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Review

Live birth rate of gonadotropin-releasing hormone antagonist versus luteal phase gonadotropin-releasing hormone agonist protocol in IVF/ICSI: a systematic review and meta-analysis

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Abbreviations:
CI: confidence interval; COS: controlled ovarian stimulation; CPR: clinical pregnancy rate; GnRH-a: gonadotrophin-releasing hormone agonist; GnRH-ant: gonadotrophin-releasing hormone antagonist; ICSI: intracytoplasmic sperm injection; IVF: in vitro fertilization; LH: luteinizing hormone; OCP: oral contraception pill; OHSS: ovarian hyperstimulation syndrome; PCOS: polycystic ovary syndrome; POR: poor ovarian response; RR: relative risk; WMD: weighted mean difference

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Abstract

In vitro fertilization (IVF) and embryo transfer and intracytoplasmic sperm injection (ICSI) have allowed millions of infertile couples to achieve pregnancy. As an essential part of IVF/ICSI enabling the retrieval of a high number of oocytes in one cycle, controlled ovarian stimulation (COS) treatment mainly composes of the standard long gonadotrophin-releasing hormone agonist (GnRH-a) protocol and the gonadotrophin-releasing hormone antagonist (GnRH-ant) protocol. However, the effectiveness of GnRH-ant protocol is still debated because of inconsistent conclusions and insufficient subgroup analyses. This systematic review and meta-analysis included a total of 52 studies, encompassing 5193 participants in the GnRH-ant group and 4757 in the GnRH-a group. The findings of this study revealed that the GnRH-ant protocol is comparable with the long GnRH-a protocol when considering live birth as the primary outcome, and it is a favourable protocol with evidence reducing the incidence of ovarian hyperstimulation syndrome in women undergoing IVF/ICSI, especially in women with polycystic ovary syndrome. Further research is needed to compare the subsequent cumulative live birth rate between the two protocols among the general and poor ovarian response patients since those patients have a lower clinical pregnancy rate, fewer oocytes retrieved or fewer high-grade embryos in the GnRH-ant protocol.

Introduction

In vitro fertilization (IVF) and embryo transfer and intracytoplasmic sperm injection (ICSI) have allowed millions of infertile couples to achieve pregnancy. The number of assisted reproductive technology (ART) cycles in most regions has increased in recent years (Ref. 1). Controlled ovarian stimulation (COS) is an essential part of IVF/ICSI, enabling the retrieval of a high number of oocytes in one cycle. The gonadotrophin-releasing hormone antagonist (GnRH-ant) protocol and the standard long gonadotrophin-releasing hormone agonist (GnRH-a) protocol are the most commonly used stimulation protocols.

Since its development in the 1980s, GnRH-a has played an essential role in COS among patients undergoing ART (Ref. 2). GnRH-a treatment can prevent a premature luteinizing hormone (LH) surge, leading to an increased numbers of retrieved oocytes, higher pregnancy rates and a decreased number of cycle cancellations (Ref. 3). Ovarian hyperstimulation syndrome (OHSS) is a rare but potentially fatal complication of COS (Ref. 4). GnRH-a is associated with an increased risk of OHSS or other side effects (Ref. 5). GnRH antagonists were discovered in the 1990s and can competitively block GnRH receptors and cause rapid suppression of gonadotropin release (Ref. 6). This protocol is more convenient for patients because of the shorter treatment time and fewer injections (Ref. 7). GnRH-ant directly inhibits gonadotropins and prevents the LH surge, resulting in a 10% lower incidence of OHSS with GnRH-ant than with GnRH-a (Refs 8, 9).

Nevertheless, the effectiveness of GnRH-ant is still debated. Indeed, multiple meta-analyses and randomized controlled trials (RCTs) of the GnRH-a and GnRH-ant protocols on pregnancy and live birth rates have yielded conflicting findings. A Cochrane systematic review published in 2006 indicated that the GnRH-ant protocol leads to significantly lower clinical pregnancy and live birth rates than the long GnRH-a protocol (Ref. 10). A subsequent Cochrane systematic review published in 2011 showed no significant difference in the live birth rates between the GnRH-a and GnRH-ant groups (Ref. 11). Another Cochrane systematic review of 73 RCTs published in 2016 reported that the GnRH-a and GnRH-ant protocols have equivalent live birth rates (Ref. 12). In a review accounting for patient type, Lambalk *et al.* found that GnRH antagonists compromise the effectiveness of IVF in the general population of IVF patients. However, in women with polycystic ovary syndrome (PCOS) and those with

poor ovarian response (POR), there was no evidence of a difference in ongoing pregnancy rate between the antagonist and agonist groups. In contrast, antagonists resulted in significantly lower OHSS rates in general IVF patients and women with PCOS (Ref. 13). Despite many published studies regarding ovarian stimulation in IVF/ICSI, the available recommendations still fail to reach a consensus on the best therapy regarding benefits and risks. Based on the above controversial issues, a more in-depth evaluation of the available literature is needed to provide consistent recommendations for optimizing IVF/ICSI.

Methods

The protocol of this systematic review was prospectively registered in PROSPERO (reference: CRD42022363446). This meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (Table S1).

Literature search strategy and selection criteria

PubMed, Embase, the Cochrane Library and the Web of Science were searched for potentially eligible reports from their inception until 27 December 2022. The search terms included 'Gonadotropin-Releasing Hormone', 'Gonadotropin-Releasing Hormone antagonist', 'Gonadotropin-Releasing Hormone agonist', 'Buserelin', 'Triptorelin', 'Goserelin', 'Leuprorelin', 'Nafarelin', 'Cetrorelix', 'Ganirelix', 'teverelix', 'Assisted Reproductive Techniques (ART)', 'In Vitro Fertilization (IVF)', 'Intracytoplasmic Sperm Injection (ICSI)' and 'Randomized Controlled Trials (RCT)'. The detailed search terms are shown in Tables S2–S5.

