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Systematic review

Pituitary block with gonadotrophin-releasing hormone antagonist during intrauterine insemination cycles: a systematic review and meta-analysis of randomised controlled trials

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Background Several randomised controlled trials (RCTs) have investigated the usefulness of pituitary block with gonadotrophin-releasing hormone (GnRH) antagonists during intrauterine insemination (IUI) cycles, with conflicting results.

Objective The aim of the present systematic review and meta-analysis of RCTs was to evaluate the effectiveness of GnRH antagonist administration as an intervention to improve the success of IUI cycles.

Search strategy Electronic databases (MEDLINE, Scopus, EMBASE, Sciencedirect) and clinical registers were searched from their inception until October 2017.

Selection criteria Randomised controlled trials of infertile women undergoing one or more IUI stimulated cycles with GnRH antagonists compared with a control group.

Data collection and analysis The primary outcomes were ongoing pregnancy/live birth rate (OPR/LBR) and clinical pregnancy rate (CPR). Pooled results were expressed as odds ratio (OR) or mean differences with 95% confidence interval (95% CI). Sources of heterogeneity were investigated through sensitivity and subgroups analysis. The body of evidence was rated using GRADE methodology. Publication bias was assessed with funnel plot, Begg's and Egger's tests.

Main results Fifteen RCTs were included (3253 IUI cycles, 2345 participants). No differences in OPR/LBR (OR 1.14, 95% CI 0.82–1.57, $P = 0.44$) and CPR (OR 1.28, 95% CI 0.97–1.69, $P = 0.08$) were found. Sensitivity and subgroup analyses did not provide statistical changes in pooled results. The body of evidence was rated as low (GRADE 2/4). No publication bias was detected.

Conclusion Pituitary block with GnRH antagonists does not improve OPR/LBR and CPR in women undergoing IUI cycles.

Keywords Clinical pregnancy, gonadotrophin-releasing hormone antagonists, intrauterine insemination, ongoing pregnancy, premature luteinisation.

Tweetable abstract Pituitary block with GnRH antagonists does not improve the success of IUI cycles.

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Introduction

Intrauterine insemination (IUI) with controlled ovarian stimulation is the treatment of first choice for subfertile couples due to low costs, minimal invasiveness and requirement of minimal clinical surveillance.[1–3] The rationale is to increase the natural chances of conceiving by obtaining two or three dominant follicles and performing IUI after multiple ovulation triggering.[4]

Different strategies have been proposed to improve the outcome of IUI-stimulated cycles, including endometrial

scratching,[5] various ovarian stimulation protocols[6,7] and pituitary block with gonadotrophin-releasing hormone (GnRH) antagonists (GnRH-ant).[4]

These antagonists are synthetic analogues of GnRH that exert a competitive block of GnRH receptors in the anterior pituitary gland.[8–10] The introduction of GnRH-ant during IUI-stimulated cycles may prevent spontaneous ovulation and premature luteinisation, and may improve clinical pregnancy rate.[11,12] However, since their first use in 2001,[13] the effectiveness of this strategy remains a subject of debate.

Hence, the aim of the present systematic review was to evaluate the effects of GnRH-ant administration in women undergoing IUI-stimulated cycles.

Methods

Study design

This is a systematic review and meta-analysis of randomised controlled trials (RCTs) evaluating the effectiveness of GnRH-ant use in IUI cycles. The study protocol was registered in PROSPERO before the start of the literature search (CRD42017081201). The review was written following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[14]

Search strategy

Electronic databases (Medline, Scopus, Embase, Sciencedirect, the Cochrane library, Clinicaltrials.gov, Cochrane Central Register of Controlled Trials, EU Clinical Trials Register and World Health Organization International Clinical Trials Registry Platform) were searched from their inception until October 2017.

Key search terms were the following text words: gonadotrophin-releasing hormone antagonists OR gonadotrophin-releasing hormone analogues OR GnRH antagonists OR cetrorelix OR ganirelix [Mesh/Emtree] AND insemination OR IUI.

