	Intervention GnRH-ant	GnRh-a	Outcome
Qiao J[15]	2012	China	RCT	113	120	29.3	29.1	Ganirelix 0.25 mg	Triptorelin 0.05 mg	F1, F2, F3, F5
Lifeng Tian[17]	2020	China	RCT	80	101	28.25	28.99	Cetrotide 250 ug/d	Leuprorelin 3.75 mg	F1, F2, F3, F4, F5, F6, F8, F9, F10, F11
Xixi Chen[18]	2011	China	RCT	50	50	32.64	31.64	Cetrotide 0.25 mg/d	Triptorelin,1.0-1.5 mg	F5, F7
Wenzheng Guan[19]	2018	China	RCT	59	61	38.74	38.97	Cetrotide,0.25~0.5 mg	Triptorelin 0.05 mg/d	F1, F2, F3, F4, F5, F9
Lu Fang[20]	2012	China	RCT	131	130			GnRH-ant 0.25 mg	GnRH-a 1.25 mg	F2, F5, F9, F11, F12,
Zhang F[21]	2021	China	RCT	100	100	31.3	30.5	GnRH-ant 0.25 mg/d	GnRH-a	F1, F2, F5, F9, F11, F12
Xu B[16]	2020	China	RCT	273	273	30.24	29.97	Cetrotide 0.25 mg/d	Triptorelin 3.75 mg	F2, F3, F5, F6, F7, F8, F9, F12
Mei Shuai[22]	2020	China	RCT	100	100	27.96	28.02	Ganirelix 250 ug	Triptorelin3.75 mg	F1, F2, F4, F5, F6, F7, F9, F10, F11

GnRH-ant: Gonadotrophin-releasing hormone antagonist regimen
GnRh-a: Gonadotrophin-releasing hormone agonist regimen
RCT: Randomized controlled trial
F1: Gonadotrophins requirement
F2: Total duration of gonadotrophins stimulation
F3: Quantity of high-quality embryos
F4: Implantation rate
F5: Clinical pregnancy rate
F6: Estradiol level at the time of HCG application
F7: High-quality embryo rate
F8: Endometrial thickness at the time of HCG application
F9: Count of oocytes retrieved
F10: Luteinizing hormone level at the time of HCG application
F11: Likelihood of developing ovarian hyperstimulation syndrome
F12: Abortion rate