The literature search was performed independently by two authors (Liu CH and Tian T) based on specific inclusion and exclusion criteria. The inclusion criteria were (1) studies comparing a standard luteal long GnRH-a protocol with the GnRH-ant protocol; (2) RCT as the study design and (3) studies written in English. The exclusion criteria include (1) single-dose GnRH-a or GnRH-ant; (2) reviews, comments, conference abstracts, short articles or study protocols or (3) articles including donor oocyte cycles. Then, the resulting article list was compared. Discrepancies were resolved by discussion. A third investigator (Yang R) was invited to the discussion if necessary.

Data extraction

The following data were extracted from the identified studies: study design, sample size, type of intervention, dosage of the intervention, type of control, dosage of the control, agonist protocol type, antagonist protocol type, live birth rate, clinical pregnancy rate (CPR), ongoing pregnancy rate, number of high-grade embryos, number of oocytes retrieved and OHSS. Data extraction was performed by two investigators (Liu CH and Tian T). Discrepancies were solved by discussion until a consensus was reached. The main report was used if a study with multiple publications was found.

Outcomes

The primary outcome was the live birth rate. The secondary outcomes were CPR, ongoing pregnancy rate, number of oocytes retrieved and number of high-grade embryos. The rates of OHSS and miscarriage were used to estimate the safety of the COS protocols.

Quality assessment

The level of evidence of all articles was assessed independently by two authors (Wang Y and Liu CH) according to version 2 of the Cochrane risk-of-bias assessment tool for randomized trials (RoB2) (Ref. 14) (Table S6).

Statistical analysis

We performed this meta-analysis according to the intention-to-treat principle. A fixed-effects model was applied if no significant heterogeneity was identified ($I_2 < 50\%$), and a random-effects model was used when significant heterogeneity was detected ($I_2 \geq 50\%$). For between-group comparisons of the number of oocytes and the number of high-grade embryos between groups, data are reported as the weighted mean difference (WMD) with the corresponding 95% confidence interval (CI). Pregnancy outcomes are reported as the relative risk (RR) with 95% CI. Subgroup analyses were performed for different populations (general population, women with PCOS and those with POR), oral contraception pill (OCP) or oestradiol valerate pretreatment (yes or no), fixed or flexible antagonist protocol and specific antagonist and agonist drugs. R software (version 4.1.0, Austria) was used for all statistical analyses, including the 'Meta' package for meta-analysis and other R Core Teams. Statistical significance was defined as a two-sided P value < 0.05.

Results

Study selection and description of the included studies

The literature search process is summarized in Figure 1. The initial searches yielded 7202 studies. After checking for the duplication and relevance of the comparisons, 52 studies were included in the final meta-analysis. The quality of each included study was estimated (Table S6).

The characteristics of all 52 studies are presented in Table 1. A total of 5193 participants were included in the antagonist group, and 4757 were included in the agonist group. Thirty-six trials were performed among the general IVF population, eight were performed among women with poor response and eight were performed among women with PCOS. Thirty-four trials used cetrorelix, 15 used ganirelix, two used cetrorelix or ganirelix and one did not report the type of antagonist. Types of agonists used included buserelin (15 studies), leuprorelin (13 studies), triptorelin (20 studies) and nafarelin (4 studies).

Comparison of live birth rates between the GnRH-ant and GnRH-a groups

Thirteen studies reported the live birth rate. In the overall analysis, the live birth rate was not significant between the groups, with an RR of 0.95 (95% CI: 0.86–1.06) (Fig. 2). In the subgroup analyses of different population types, hormonal pretreatments, fixed or flexible protocols and types of agonists and antagonists, there were no differences in the live birth rates between the GnRH-ant and GnRH-a groups (Fig. 2).

Comparisons of other outcomes between the GnRH-ant and GnRH-a groups

The comparisons of all outcomes between the GnRH-ant and GnRH-a groups are presented in Table 2. There were no significant differences in the ongoing pregnancy rate or miscarriage rate between the GnRH-ant and GnRH-a groups. Compared with that in the GnRH-a group, the OHSS rate (RR: 0.79, 95% CI: 0.71–0.88), moderate-to-severe OHSS rate (RR: 0.49, 95% CI: 0.37–0.64), number of oocytes retrieved (WMD: −0.88, 95% CI: −1.00 to −0.76), number of high-grade embryos (WMD:

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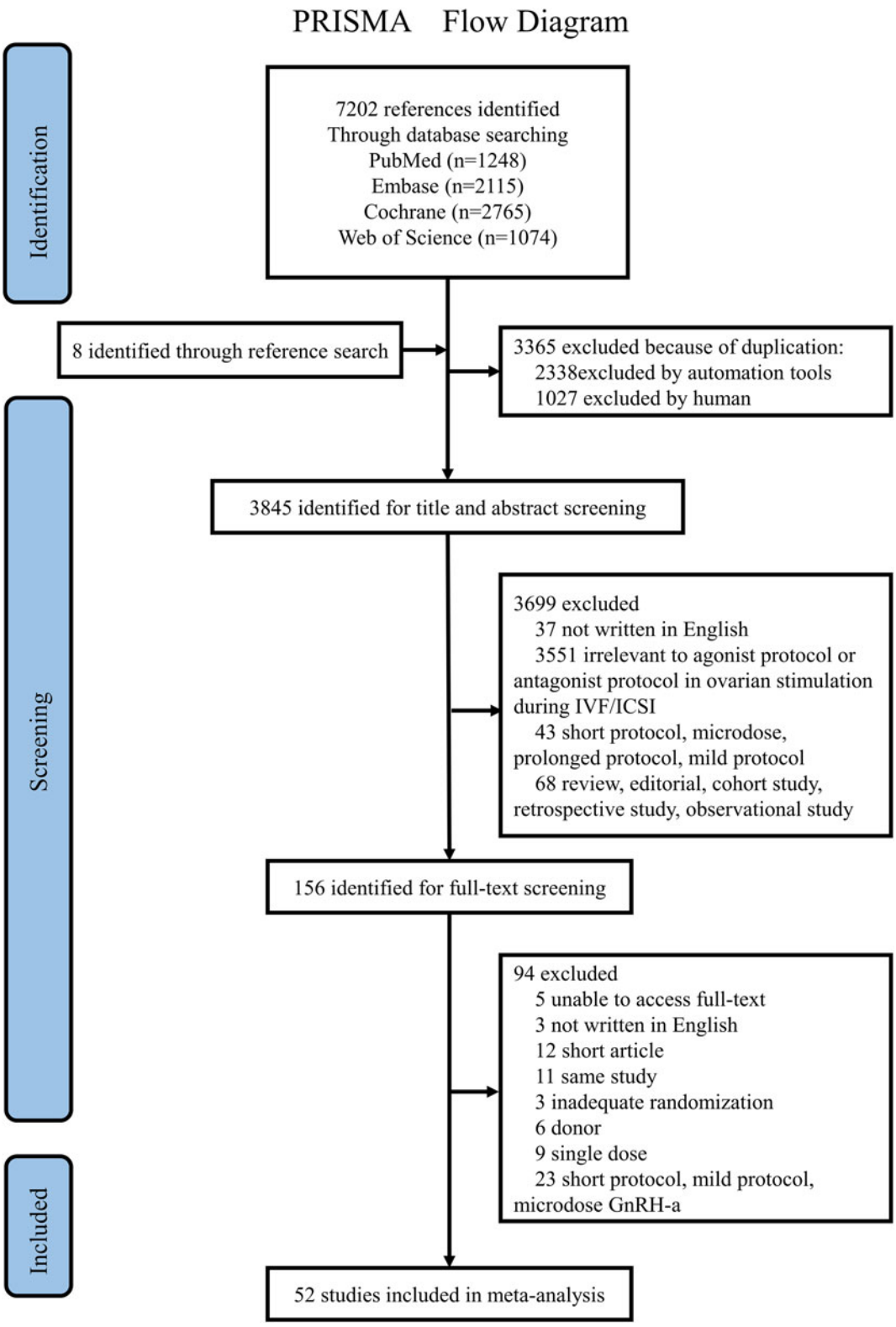

Figure 1. Study flow diagram.

−0.18, 95% CI: −0.23 to −0.13) and CPR (RR: 0.90, 95% CI: 0.85–0.96) in the antagonist group were significantly lower.

Subgroup analyses

Population type

In the general population, the total OHSS rate was significantly lower in the antagonist protocol group (Fig. 3). There were also fewer oocytes retrieved, fewer high-grade embryos and a lower CPR in the GnRH-ant group. In women with PCOS, GnRH antagonists resulted in significantly lower total rates of OHSS (Fig. 3) and moderate-to-severe OHSS (Fig. 4). Among poor responders, oocyte retrieval number was lower with antagonist treatment. Regarding other variables, there were no differences between the antagonist and agonist groups.

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Table 1. Characteristics of the included studies

Authors	Number of patients	Population	Type of antagonist	Antagonist protocol	Dosage (mg/day)	Type of agonist	Agonist protocol	Dosage
Albano *et al.* (Ref. 15)	198/95	General	Cetrorelix	Fixed MD S6	0.25	Buserelin	Long MD	4 × 150 μg/day
Aydin *et al.* (Ref. 16)	40/40	General	Cetrorelix	Fixed MD S6	0.25	Leuprorelin	Long MD	0.1 mg/day
Badrawi *et al.* (Ref. 17)	50/50	General	Ganirelix	Flex MD (≥14 mm)	0.25	Buserelin	Long MD	6 × 100 μg/day
Bahçeci *et al.* (Ref. 18)	73/75	PCOS	Cetrorelix	OCP/flex MD (≥14 mm)	0.25	Leuprorelin	Long MD	0.5 mg/day
Barmat *et al.* (Ref. 19)	40/40	General	Cetrorelix	OCP/flex MD (≥12–14 mm)	0.25	Leuprorelin	Long MD	0.5 mg/day
Borm *et al.* (Ref. 20)	486/244	General	Ganirelix	Fixed MD S6	0.25	Buserelin	Long MD	4 × 0.15 mg/day
Check *et al.* (Ref. 21)	30/30	General	Ganirelix	Flex MD (≥14 mm and oestradiol ≥1000 pg/ml)	0.25	Leuprorelin	Long MD	0.5 mg/day
Cheung *et al.* (Ref. 22)	33/33	Poor responders	Cetrorelix	OCP/fixed MD S6	0.25	Buserelin	Long MD	0.6 mg/day
Cota *et al.* (Ref. 23)	32/32	General	Cetrorelix	Flex MD (≥14 mm)	0.25	Leuprorelin	Long MD	1 mg/day
Dakhly *et al.* (Ref. 24)	78/71	Poor responders	Cetrorelix	Flex MD (≥12–14 mm)	0.25	Triptorelin	Long MD	0.1 mg/day
Depalo *et al.* (Ref. 25)	69/67	General	Cetrorelix	Flex MD (≥12–14 mm)	0.25	Triptorelin	Long MD	0.1 mg/day
Devjak *et al.* (Ref. 26)	10/11	General	Cetrorelix	Flex MD (≥14 mm)	0.25	Buserelin	Long MD	0.6 mg/day
van Hooren and European (Ref. 27) (Middle 2001)	236/119	General	Ganirelix	Fixed MD S6	0.25	Triptorelin	Long MD	0.1 mg/day
Ferrari *et al.* (Ref. 28)	30/30	General	Cetrorelix	Flex MD (≥14 mm)	0.25	Leuprorelin	Long MD	0.5 mg/day
Firouzabadi *et al.* (Ref. 29)	118/117	General	Ganirelix	Fixed MD S6	0.25	Buserelin	Long MD	0.5 mg/day
Fluker *et al.* (Ref. 30)	208/105	General	Ganirelix	Fixed MD S6	0.25	Leuprorelin	Long MD	1.0 mg/day
Friedler *et al.* (Ref. 31)	40/38	General	Cetrorelix	Flex MD (≥12 mm)	0.25	Nafarelin	Long MD	3 × 0.2 mg/day
Fusi *et al.* (Ref. 32)	136/137	Poor responders	NA	Flex MD (≥13 mm)	NA	Triptorelin	Long MD	0.1 mg/day
Garcia-Velasco *et al.* (Ref. 33)	115/113	General	Ganirelix	OCP/fixed MD S5/S6	0.25	Triptorelin	Long MD	Decapeptyl, Ipsen Pharma
Gizzo *et al.* (Ref. 34)	90/180	General	Ganirelix	Flex MD (≥14 mm)	0.25	Triptorelin	Long MD	0.1 mg/day
Haydardedeoglu *et al.* (Ref. 35)	150/150	PCOS	Ganirelix	OCP/fixed MD S6	0.25	Leuprorelin	Long MD	1 mg/day
Hershko Klement *et al.* (Ref. 36)	31/29	General	Cetrorelix	Oestradiol valerate/flex MD		Triptorelin	Long MD	
Hohmann *et al.* (Ref. 37)	97/45	General	Cetrorelix	Flex MD (≥14 mm)	0.25	Triptorelin	Long MD	1 mg/day
Hosseini *et al.* (Ref. 38)	57/55	PCOS	Cetrorelix	OCP/flex MD (≥14 mm)	0.25	Buserelin	Long MD	0.5 mg/day
Hsieh *et al.* (Ref. 39)	86/58	General	Cetrorelix	Fixed MD S7	0.25	Leuprorelin	Long MD	0.5 mg/day
Huirne *et al.* (Ref. 40)	91/91	General	Cetrorelix	OCP/fixed MD S6	0.25	Buserelin	Long MD	0.5 mg/day
Kaya *et al.* (Ref. 41)	40/40	General	Cetrorelix	Flex MD (≥13 mm)	0.25	Leuprorelin	Long MD	NA
Kim *et al.* (Ref. 42)	40/40/40	Poor responders	Cetrorelix	OCP/flex MD; flex MD (≥14 mm)	0.25	Triptorelin	Long MD	0.1 mg/day
Kim *et al.* (Ref. 43)	106/105	PCOS	Cetrorelix	OCP/flex MD (≥13 mm)	0.25	Triptorelin	Long MD	0.1 mg/day
Koichi *et al.* (Ref. 44)	63/66	General	Cetrorelix	OCP/flex MD (≥14 mm)	0.25	Buserelin	Long MD	0.9 mg/day