Inclusion criteria

- *Language*: Studies reported in English language
- *Study designs*: Randomised controlled trials
- *Population*: Infertile women undergoing one or more IUI-stimulated cycles
- *Intervention*: GnRH-ant administration
- *Timing of intervention*: During the course of ovarian stimulation
- *Comparator*: Infertile women undergoing IUI-stimulated cycles not receiving GnRH-ant

Outcomes:

- *Primary outcomes*: Ongoing pregnancy/live birth rate, clinical pregnancy rate
- *Secondary outcomes*: Miscarriage rate, multiple pregnancies, premature luteinisation, premature luteinising hormone (LH) rise, preovulatory follicles, endometrial thickness, total dose of gonadotrophins, ovarian hyperstimulation syndrome, cancelled cycles, spontaneous ovulation

- *Outcomes definitions*:
  - *Ongoing pregnancy (per cycle [OPR/LBR]):* 'Ongoing pregnancy' defined as a pregnancy beyond 12 weeks of gestation
  - *Live birth (per cycle [OPR/LBR])*: 'Live birth' defined as the delivery of one or more living and viable infants
  - *Clinical pregnancy rate (per cycle [CPR])*: Defined as the presence of a gestational sac on transvaginal ultrasound or other definitive clinical signs
  - *Multiple pregnancies (per cycle)*: Defined as the presence of more than one gestational sac on transvaginal ultrasound
  - *Miscarriage rate (per clinical pregnancy)*: Defined as fetal loss before the 20th week of gestation
  - *Premature luteinisation (per cycle)*: Serum rise of progesterone $\geq$ 2 ng/mL before ovulation induction with/without concomitant LH elevation ($\geq$ 10–15 IU/l)
  - *Premature LH surge (per cycle)*: As defined by original trials (serum LH $\geq$ 10–15 mIU/ml before ovulation induction)
  - *Preovulatory follicles (per cycle):* Number of follicles $\geq$ 16 mm (at transvaginal ultrasound) on the day of ovulation induction
  - *Endometrial thickness (per cycle)*: Maximum anterior–posterior thickness of the endometrial echo (mm) on the day of ovulation induction (on transvaginal ultrasound)
  - *Total gonadotrophin dose (per cycle)*: The total amount of gonadotrophins administered before ovulation induction
  - *Cancelled cycles*: Cycles cancelled due to inadequate ovarian response (poor/excessive)
  - *Spontaneous ovulation (per cycle)*: Cycles cancelled due to spontaneous ovulation
  - *Ovarian hyperstimulation syndrome (per cycle [OHSS]):* defined as the occurrence of moderate or severe OHSS before or after IUI.

Study selection and data extraction

Titles and abstracts were independently screened by two authors (AV, GS). The same authors independently assessed studies for inclusion and extracted data about study features (design, country and time of the study), populations (participant number and characteristics), type of intervention, ovarian stimulation cycles (drugs, timing of ovulation induction) and IUI outcomes. A manual search of references of included studies was also performed

to avoid missing relevant data. The results were compared, and any disagreement was resolved by consensus.

Risk of bias

Two authors (AV, MN) independently assessed the methodological quality of included studies by using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions. Seven specific domains related to risk of bias were assessed: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective data reporting; other bias. Authors' judgements were expressed as 'low risk', 'high risk' or 'unclear risk' of bias. For the estimation of 'selective data reporting', we evaluated study protocols, when available. If not available, studies were judged at unclear risk of bias. Results were compared and disagreements were resolved by consensus.