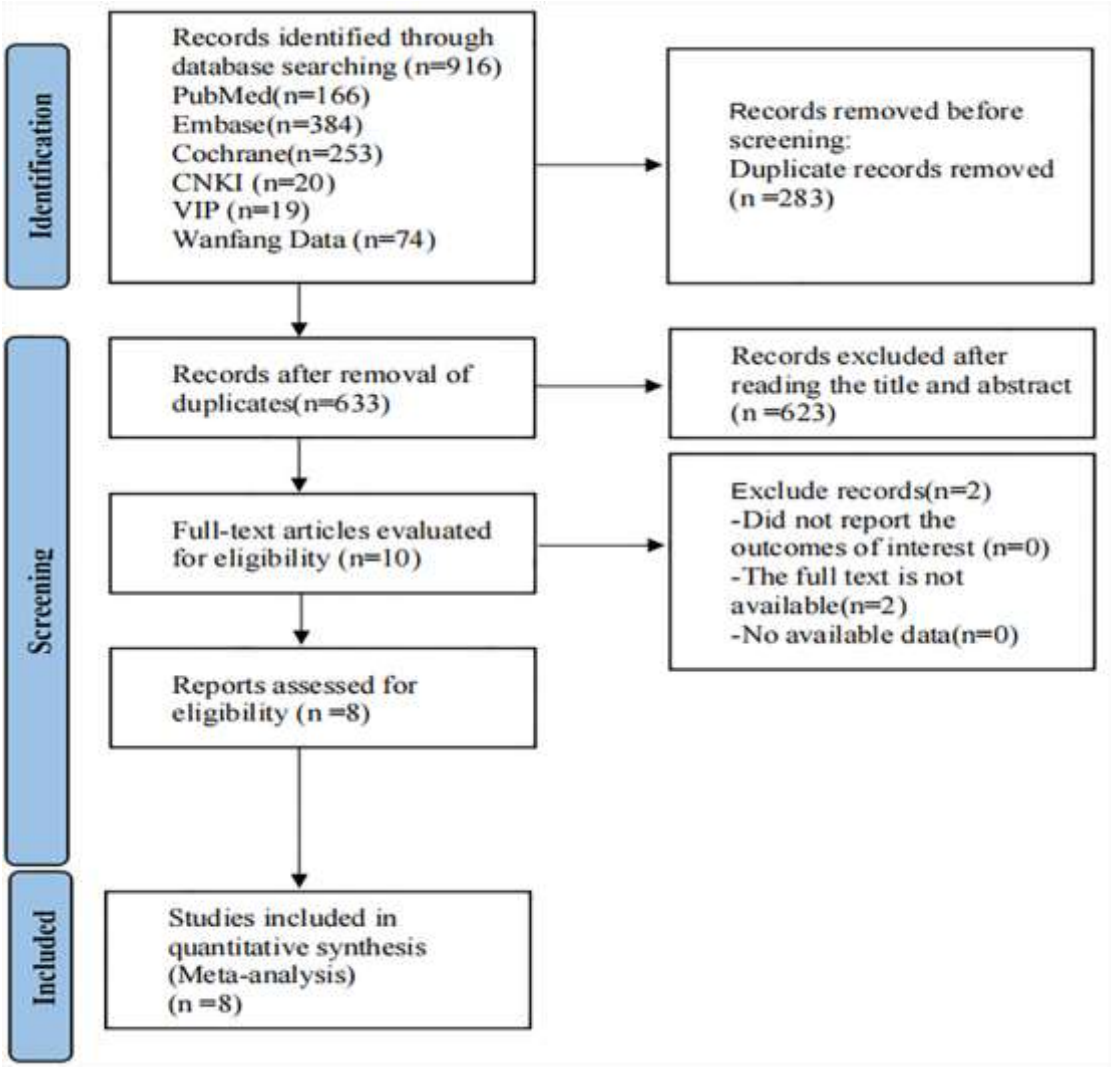

Figure 1: PRISMA flow diagram of the research procedure. PRISMA, preferred reporting items for systematic review and meta-analysis