Lainas *et al.* (Ref. 45)	26/52	PCOS	Ganirelix	OCP/fixed MD S1	0.25	Triptorelin	Long MD	0.1 mg/day
Lainas *et al.* (Ref. 46)	110/110	PCOS	Ganirelix	OCP/flex MD (≥14 mm)	0.25	Triptorelin	Long MD	0.1 mg/day
Lee *et al.* (Ref. 47)	20/20	General	Cetrorelix	Fixed MD S5	0.25	Buserelin	Long MD	
Loutradis *et al.* (Ref. 48)	58/58	General	Cetrorelix	Flex MD (≥14 mm)	0.25	Triptorelin	Long MD	1 mg/day
Moraloglu *et al.* (Ref. 49)	45/48	General	Cetrorelix	OCP/flex MD (≥14 mm)	0.25	Leuprorelin	Long MD	1 mg/day
Pabuccu *et al.* (Ref. 50)	134/132	General	Cetrorelix	Flex MD (≥14 mm + E2 >600 pg/ml)	0.25	Triptorelin	Long MD	0.1 mg/day
Papanikolaou *et al.* (Ref. 51)	96/94	General	Ganirelix or cetrorelix	Fixed MD S6	0.25	Buserelin	Long MD	0.6 mg/day
Prapas *et al.* (Ref. 52)	182/182	Poor responders	Ganirelix	OCP/fixed MD S6	0.25	Triptorelin	Long MD	0.1 mg/day
Qiao *et al.* (Ref. 53)	113/120	General	Ganirelix	Fixed MD S6	0.25	Triptorelin	Long MD	0.05 mg/day
Rabati and Zeidi (Ref. 54)	69/67	General	Cetrorelix	Flex MD (≥14 mm)	0.25	Buserelin	Long MD	0.5 mg/day
Rombauts *et al.* (Ref. 55)	117/117/117	General	Ganirelix	OCP/flex MD; flex MD (≥14 mm)	0.25	Nafarelin	Long MD	0.8 mg/day
Serafini *et al.* (Ref. 56)	107/106	General	Cetrorelix	Flex MD (≥13–14 mm)	0.25	Leuprorelin	Long MD	0.5 mg/day
Shin *et al.* (Ref. 57)	25/11	PCOS	Cetrorelix	OCP fixed MD S1/S6	0.25	Triptorelin	Long MD	0.1 mg/day
Sunkara (Ref. 58)	37/37	Poor responders	Cetrorelix	Flex MD (≥14 mm)	0.25	Nafarelin	Long MD	2 × 0.4 mg/day
Tazegul *et al.* (Ref. 59)	48/48	Poor responders	Cetrorelix or ganirelix	Flex MD (≥14 mm)	0.25	Leuprorelin	Long MD	1 mg/day
Tehraninejad *et al.* (Ref. 60)	48/47	PCOS	Cetrorelix	OCP/flex MD (≥12–14 mm)	0.25	Buserelin	Long MD	0.5 mg/day
Tehraninejad *et al.* (Ref. 61)	150/150	General	Cetrorelix	Flex MD (≥14 mm)	0.25	Buserelin	Long MD	0.5 mg/day
Toftager *et al.* (Ref. 62)	550/549	General	Ganirelix	Fixed MD S6	0.25	Nafarelin	Long MD	3 × 0.2 mg/day
Trenkic *et al.* (Ref. 63)	45/45	PCOS	Cetrorelix	OCP flex MD (≥14 mm or E2 >300 pg/ml)	0.25	Triptorelin	Long MD	0.1 mg/day
Xavier *et al.* (Ref. 64)	66/65	General	Cetrorelix	Flex MD (≥13 mm or E2 ≥400 pg/ml)	0.25	Buserelin	Long MD	0.6 mg/day
Xu *et al.* (Ref. 65)	273/273	General	Cetrorelix	Flex MD (>14 mm; E2 >300 pg/ml; LH serum levels >10 IU/l)	0.25	Triptorelin	Long MD	0.1 mg/day
Ye *et al.* (Ref. 66)	109/111	General	Cetrorelix	Oestradiol valerate/flex MD (≥12–14 mm)	0.25	Triptorelin	Long MD	0.1 mg/day

MD, multiple dose; S5/S6/S7, stimulation day 5/6/7; PCOS, polycystic ovary syndrome; Flex, flexible; OCP, oral contraceptive pretreatment.