Statistical analysis

Data analysis was performed by two authors (AV, GS) using Review Manager Version 5.3 (The Cochrane Collaboration, Software Update, Oxford, UK). All analyses were carried out with an intention-to-treat approach (number of events per woman randomised), using the random effects model of DerSimonian and Laird (assuming that the data being analysed were drawn from a hierarchy of different populations). Dichotomous variables were analysed using the odds ratio (OR) with a 95% CI. Continuous variables were compared using the means and standard deviations of outcome measures and expressed as mean differences (MD) among groups (95% CI). Significance level was set at $P < 0.05$. Heterogeneity was measured using I-squared (Higgins I^2). A subgroup analysis was also performed to evaluate the specific influence of different interventions (cetrorelix, ganirelix), intervention schemes (fixed, flexible) and populations [polycystic ovarian syndrome (PCOS), non-PCOS] on pooled results. In addition, we performed a sensitivity analysis by serially excluding each study and different study subgroups (according to the methodological quality judgement) from the pooled analysis.

Publication bias was assessed (for the primary outcomes) with the use of funnel plot (when at least ten studies were included in data analysis, according to Cochrane Handbook Recommendations) and statistically by using Begg's and Egger's tests.

Grading of evidence

Two authors (AV and MN) independently evaluated the quality of evidence for the primary outcomes using GRADE (Grading of Recommendations Assessment Development and Evaluation working group) methodology.[15] The GRADE criteria allow the assessment of a body of evidence on the basis of study design, risk of bias, indirectness, inconsistency, imprecision, large effect size, plausible confounding, dose–response gradient and publication bias. Dose–response gradient was not evaluated because the intervention had standard dose. Disagreements between reviewers were resolved by consensus.

Results

Study selection

In all, 23 studies were assessed for eligibility. Eight studies were subsequently excluded after the examination of full-text: two studies were not RCT.[16,17] Ragni et al.[13] aimed to evaluate the luteal phase profile in women undergoing IUI-stimulated cycles with/without GnRH-ant. Two studies evaluated the effectiveness of different stimulation protocols in women receiving gonadotrophins plus GnRH-ant before IUI.[18,19] Two additional studies investigated the benefits of GnRH-ant use to avoid IUI on weekends.[20,21] In Nada et al.,[22] the intervention (GnRH-ant) group and control (GnRH-ant-free) group received different stimulation drugs (respectively gonadotropins and clomiphene citrate). Finally, 15 trials[4,11,12,23–34] were included in the meta-analysis (Figure S1).

Included studies

The 15 trials included 3253 IUI cycles and 2345 participants. A total of 1610 IUI cycles were assigned to the intervention group and 1643 to the control group. One study[34] involved three study groups, of which two received the intervention with different timing. Two were placebo-controlled trials.[4,30] Study characteristics are summarised in the (Table S1).

Participants

The majority of the trials included women with unexplained infertility, mild endometriosis (stage I–II) and normal semen analysis/mild male factor. Two studies[12,25] included also women with PCOS, and two additional studies[29,34] involved only women with PCOS.

In seven studies[4,23–28] participants had no history of previous assisted reproductive treatments, in one study[29] women had three or more previous IUI failures and in another study[30] women had no more than three previous IUI failures. In two studies women had history of one[34] or two[31] previous ovarian stimulation cycles with clomiphene citrate. In the remaining studies[11,12,32,33] previous assisted reproductive treatments attempts were not specified.

IUI cycles

In nine trials,[11,12,23,25–27,30,31,33] women underwent a single IUI-stimulated cycle, whereas in other studies they underwent up to three[4,29,34] or four[24,28,32] cycles.

Most studies used recombinant follicle-stimulating hormone daily (50–150 IU starting dose) for ovarian stimulation, starting from day 2–4, whereas Kamath et al.[12]

administered human menopausal gonadotrophin 75 IU daily (from day 3). Two other studies used the combination of letrozole (5 mg daily from day 3 to 7) plus recombinant follicle-stimulating hormone (150 UI on days 4, 6, 8 and then daily until ovulation induction)[33] or clomiphene citrate (100 mg daily from day 3 to 7) plus human menopausal gonadotrophin (75/150 UI from day 8).[23]