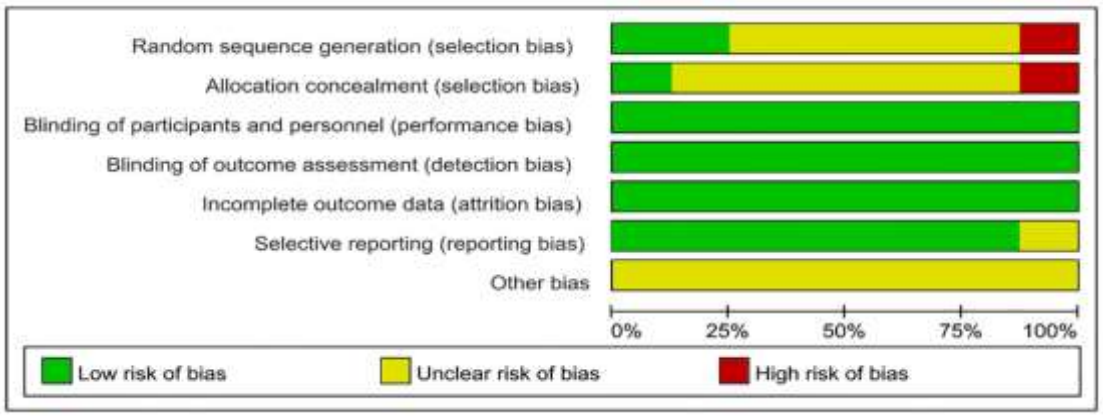

Figure 2: Risk of bias graph of enrolled RCTs

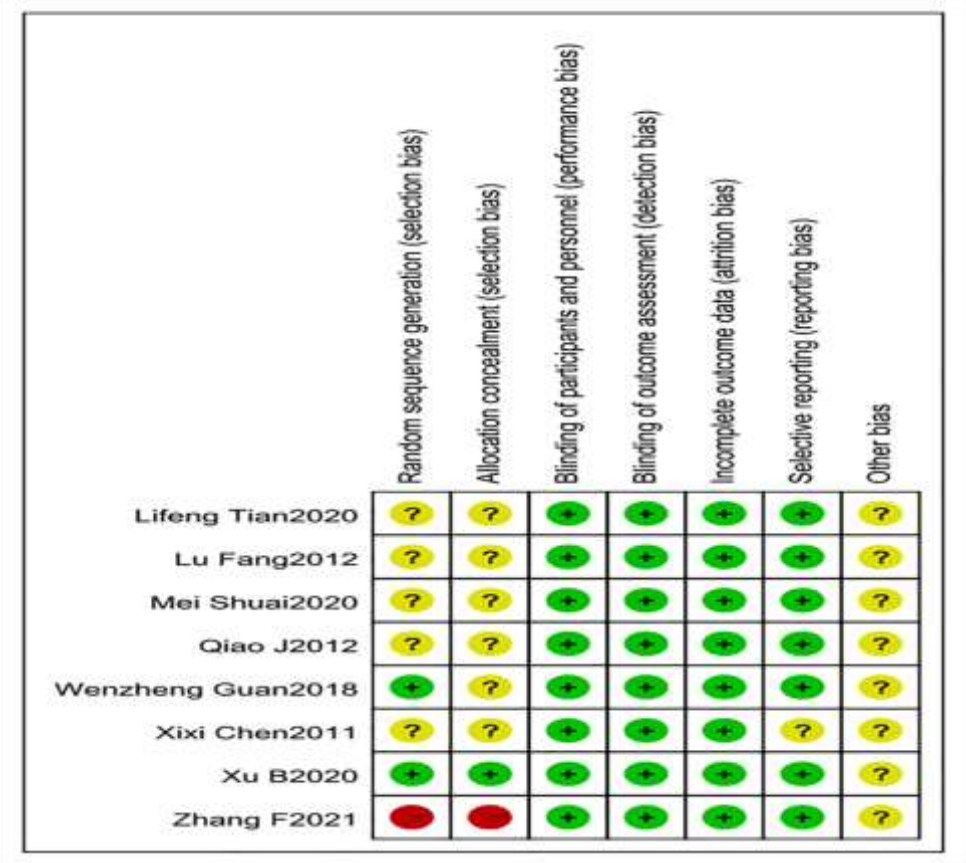

Figure 3: Risk of bias summary of enrolled RCTs

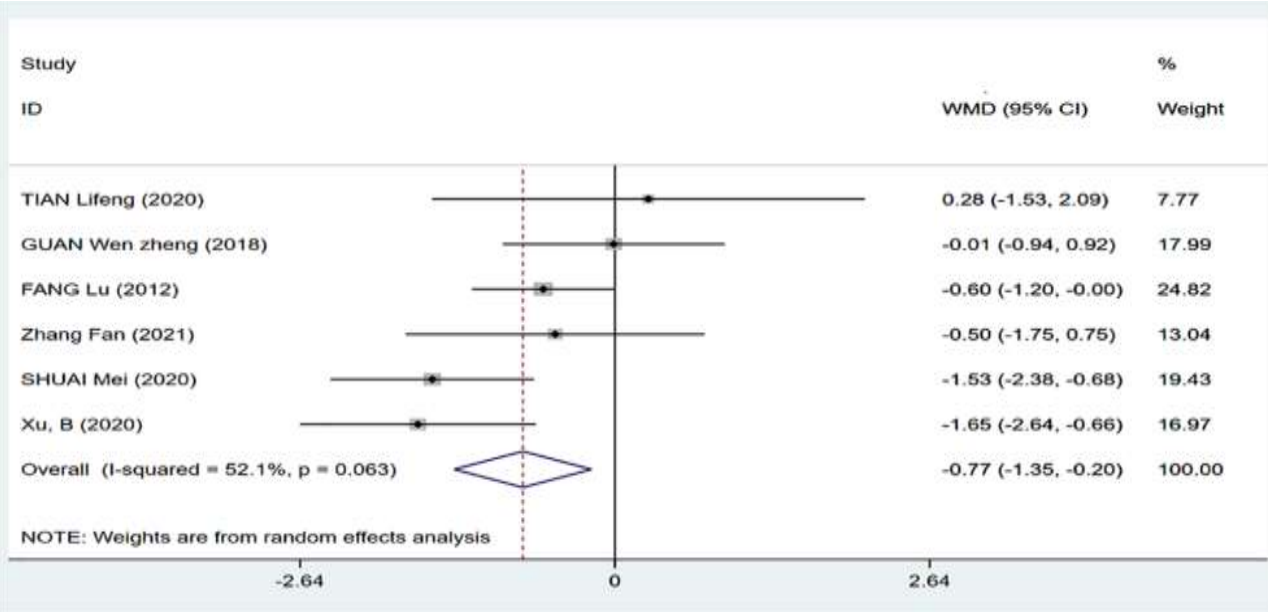

Figure 4: Forest plot comparing the count of oocytes retrieved in the GnRH-ant group versus the GnRH-a group