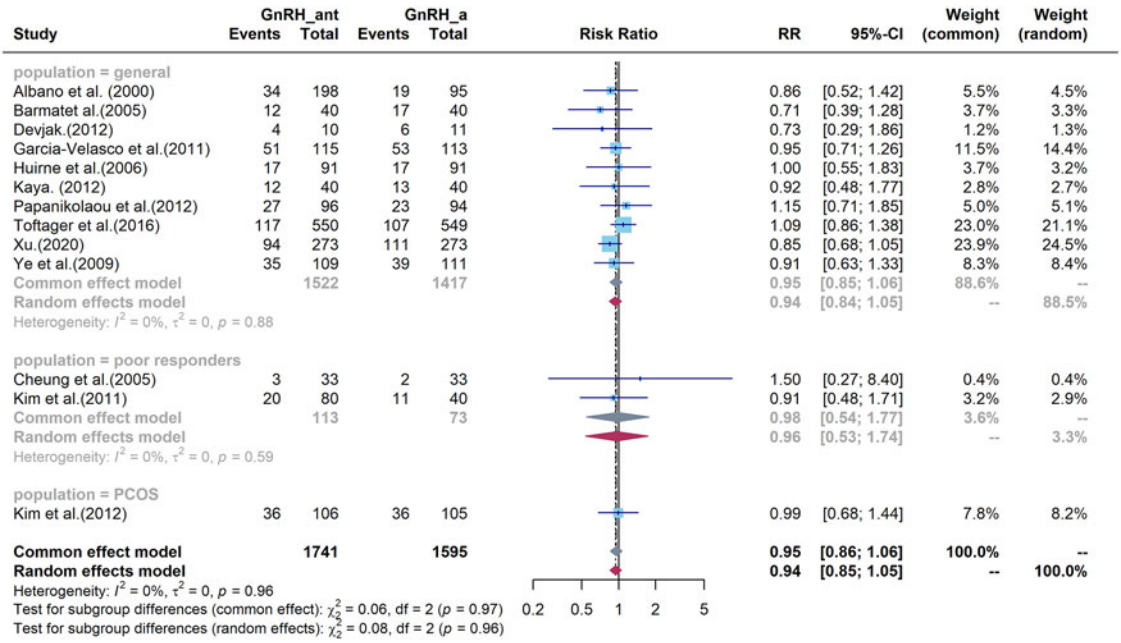

Figure 2. Live birth rate according to patient population.

Hormonal pretreatment

In the OCP subgroup, antagonist treatment resulted in a lower CPR (RR: 0.90, 95% CI: 0.81–0.99), OHSS rate, moderate-to-severe OHSS rate and fewer oocytes than the agonist treatment. The results of the comparison of the antagonist and agonist groups were similar to those with the non-OCP pretreatment, except the antagonist treatment resulted in the same number of high-grade embryos (WMD −0.07, 95% CI: −0.22–0.09). In oestradiol valerate pretreatment subgroup, the antagonist and agonist groups showed similar rates of live birth rate, CPR, etc.

Fixed or flexible antagonist protocol

Compared with the agonist protocol, the flexible and fixed antagonist protocols had lower OHSS, moderate-to-severe OHSS and oocyte retrieval rates. However, no difference in the CPR or the number of high-grade embryos was found between the fixed antagonist and agonist groups. Flexible antagonist treatment resulted in a lower CPR (RR: 0.89, 95% CI: 0.83–0.96) and number of high-grade embryos (WMD: −0.18, 95% CI: −0.24 to −0.13).

Specific types of antagonists and agonists

The trends for cetrorelix and ganirelix were the same as those in the general population. In the subgroup analysis based on GnRH analogue types, there was no difference in the live birth rate, ongoing pregnancy rate or miscarriage rate between agonist and antagonist protocols. With antagonist treatment, the rates of OHSS and moderate-to-severe OHSS were lower, there were fewer oocytes than with buserelin, and there were fewer high-grade embryos than with leuprorelin. Additionally, compared with triptorelin, antagonist treatment resulted in lower clinical pregnancy and moderate-to-severe OHSS rates, fewer oocytes and fewer high-grade embryos and compared with nafarelin, antagonist treatment resulted in a lower moderate-to-severe OHSS rate and fewer oocytes.

Discussion

With the changes in the COS protocols used, studies comparing antagonists and agonists have been published (Refs 10, 11, 12, 13, 67). The current study incorporated more new pieces of literature and focused on the live birth rate rather than the ongoing pregnancy rate as the primary outcome. We established strict eligibility criteria and excluded early follicle phase start-up antagonist and long-acting follicular agonist protocols. In addition, we performed subgroup analyses according to the type of patient, use of oral contraception pretreatment, specific antagonist and agonist drug use and fixed or flexible antagonist protocol. In this study, we obtained a clearer view of the effect of the GnRH-ant versus GnRH-a intervention. Our meta-analysis showed no evidence of differences in live birth or ongoing pregnancy rates between the GnRH-a and GnRH-ant protocols in total and all subgroup analyses. GnRH antagonists could reduce the OHSS rate, especially the moderate-to-severe OHSS rate, compared with the GnRH-a protocol. On the other hand, the use of GnRH antagonists could reduce the CPR, the number of oocytes retrieved or the number of high-grade embryos in general population and POR patients.