Ovulation induction was triggered with 5000–10 000 UI of urinary human chorionic gonadotrophin (hCG) in most studies, except for four[4,25,29,33,34] (which used recombinant hCG, 250 μg). Recombinant/urinary hCG was administered when at least one follicle (but no more than three) was $\geq$ 17–20 mm (in mean diameter) at transvaginal ultrasound scan. A single IUI (30–48 hours later) or double IUI (20 and 34 hours[32] or 12 and 36 hours[25] after hCG trigger) was subsequently performed. In nine studies, IUI was followed by luteal phase support with vaginal progesterone (50–800 mg/day), whereas in the remaining studies[4,27,29] it was not administered or not reported.[28,31,33]

Intervention

Pituitary block was performed with ganirelix[11,26–30,34] (0.25 mg daily) or cetrorelix[4,12,23–25,31–33] (0.25 mg daily) with a flexible scheme (except for Williams et al.[28] and one group in the study by Stadtmauer et al.,[34] where GnRH-ant was started respectively on day 1 or 6 of ovarian stimulation). GnRH-ant was started when at least one follicle $\geq$ 13 mm,[25,27,34] 14 mm,[4,12,29–33] 15 mm[24] or 16 mm[11,23,26] in mean diameter was observed at transvaginal ultrasound scan and continued until ovulation induction.

Assessment of the risk of study BIAS

Random sequence generation: All studies but one[24] used adequate method of random sequence generation (computer randomisation or random number tables).

Allocation concealment: Seven studies[11,23–26,29–31] did not provide information about the method of allocation, so were judged at unclear risk of bias. Remaining studies were at low risk of bias.

Blinding of participants and personnel: All studies but two[4,30] were not blinded for participants and personnel, so were judged at high risk of bias.

Blinding of outcome assessment: Three studies[4,28,30] were assessor-blinded, the remaining were at high risk of bias.

Incomplete outcome data: All studies but four[23,25,31,33] were judged at low risk of bias. Two studies[25,33] were judged at unclear risk of bias as the missing data were not about primary outcomes, while two other studies[23,31] were considered at high risk of bias due to missing relevant data about primary outcomes.

Selective data reporting: All studies were judged at unclear risk of selective data reporting due to absence of recorded study protocol, except for the study by Cantineau et al.[4]

Other bias: Three studies[23,24,31] were judged at high risk of other bias due to missing information about study methodology and/or patient characteristics. Lambalk et al.[30] was judged at unclear risk of bias because luteal phase support was variable according to preference of clinicians. Another study[25] was judged at unclear risk of bias because it was published as a short communication (Figure S2).

Effects of intervention

Primary outcomes

Analysis of 1964 IUI cycles from seven studies[4,11,27,29,30,34] did not show any difference in OPR/LBR between groups (OR 1.14, 95% CI 0.82–1.57, I^2 = 31%, P = 0.44) (Figure 1A). Similarly, the analysis of 3192 IUI cycles did not show any advantage from GnRH-ant in terms of CPR (OR 1.28, 95% CI 0.97–1.69, I^2 = 39%, P = 0.08) (Figure 1B and Video S1).

Secondary outcomes

Significantly lower risks of premature luteinisation (OR 4.39, 95% CI 2.73–7.05, I^2 = 0%, P > 0.00001) (Figure 2A) and premature LH rise (OR 3.98, 95% CI 2.53–6.26, I^2 = 28%) (Figure 2B) were observed in women receiving intervention, in addition to lower cycle cancellation due to spontaneous ovulation (OR 2.40, 95% CI 1.12–5.15, I^2 = 1%). In contrast, endometrial thickness was found to be lower in the GnRH-ant group in comparison to controls (MD = –0.39; 95% CI –0.70 to –0.08], I^2 = 40%).

No difference was observed in terms of miscarriage rate (OR 1.11, 95% CI 0.65–1.89, I^2 = 0%, P = 0.71), multiple pregnancies (OR 1.49, 95% CI 0.82–2.70, I^2 = 0%), preovulatory follicles (MD = –0.07; 95% CI –0.34 to 0.48, I^2 = 97%) and total gonadotrophin dose (MD = –26.51; 95% CI –22.85 to 75.86, I^2 = 84%) among groups. Similarly, no substantial difference in OHSS risk and cancelled cycles due to poor response/hyper-response was observed.