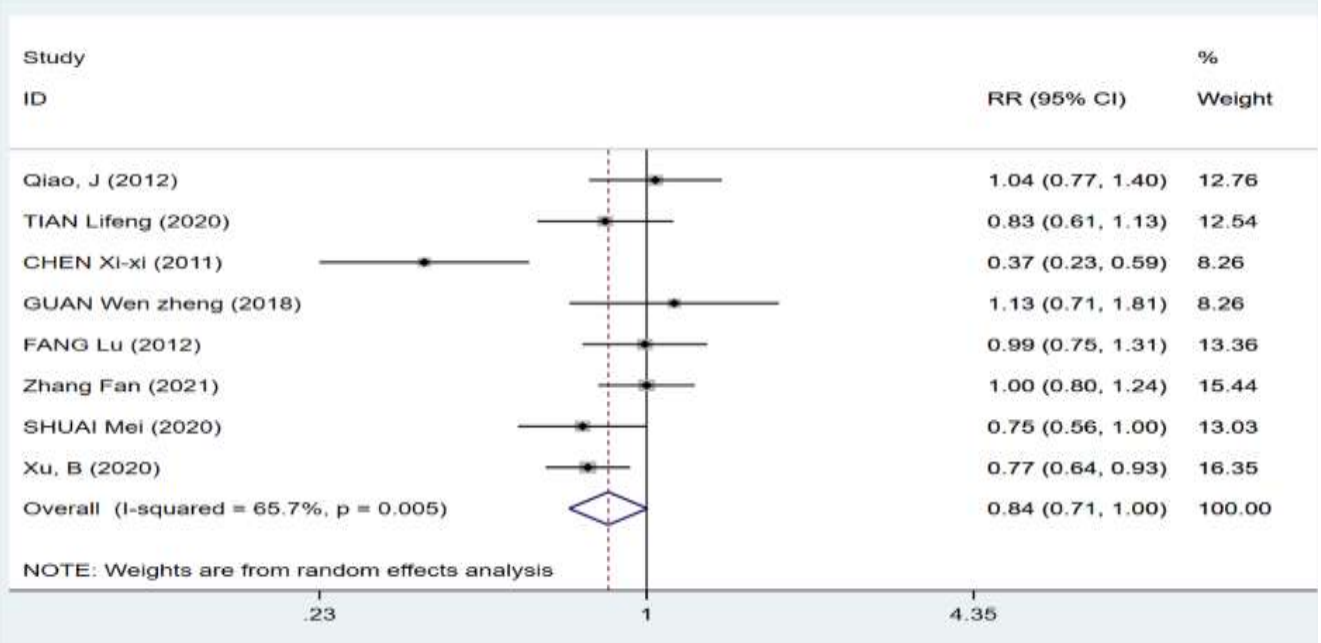

Figure 5: Forest plot comparing the clinical pregnancy produced by the GnRH-ant regimen versus the GnRH-a regimen

The research findings demonstrated that the GnRH-ant required markedly less Gn usage in comparison to the GnRH-a, with a statistically marked difference (WMD [95%CI] =-389.65 [-566.83, -212.48], *P*<0.001). It was depicted in Figure 6A.

Duration of continuous stimulation with Gn

The meta-analysis incorporated 7 articles[15-17,19-22] (1,740 cases) investigating the duration of continuous stimulation with Gn. Due to heterogeneity among experiments (*P*<0.001, I^2=96.4%), an REM was employed for meta-analysis. The research findings revealed a markedly significant decrease in the duration of continuous Gn stimulation in the GnRH-ant regimen in comparison to the GnRH-a regimen, with a statistically marked difference (WMD [95%CI] =-2.00 [-2.79, -1.21], *P*<0.001). It was depicted in Figure 6B.

Quantity of high-quality embryos

The meta-analysis incorporated 4 articles[15-17,19] (1,070 cases) investigating the quantity of high-quality embryos. Due to the absence of heterogeneity across experiments (*P*=0.169, I^2=40.4%), an FEM was employed for meta-analysis. The research findings demonstrated no marked discrepancy in the counts of high-quality embryos produced by the GnRH-ant and GnRH-a groups (WMD [95%CI] =0.11 [-0.11, 0.33], *P*=0.322). It was depicted in Figure 6C.

High-quality embryo rate

The meta-analysis incorporated 2 articles[18,22] investigating the high-quality embryo rate. Due to the absence of heterogeneity across experiments (*P*=0.105, I^2=62.0%), an FEM was employed for meta-analysis. The research findings demonstrated no marked discrepancy in the high-quality embryo rate produced by the GnRH-ant and GnRH-a groups (RR [95%CI] =0.94 [0.82, 1.08], *P*=0.384). It was depicted in Figure 6D.

Implantation rate

The meta-analysis incorporated 2 articles[17,22] investigating the implantation rate. Due to the absence of heterogeneity across experiments (*P*=0.690, I^2=0.0%), an FEM was employed for meta-analysis.