A previous meta-analysis and systematic review showed that where ongoing pregnancy rates are concerned, the use of the long agonist protocol remains superior and can still be regarded as a potential first choice (Ref. 13). That review focused on the ongoing pregnancy rate rather than the live birth rate because they thought almost all published studies reported ongoing pregnancy. However, considering that the live birth rate was still the most effective evaluation index for IVF treatment, we chose the live birth rate as the primary outcome. We found that the GnRH-ant protocol has a comparable live birth rate to the long GnRH-a protocol among women undergoing IVF/ICSI, consistent with two previous meta-analyses (Refs 11, 12).

In addition to the live birth rate, we estimated the safety of COS by comparing the rates of OHSS, moderate-to-severe OHSS and miscarriage. Our study did not observe any significant difference in miscarriage rates or ongoing pregnancy rates between the GnRH-ant and long GnRH-a protocols. It was notable that the use of the GnRH-ant protocol reduced the rates of total OHSS and moderate-to-severe OHSS compared with the GnRH-a protocol, and we found that the difference was more significant for moderate-to-severe OHSS (RR: 0.49, 95% CI: 0.37–0.64) than for OHSS (RR: 0.79, 95% CI: 0.71–0.88) when

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Table 2. Comparisons of all outcomes between the GnRH-ant and GnRH-a groups

	Live birth rate	Ongoing pregnancy	Clinical pregnancy	OHSS	Moderate or severe OHSS	Miscarriage	Oocyte retrieval	Number of high grade embryos
	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	WMD (95% CI)	WMD (95% CI)
In total	0.95 (0.86–1.06)	0.95 (0.88–1.02)	0.90 (0.85–0.96)	0.79 (0.71–0.88)	0.49 (0.37–0.64)	0.93 (0.72–1.19)	−0.88 (−1.00 to −0.76)	−0.18 (−0.23 to −0.13)
Patient type								
General	0.95 (0.85–1.06)	0.94 (0.86–1.03)	0.90 (0.84–0.96)	0.84 (0.75–0.94)	0.55 (0.40–0.79)	0.86 (0.65–1.15)	−1.38 (−1.55 to −1.22)	−0.19 (−0.25 to −0.14)
Poor responders	0.98 (0.54–1.77)	0.95 (0.61–1.46)	0.81 (0.66–1.00)	NA	NA	0.82 (0.19–3.56)	−0.37 (−0.54 to −0.19)	−0.35 (−0.74 to 0.04)
PCOS	0.99 (0.68–1.44)	0.96 (0.82–1.14)	1.00 (0.87–1.15)	0.52 (0.37–0.73)	0.44 (0.27–0.71)	1.21 (0.71–2.06)	0.38 (−0.54 to 1.30)	−0.00 (−0.18 to 0.18)
Hormonal pretreatment								
Non-OCP	0.97 (0.84–1.11)	0.96 (0.87–1.06)	0.91 (0.84–0.98)	0.85 (0.76–0.95)	0.59 (0.42–0.83)	0.98 (0.69–1.39)	−0.94 (−1.15 to −0.73)	−0.19 (−0.25 to −0.14)
OCP	0.94 (0.78–1.14)	0.91 (0.81–1.04)	0.90 (0.81–0.99)	0.52 (0.38–0.71)	0.41 (0.26–0.65)	0.79 (0.54–1.16)	−0.86 (−1.00 to −0.71)	−0.07 (−0.22 to 0.09)
Oestradiol valerate	0.91 (0.63–1.33)	NA	0.87 (0.69–1.10)	1.53 (0.26–8.96)	NA	1.53 (0.65–3.59)	−0.63 (−1.93 to 0.67)	−0.60 (−1.50 to 0.30)
Protocol of antagonist								
Fixed	1.03 (0.88–1.21)	0.96 (0.87–1.05)	0.93 (0.84–1.02)	0.86 (0.77–0.97)	0.53 (0.37–0.77)	0.80 (0.53–1.21)	−0.98 (−1.12 to −0.83)	−0.16 (−0.34 to 0.02)
Flex	0.87 (0.75–1.02)	0.93 (0.81–1.06)	0.90 (0.85–0.96)	0.60 (0.47–0.77)	0.44 (0.29–0.66)	1.01 (0.74–1.38)	−0.65 (−0.87 to −0.43)	−0.18 (−0.24 to −0.13)
Types of antagonists								
Cetrorelix	NA	0.95 (0.80–1.12)	0.90 (0.83–0.98)	0.61 (0.48–0.78)	0.40 (0.27–0.61)	1.09 (0.80–1.49)	−0.72 (−0.98 to −0.47)	−0.18 (−0.23 to −0.13)
Ganirelix	1.04 (0.87–1.25)	0.95 (0.86–1.04)	0.90 (0.82–0.99)	0.86 (0.76–0.97)	0.57 (0.40–0.83)	0.65 (0.39–1.09)	−0.97 (−0.11 to −0.83)	−0.19 (−0.36 to −0.01)
Geni- or cetrorelix	1.15 (0.71–1.85)	1.05 (0.70–1.58)	1.16 (0.79–1.69)	1.96 (0.18–21.23)	NA	NA	−0.03 (−0.85 to 0.79)	NA
Type of agonists								
Buserelin	0.99 (0.75–1.32)	0.95 (0.82–1.10)	0.96 (0.85–1.08)	0.56 (0.44–0.72)	0.44 (0.27–0.71)	1.20 (0.76–1.88)	−1.06 (−1.47 to −0.65)	0.14 (−0.11 to 0.40)
Leuprorelin	0.80 (0.52–1.24)	0.87 (0.71–1.07)	0.91 (0.79–1.04)	0.95 (0.53–1.68)	0.69 (0.25–1.90)	0.90 (0.52–1.56)	−0.51 (−1.07 to 0.06)	−0.20 (−0.25 to −0.14)
Triptorelin	0.90 (0.78–1.04)	0.93 (0.83–1.05)	0.88 (0.82–0.96)	0.81 (0.40–1.62)	0.39 (0.22–0.69)	0.87 (0.59–1.27)	−0.85 (−0.99 to −0.72)	−0.18 (−0.33 to −0.03)
Nafarelin	1.09 (0.86–1.38)	1.03 (0.85–1.26)	0.73 (0.40–1.31)	0.89 (0.79–1.00)	0.59 (0.38–0.94)	1.42 (0.15–1.19)	−1.48 (−2.08 to −0.88)	−0.65 (−1.66 to 0.36)

RR, relative risk; CI, confidence interval; OHSS, ovarian hyperstimulation syndrome; WMD, weighted mean difference; NA, not available.