Subgroup analysis and sensitivity analysis

Subgroup analysis according to type of intervention (cetrorelix versus ganirelix), intervention scheme (fixed versus flexible) and type of patients (PCOS versus non-PCOS) showed no statistical difference among subgroups (Figure 1A,B).

The serial exclusion of each study or specific study subgroups according to authors' quality judgement (studies at low risk of bias in at least four domains) did not provide substantial changes to pooled results.

Publication bias and quality of evidence

No publication bias was found for the outcome OPR/LBR (Begg's test: P = 0.05; Egger's test: P = 0.07). Similarly, the

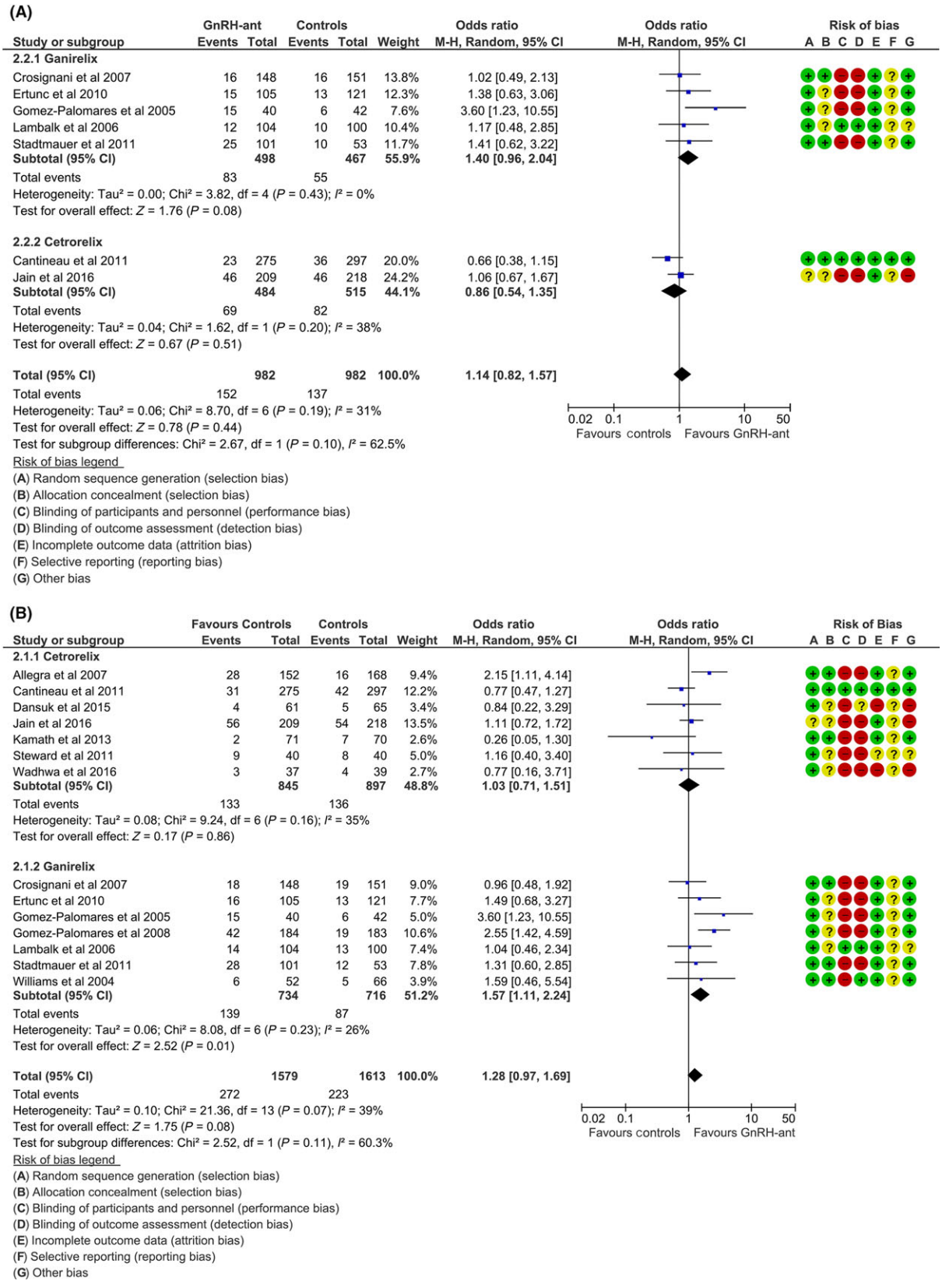

Figure 1. Gonadotrophin-releasing hormone antagonist effects on ongoing pregnancy/live birth rate (A), and clinical pregnancy rate (B).