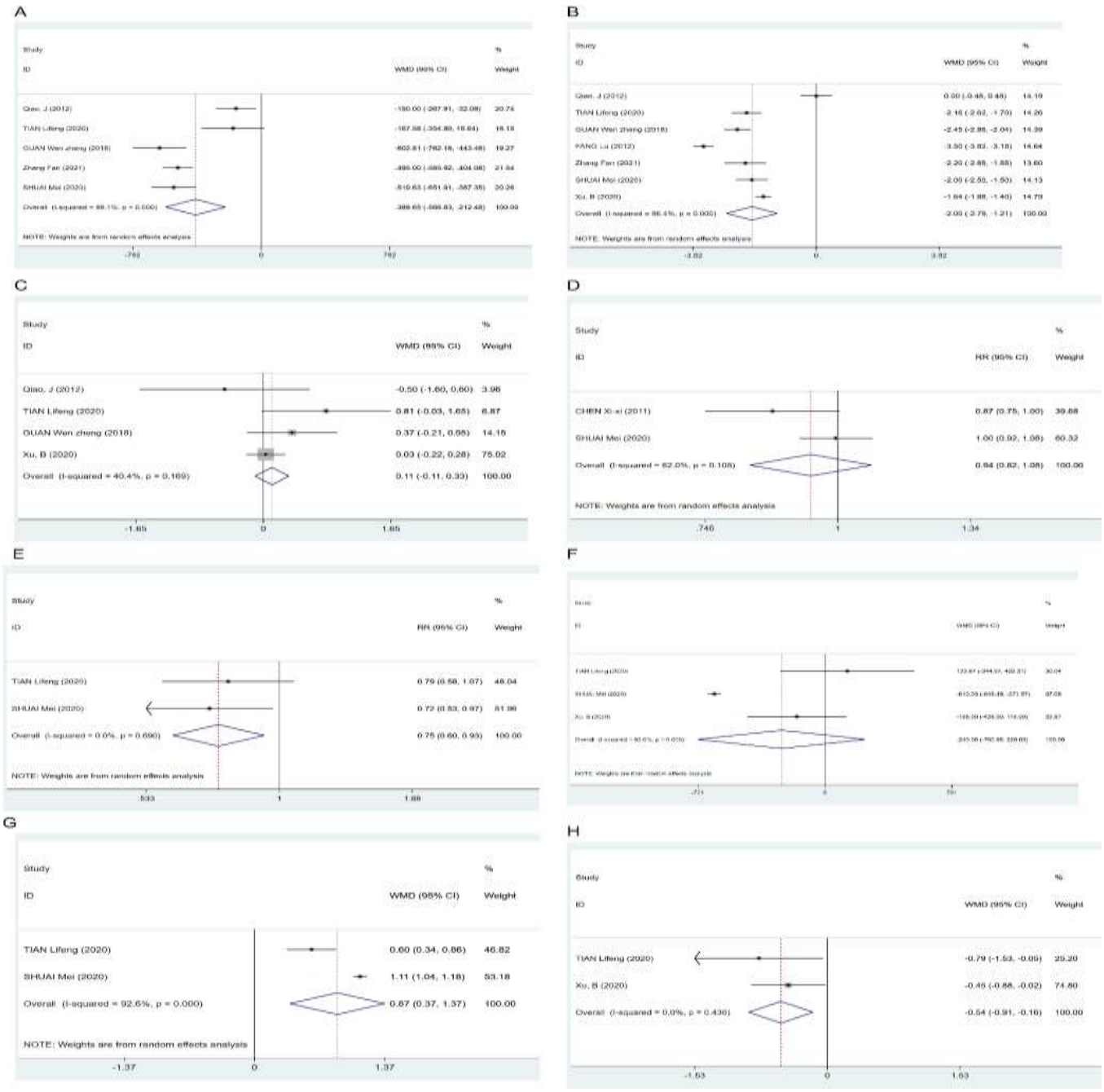

Figure 6: (A) Forest plot comparing the total Gn usage applied in the GnRH-ant regimen versus the GnRH-a regimen; (B) Forest plot comparing the duration of continuous stimulation with Gn between GnRH-ant regimen group and GnRH-a regimen group; (C) Forest plot comparing the quantity of high-quality embryos produced by the GnRH-ant regimen versus the GnRH-a regimen (D) Forest plot comparing the high-quality embryo rate produced by the GnRH-ant regimen versus the GnRH-a regimen; (E) Forest plot comparing the implantation rate produced by the GnRH-ant regimen versus the GnRH-a regimen (F) Forest plot comparing the E2 level on the day of HCG between GnRH-ant regimen group and GnRH-a regimen group; (G) Forest plot comparing the LH level at the time of HCG application in the GnRH-ant group versus the GnRH-a group; (H) Forest plot comparing the endometrial thickness on the day of HCG between GnRH-ant regimen group and GnRH-a regimen group.

The research findings demonstrated a decreased implantation rate in the GnRH-ant group in comparison to the GnRH-a group, with a statistically marked difference (RR [95%CI] =0.75 [0.60, 0.93], *P*=0.009). It was depicted in Figure 6E.