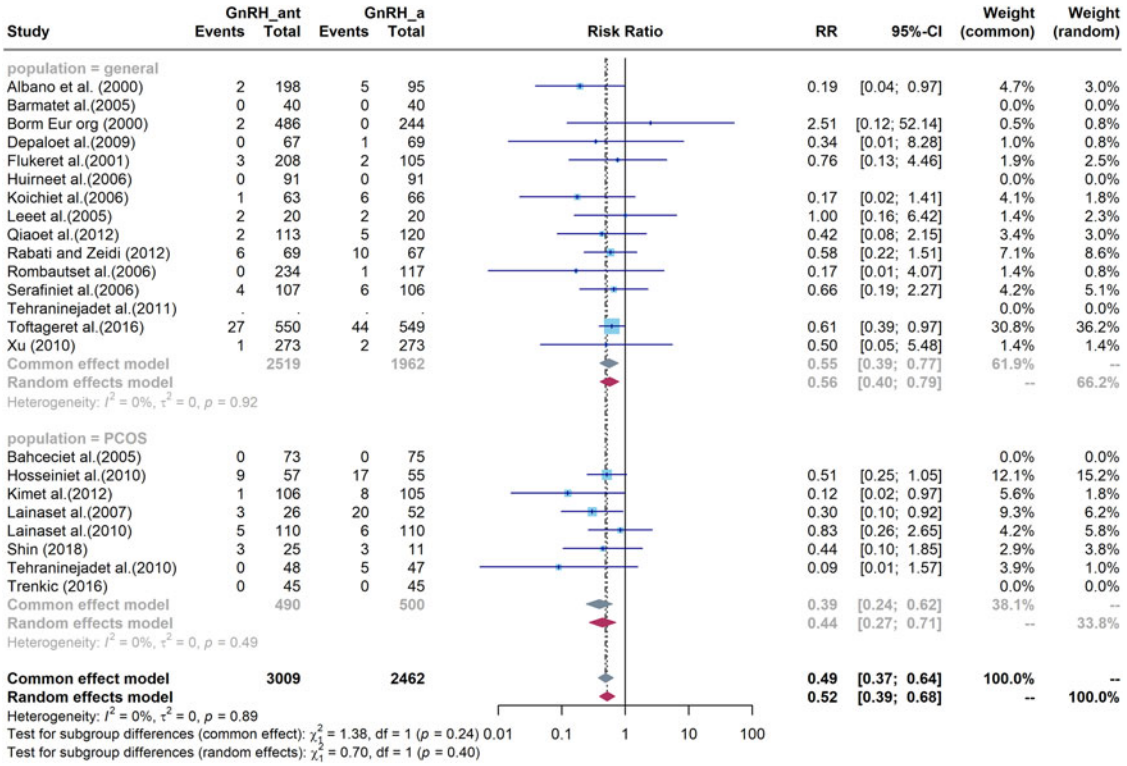

Figure 3. OHSS rate according to patient population.

antagonists were compared with agonists. Subgroup analysis showed that in both general and PCOS populations, the rates of OHSS and moderate-to-severe OHSS were lower in the GnRH-ant group.

For general people, the rate of OHSS and moderate-to-severe OHSS rates were lower in the GnRH-ant group. Also, we did not find a difference in the live birth rate. However, the rates of clinical pregnancy, oocyte retrieval and number of high-quality embryos were lower in the GnRH-ant. For poor responders, we only found that there was fewer oocyte retrieval in the antagonist group. A retrospective analysis compared the efficiency of the GnRH-ant protocol and the GnRH-a protocol for patients with