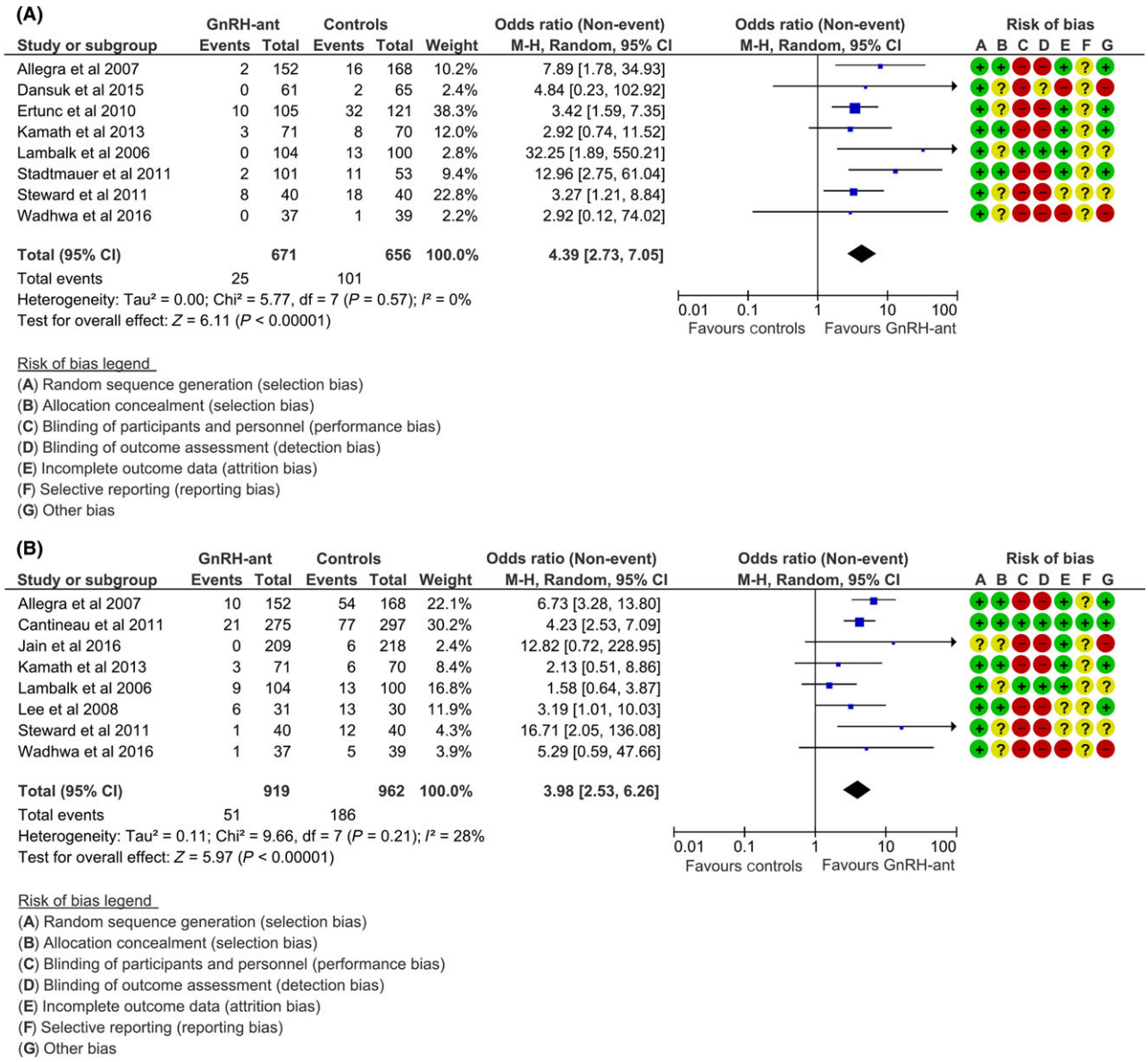

Figure 2. Gonadotrophin-releasing hormone antagonist effects on premature luteinisation (A), and premature luteinising hormone rise (B).

visual inspection of funnel plot, Begg's ($P = 0.50$) and Egger's test ($P = 0.82$) did not show the presence of publication BIAS for the outcome *CPR* (Figure S3).

The quality of evidence for OPR/LBR and CPR was judged as low due to concerns about the overall methodological quality of included studies, moderate inconsistency and small number of events included (Table 1).

Discussion

In spite of recent insights about endometrial-factor infertility,[35–37] the introduction of novel targeted drugs[38–40] and individualised ovarian stimulation protocols,[41,42] the success rate of IUI is still suboptimal.[12,43,44] Recently, several RCTs have investigated the effectiveness of pituitary block with GnRH-ant during controlled ovarian stimulation and IUI, with controversial results. Our study goal was to summarise the available evidence on this topic.

Main findings

The present meta-analysis, from 15 RCTs, included a total number of 3253 IUI cycles and 2345 women. We found that GnRH-ant use did not improve OPR/LBR and CPR in women undergoing IUI stimulated cycles (P = ns). Nevertheless, GnRH-ant were effective in reducing the risk

Table 1. Evidence profile: gonadotrophin-releasing hormone antagonists compared with no pituitary block in women undergoing intrauterine insemination cycles

Patient or population: intrauterine insemination (IUI)
Setting: not applicable
Intervention: gonadotrophin-releasing hormone (GnRH) antagonists