E2 level at the time of HCG application

The meta-analysis incorporated 3 articles[16,17,22] (926 cases) investigating E2 levels at the time of HCG application. Due to heterogeneity among experiments (*P*<0.001, I^2=92.0%), an REM was employed for meta-analysis. The research findings demonstrated no marked discrepancy in the E2 level at the time of HCG application produced by the GnRH-ant and the GnRH-a groups (WMD [95%CI] =-240.06 [-700.95, 220.83], *P*=0.307). It was depicted in Figure 6F.

LH level at the time of HCG application

The meta-analysis incorporated 2 articles[17,22] (380 cases) investigating the LH level at the time of HCG application. Due to heterogeneity across experiments (*P*<0.001, I^2=92.6%), an REM was employed for meta-analysis. The research findings demonstrated an elevated LH level at the time of HCG application among individuals undergoing GnRH-ant in comparison to those undergoing GnRH-a, with a statistically marked difference (WMD [95%CI] = 0.87 [0.37, 1.37], *P*=0.001). It was depicted in Figure 6G.

Endometrial thickness at the time of HCG application

The meta-analysis incorporated 3 studies[16,17,22] (926 cases) investigating the endometrial thickness at the time of HCG application. Due to the absence of heterogeneity across experiments (*P*=0.436, I^2=0.0%), an FEM was employed for meta-analysis. The research findings demonstrated a decreased endometrial thickness at the time of HCG application among individuals undergoing GnRH-ant in comparison to those undergoing GnRH-a, with a statistically marked difference (WMD [95%CI]=-0.54 [-0.91, -0.16], *P*=0.005). It was depicted in Figure 6H.

Outcome measures of safety

Incidence of OHSS

The meta-analysis incorporated 4 articles[17,20-22] investigating the incidence of OHSS. Due to the absence of heterogeneity across experiments (*P*=0.720, I^2=0.0%), an FEM was employed for meta-analysis. The research findings demonstrated a decreased likelihood of developing OHSS in the GnRH-ant group in comparison to the GnRH-a group, with a statistically marked difference (RR [95%CI] =0.33 [0.11, 0.94], *P*=0.037). The sensitivity analysis findings suggested that the RR values remained unaffected, indicating the stability of the results. It was depicted in Figure 7.

Abortion rate

The meta-analysis incorporated 3 studies[16,20,21] investigating the abortion rate. Due to the absence of heterogeneity across experiments (*P*=0.883, I^2=0.0%), an FEM was employed for meta-analysis. The research findings demonstrated no marked discrepancy in the abortion rate produced by the GnRH-ant and the GnRH-a groups (RR [95%CI] =1.13 [0.56, 2.29], *P*=0.729). It was depicted in Figure 8.

Publication bias assessment

The Egger's test for total Gn usage (*P*=0.741), failed to affirm the presence of publication bias. The test on the duration of continuous stimulation with Gn (*P*=0.826), failed to affirm the presence of publication bias. The test on the quantity of high-quality embryos (*P*=0.660), failed to affirm the presence of publication bias. The measurement on the clinical pregnancy (*P*=0.599), failed to affirm the presence of publication bias. The measurement on the E2 level at the time of HCG application (*P*=0.045), signified the existence of publication bias among the enrolled articles. The test on the counts of retrieved oocytes (*P*=0.764), failed to affirm the presence of publication bias. The test on the incidence of OHSS (*P*=0.377), failed to affirm the presence of publication bias. The test on the abortion rate (*P*=0.583), failed to affirm the presence of publication bias.