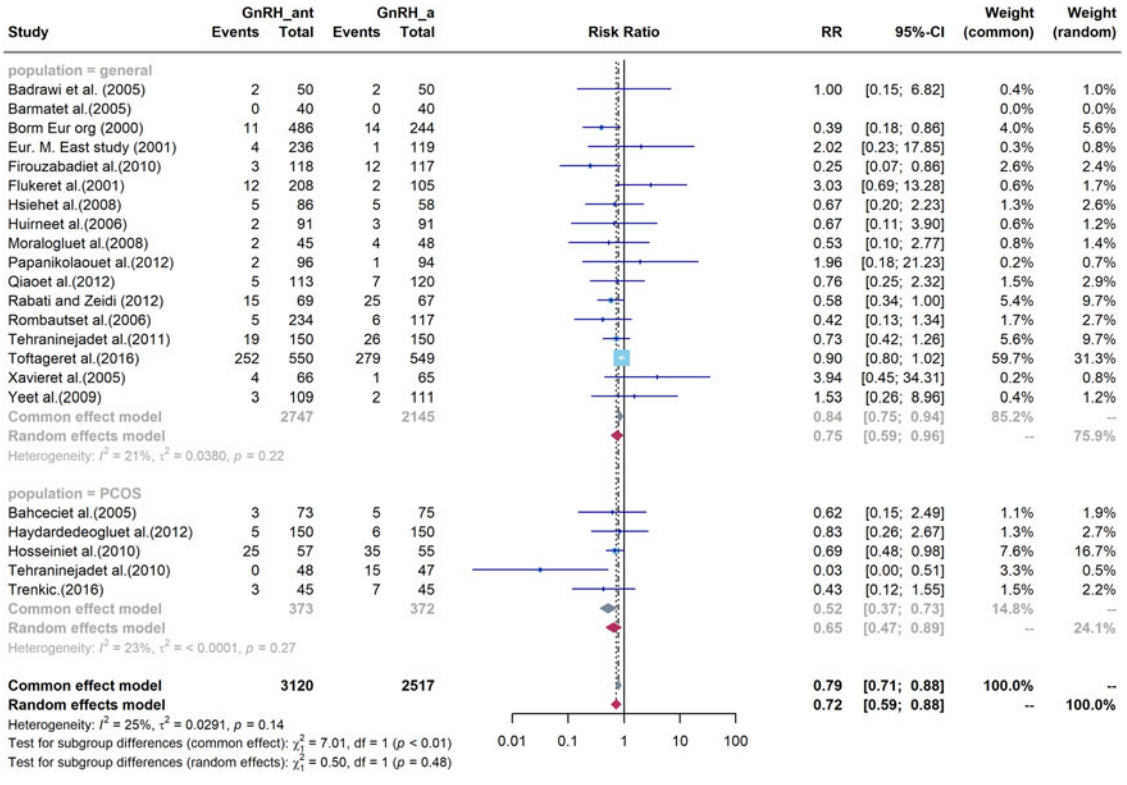

Figure 4. Moderate-to-severe OHSS rate according to patient population.

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diminished ovarian reserve concluded that the GnRH-a protocol was more effective than the GnRH-ant protocol (Ref. 68). However, another recent study found no difference in cumulative live-birth rate (LBR) in POR patients (Ref. 69). For PCOS patients, we only found that there were lower OHSS and moderate-to-severe OHSS rates in the antagonist group. Since PCOS patients have a higher risk of OHSS, GnRH antagonists COS protocol should be recommended for this subgroup, which was consistent with the previous article (Ref. 13).

OCP pretreatment prior to gonadotrophin can assist in the synchronization of follicular development and prevent LH surges in COS (Ref. 70). During the OCP pretreatment cycle, the woman's own hormone production would be suppressed, and side events such as cyst formation might be reduced. A previous study showed that compared with no pretreatment, OCP pretreatment was associated with fewer clinical pregnancies and a lower rate of live birth in PCOS patients (Ref. 71). Another systematic review showed that among women undergoing COS in antagonist protocols, OCP pretreatment was associated with a lower live birth rate and ongoing pregnancy than without OCP pretreatment (Ref. 72). It has been postulated that OCP could have a negative impact on endometrial receptivity and endometrial thickness (Ref. 73). Based on this evidence, it has been recommended that OCP pretreatment be avoided for the GnRH-ant protocol (Ref. 72). In our studies, in antagonist or agonist cycles, there was insufficient evidence to determine whether the groups differed in OCP pretreatment or non-OCP pretreatment.

In two studies, patients were pretreated with oestradiol valerate (Refs 36, 66). Luteal oestradiol pretreatment in IVF protocols can improve follicle synchronization and retrieval of mature oocytes. It has been reported that for poor responders, oestradiol pretreatment can decrease the cancellation rate of cycles (Ref. 74). Recently, it has been suggested that luteal phase oestradiol pretreatment combined with suppressing endogenous follicle-stimulating hormone (FSH) and preventing premature luteinization can significantly improve pregnancy outcomes in POR patients (Ref. 75). In the antagonist protocol, oestrogen pretreatment has been reported to contribute to consistent follicle development and increased oocyte retrieval, but a higher gonadotropin dosage is required (Ref. 72). The two publications in our study showed that in general population, none of the outcomes had a difference between women who used antagonists and agonists with oestradiol valerate pretreatment. However, these findings should be interpreted cautiously because of the few relevant studies.

A meta-analysis of fixed versus flexible protocols in antagonists showed that there was no significant difference in pregnancy rate between the flexible and fixed protocols (Ref. 76). Subgroup analysis based on the type of antagonist demonstrated that cetrorelix and ganirelix might have the same effectiveness. A fixed antagonist protocol may lead to better clinical outcomes than a flexible protocol when compared with agonists. Specifically, there is no significant difference in CPR or number of high-grade embryos between fixed antagonist cycles and agonist cycles, whereas there are differences in CPR and number of high-grade embryos between flexible antagonist cycles and agonist cycles.

A meta-analysis of the type of analogue used for IVF with gonadotrophins and GnRH analogues found that the probability of live birth after ovarian stimulation for IVF does not depend on the type of analogue used for pituitary suppression (Ref. 67). In our analysis, subgroup analysis based on different types of agonists showed there is no difference in live birth rate or ongoing pregnancy among the four kinds of agonists compared with the antagonist protocol.

This study had some limitations. First, in subgroups such as oestradiol valerate pretreatment, the numbers of studies were relatively small, which may lead to false-negative results and might influence the results. Second, owing to potential population heterogeneity, our study could not directly compare the occurrence of these outcomes between OCP pretreatment and non-OCP pretreatment or between different specific agonists and antagonists. More high-quality RCTs on women undergoing pretreatments with OCP or oestrogen in GnRH-a and GnRH-ant protocols in IVF/ICSI are needed.

Conclusion

In this comprehensive meta-analysis, we incorporated data from 52 RCTs encompassing 5193 participants in the antagonist group and 4757 in the agonist group. Our findings indicate that the GnRH-ant protocol stands on par with the long agonist protocol in terms of the live birth rate. Our analysis also supports the GnRH-ant protocol as a favourable option, supported by evidence showcasing its effectiveness in diminishing the incidence of OHSS, particularly among those with PCOS. However, it's noteworthy that within the broader context of general and patients with POR, the GnRH-ant group displayed a lower CPR along with a reduced number of retrieved oocytes and/or high-grade embryos. Therefore, future investigations involving larger sample sizes and heightened methodological rigour are imperative to delve into the exploration of subsequent cumulative live birth rates within the framework of the GnRH-ant protocol.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/erm.2023.25.

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