Comparison: no pituitary block

Outcomes	Anticipated absolute effects[a](95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)[b]	Comments
	Risk with no pituitary desensitisation	Risk with GnRH antagonists				
Ongoing pregnancy rate/Live birth rate (OPR/LBR)	140 per 1000	156 per 1000 (117–203)	OR 1.14 (0.82–1.57)	1964 (7 RCTs)	⊕⊕◯◯ Low[c,d]	
Clinical pregnancy rate (CPR)	138 per 1.000	170 per 1.000 (135–213)	OR 1.28 (0.97–1.69)	3192 (14 RCTs)	⊕⊕◯◯ Low[d,e]	

[a]The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
[b]GRADE Working Group grades of evidence: High certainty (⊕⊕⊕⊕), we are very confident that the true effect lies close to that of the estimate of the effect; Moderate certainty (⊕⊕⊕◯), we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; Low certainty (⊕⊕◯◯), our confidence in the effect estimate is limited:; the true effect may be substantially different from the estimate of the effect; Very low certainty (⊕◯◯◯), we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.
[c]Moderate inconsistency (I^2 = 39%).
[d]Small number of events per group.
[e]Moderate inconsistency (I^2 = 42%).

of premature luteinisation ($P > 0.00001$), premature LH rise ($P > 0.00001$) and spontaneous ovulation ($P = 0.02$). In contrast, GnRH-ant use correlated with lower endometrial thickness values at the time of ovulation induction ($P = 0.02$). No difference was observed in terms of miscarriage rate, multiple pregnancies, preovulatory follicles, total gonadotrophin dose, OHSS and cancelled cycles due to hypo-/hyper-response between groups.