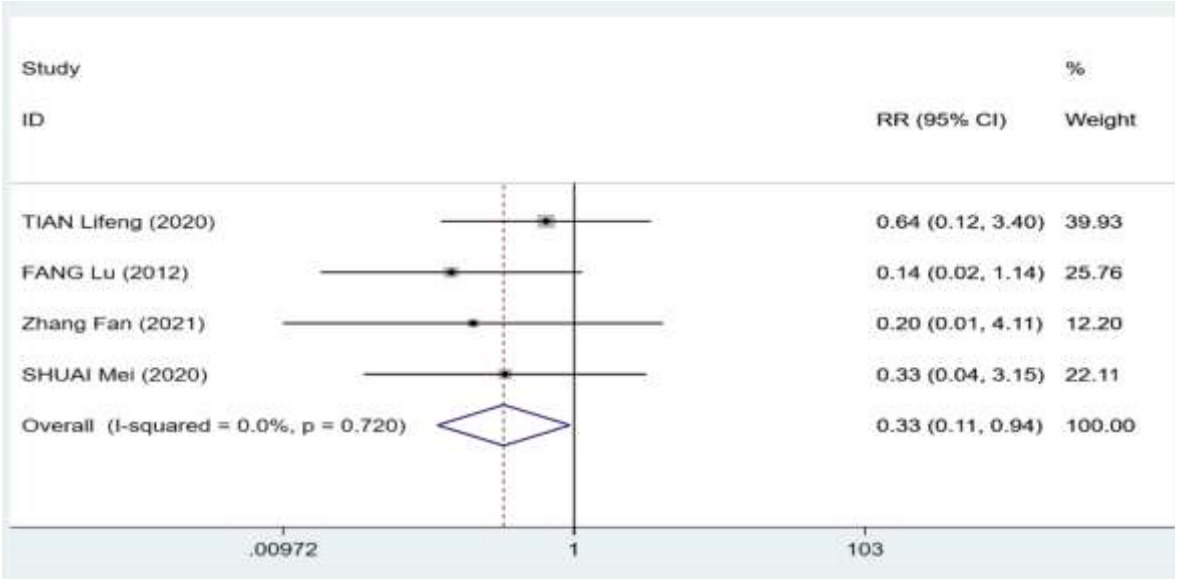

Figure 7: Forest plot comparing the likelihood of developing OHSS produced by the GnRH-ant regimen versus the GnRH-a regimen

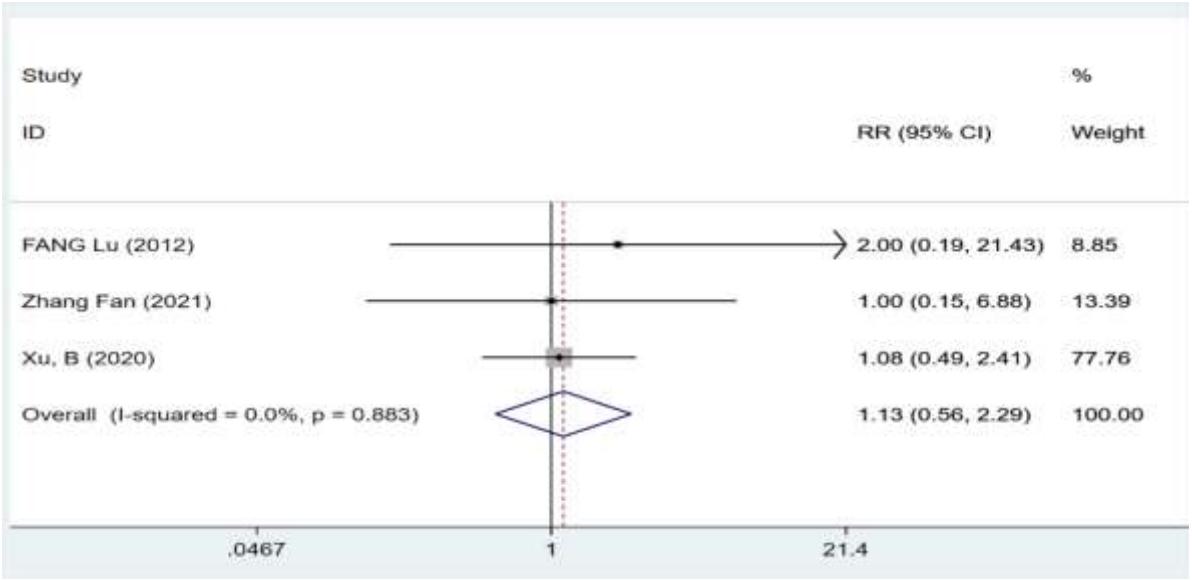

Figure 8: Forest plot comparing the abortion rate in the GnRH-ant group versus the GnRH-a group

Discussion

To date, numerous studies have explored the distinct efficacy and safety outcomes of GnRH-a and GnRH-ant protocols. These study findings revealed that, for individuals exhibiting a normal ovarian response, the GnRH-ant group revealed a decreased total Gn usage, course of Gn stimulation, quantity of retrieved oocytes, and implantation rate in comparison to GnRH-a regimen. The GnRH-ant group demonstrated a lower endometrial thickness at the time of HCG application in comparison to the GnRH-a group. Nevertheless, no statistically marked variance was observed in the clinical pregnancy in fresh cycles, the quantity of high-quality embryos, and the high-quality embryo rate

produced by the two regimens. In terms of the safety, the GnRH-ant group demonstrated a decreased occurrence of OHSS in comparison to the GnRH-a group, with no statistically marked variance observed in abortion rate between the two regimens.

Relevant studies have revealed that across individuals with unexplained infertility undergoing IVF/ICSI, clinical pregnancy and miscarriage rates were comparable produced by the GnRH-a and the GnRH-ant protocols. However, the GnRH-a protocol yields a markedly elevated number of retrieved oocytes[23]. Studies suggested that the GnRH-a yield an increased implantation rate in comparison to the GnRH-ant[24]. Findings from another study indicated a greater number of high-quality embryos in the GnRH-ant group in comparison to the GnRH-a group. However, no marked distinction in clinical pregnancy was observed produced by the two protocols[25]. The longer course of Gn stimulation and the higher total dose of Gn administered in the GnRH-a protocol may be more conducive to harness the latent potential of the ovaries, thus promoting the development and maturation of a greater number of follicles. This could explain the observed advantage in oocyte retrieval numbers[26].

Conversely, the lower total Gn dose and shorter duration of Gn administration in the GnRH-ant protocol may not effectively stimulate the ovaries, leading a comparatively lower count of retrieved oocytes. Research has indicated that endometrial thickness can influence the pregnancy outcomes of patients undergoing GnRH-a and GnRH-ant protocols[27]. Increasing endometrial thickness in older patients with diminished ovarian reserve may improve pregnancy outcomes[28]. A key element for embryo implantation and pregnancy success is the endometrium's receptivity. If both protocols effectively render the endometrium receptive, there may be no marked distinction in clinical pregnancy or other similar outcomes[29]. In terms of in vitro fertilization and embryo transfer (IVF-ET) across individuals with PCOS and POR and normal ovarian response, no statistically marked variance was noted in the quantity of high-quality embryos between the two regimens[30-32]. During the COS process in individuals with PCOS, the GnRH-ant group yield a decreased endometrial thickness at the time of HCG application in comparison to the GnRH-a group[31,33].

Several researches indicated that during the COS process in individuals with PCOS and POR and normal ovarian response, the GnRH-ant group demonstrated a decreased likelihood of developing OHSS in comparison to the GnRH-a group[10,34-37]. A study demonstrated that the counts of high-quality embryos were comparable produced by GnRH-a and GnRH-ant protocols. Nevertheless, the GnRH-ant protocol yield a reduced risk of OHSS[38]. Another study revealed a markedly reduced likelihood of developing OHSS in the GnRH-ant group in comparison to the GnRH-a group[39]. A clinical meta-analysis[40] indicated that infertile patients undergoing GnRH-a protocols had a greater likelihood of developing OHSS incomparison to those managed with GnRH-ant. One potential reason for this is that GnRH-a protocols, which utilize GnRH-a for pituitary down-regulation, may excessively inhibit the hypothalamic-pituitary-ovarian (HPO) axis. Individuals with a high ovarian response become more susceptible to Gn stimulation, predisposing them to overstimulation. This heightened sensitivity can lead to a more pronounced degree of excessive follicular development and a greater elevation in hormone levels in high responders, ultimately contributing to a higher incidence of OHSS[41,42]. Studies showed that during the COS process in individuals with PCOS and POR, normal ovarian response, and thin endometrium, no statistically marked variance was found in the abortion rate between the two regimens[32,35,40,43,44]. This study has some strengths.

The scientific method from a systematic review of evidence-based medicine has been adopted to conduct systematic, comprehensive, and targeted RCT and non-RCT studies on individuals exhibiting a normal ovarian response. Retrieval, screening, and rigorous risk of bias assessment have been conducted. Based on research data, the efficiency and safety produced by GnRH-a and GnRH-ant regimens have been evaluated, and the evidence gathered offers a valuable reference for choosing ovulation induction regimens in clinical practice.

However, certain limitations can be found in this study. Firstly, some key effectiveness

indicators, such as cumulative pregnancy and cumulative live birth rates, were not studied and analyzed in this meta-analysis due to the limited literature on relevant reports. These limited the comprehensiveness of effectiveness evaluation. Moreover, the research design included relatively few RCTs and more non-RCTs. Some of the research results showed inconsistencies after subgroup analysis, which to some extent affected the reliability of quantitative and combined results

Conclusion

Among women exhibiting a normal ovarian response, the GnRH-a protocol demonstrated a potentially superior effectiveness profile, thus attributing to an enhanced count of oocytes retrieved and improved implantation rates. As for safety considerations, the GnRH-ant protocol presented a more advantageous profile due to the reduced risk of OHSS. Considering economic factors, the GnRH-ant protocol, with its lower total Gn dosage and shorter duration of Gn stimulation, offered a more cost-effective, convenient, and simplified approach

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Author contributions

All authors contributed to the study conception and design. Writing - original draft preparation: [Jiajie Lai]; Writing - review and editing: [Rongju Liu]; Conceptualization: [Jing Lu]; Methodology: [Xiuling Wu]; Formal analysis and investigation: [Xuemei Chen]; Funding acquisition: [Rongju Liu]; Resources: [Jiajie Lai]; Supervision: [Rongju Liu], and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Availability of data and material

The original contributions presented in the study are included in the article/Supplementary Material

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