A review by Luo et al.[45] investigated the effects of GnRH-ant on IUI outcomes. The authors found that GnRH-ant were effective in improving CPR and reducing the risk of premature luteinisation, but they did not evaluate the other outcomes included in the present review (i.e. ongoing pregnancy/live birth rate). Moreover, since the study by Luo et al., new RCTs[23,24,31] have been published.

Strengths and limitations

The present meta-analysis, to our knowledge, is the largest and most comprehensive on this issue. Strict inclusion criteria and rigorous methodology represent further points of strength of our study. In addition, sensitivity and subgroup analyses did not produce statistical changes to our results, confirming their consistency.

The main limitations of our study are inherent to the limitations of the included studies. Different outcomes were calculated by pooling the results of a small number of studies and patients (i.e. OPR/LBR). Moreover, a certain heterogeneity between studies in terms of women's characteristics, timing of intervention, ovarian stimulation protocols, IUI techniques and luteal phase support should be taken into account in the interpretation of our findings.

Interpretation

Premature luteinisation and spontaneous ovulation are considered major limiting factors for success with IUI.[25,26,29] In the present meta-analysis, we found a large effect of GnRH-ant (introduced when the leading follicle is about 13–14 mm in mean diameter) in the prevention of premature luteinisation (OR 4.95, 95% CI 3.12–7.87). Nevertheless, such an effect was not correlated with any advantage in terms of OPR/LBR and CPR, in line with the results of the study with the greatest weight[4] (according to the authors' quality judgement). We may speculate but it is still not clear how much earlier, before ovulation triggering, the occurrence of LH increase can significantly affect IUI success (in terms of OPR/LBR and CPR).

Interestingly, we also found that GnRH-ant administration was correlated with lower risk of cycle cancellation due to spontaneous ovulation (OR 2.40, 95% CI 1.12–5.15). However, among ten studies (including 2398 IUI cycles, of which 236 were cancelled), only 36 cycles were interrupted due to spontaneous ovulation. Therefore,

basing on such data and given the considerable costs of GnRH-ant therapy (in Italy: cetrorelix 0.25 mg costs €56.41; ganirelix coses €63.40), this strategy does not appear to be cost-effective for the prevention of spontaneous ovulation in IUI cycles.

Conclusions

In summary, GnRH-ant use did not improve OPR/LBR and CPR in women undergoing IUI stimulated cycles. Given the benefits of GnRH-ant in reducing the risk of premature luteinisation and spontaneous ovulation, further large and well-designed placebo-controlled RCTs are needed.

Disclosure of interests

None declared. Completed disclosure of interests form available to view online as supporting information.

Contribution to authorship

AV designed the study, performed the literature search, defined inclusion criteria and selected studies for inclusion, participated in data extraction, performed the risk of bias assessment, performed statistical analysis and wrote the first draft of the manuscript; GS performed the literature search, selected studies for inclusion, participated in the statistical analysis and the final draft of the manuscript; MN critically revised the manuscript, participated in the assessment of the risk of bias within studies and the grading of evidence; AB structured the manuscript and wrote the final draft of the manuscript; MEC designed the study and critically revised the manuscript; CS participated in the study design and manuscript revision; GB participated in manuscript revision; GBN critically revised the manuscript and participated in the final draft of the manuscript; PL made critical contributions to both data selection and manuscript revision; AA participated in interpretation of results, critically revised the manuscript and participated in the final draft of the manuscript. All authors approved the final manuscript.

Details of ethics approval

Not required.

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Supporting Information

Additional Supporting Information may be found in the online in the Supporting Information section at the end of the article:

Figure S1. PRISMA flow diagram.

Figure S2. Risk of bias graph: the authors' judgment about each risk of bias item presented as percentages across the included studies.

Figure S3. Funnel plot for the outcome clinical pregnancy rate.

Table S1. General features of the studies

Video S1. Author insights.■

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