GnRH agonist during luteal phase in women undergoing assisted reproductive techniques: systematic review and meta-analysis of randomized controlled trials

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KEYWORDS: assisted reproduction; ICSI; infertility; IVF; luteal phase support; subfertility

ABSTRACT

Objective To identify, evaluate and summarize the available evidence regarding the effectiveness and safety of administering a gonadotropin releasing hormone (GnRH) agonist during the luteal phase in women undergoing assisted reproductive techniques.

Methods In this systematic review and meta-analysis, we searched for randomized controlled trials (RCTs) comparing the addition of a GnRH agonist during the luteal phase, compared with standard luteal-phase support. We searched seven electronic databases and hand-searched the reference lists of included studies and related reviews. Our primary outcome was live birth or ongoing pregnancy per randomized woman. Our secondary outcomes were clinical pregnancy per randomized woman, miscarriage per clinical pregnancy, adverse perinatal outcome and congenital malformations.

Results The evidence from eight studies examining 2776 women showed a relative risk (RR) for live birth or ongoing pregnancy of 1.26 (95% CI, 1.04–1.53; I² = 58%). Sensitivity analysis when excluding the studies that did not report live birth and those at high risk of bias resulted in one study examining 181 women with an RR of 1.07 (95% CI, 0.73–1.38). Subgroup analysis separating the studies by single/multiple doses of GnRH agonist or by ovarian stimulation with GnRH agonist/antagonist was unable to explain the observed heterogeneity. The quality of the evidence was deemed to be very low: it was downgraded because of the limitation of the included studies, imprecision, inconsistency across the studies’ results, and suspicion of publication bias. None of the included studies reported adverse perinatal outcomes or congenital malformations.

Conclusions There is evidence that adding GnRH agonist during the luteal phase improves the likelihood of ongoing pregnancy. However, this evidence is of very low quality and there is no evidence for adverse perinatal outcome and congenital malformations. We therefore believe that including this intervention in clinical practice would be premature.

INTRODUCTION

Assisted reproductive techniques (ARTs) frequently involve controlled ovarian stimulation (COS) to improve efficacy of the treatment by promoting the development of multiple follicles, and, ultimately, the formation of multiple embryos. The recruitment of multiple follicles boosts estradiol production, and abnormally high levels are observed during COS. After aspiration of these follicles, multiple corpora lutea are formed, which maintain the abnormally high production of steroids1,2. In a natural pregnancy, luteinizing hormone (LH) is produced continuously after the ovulation surge and only decreases when human chorionic gonadotropin (hCG) from the growing trophoblast takes over. Conversely, the ovarian stimulation used in ART cycles results in very high steroid levels; this inhibits the pituitary secretion of LH which is thought to shorten the luteal phase, a situation known as premature luteolysis1,2.

To overcome this issue, pharmacological support during the luteal phase is used to improve pregnancy rates. Many combinations of estradiol, progesterone and hCG are used frequently to enhance directly or indirectly the low progesterone level3. More recently, gonadotropin releasing hormone (GnRH) agonist was introduced for luteal phase support4,5. The first hypothesis for its mechanism is that the GnRH agonist extends LH...

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production throughout the luteal phase thus preventing the occurrence of premature luteolysis and consequently improving pregnancy rates1. Nonetheless, it was observed that a single dose of GnRH agonist at the time of implantation could improve the pregnancy rate in recipients after artificial endometrial preparation with GnRH downregulation followed by estrogen and progesterone5. The increase in pregnancy rates in recipients without a corpus luteum led to the hypothesis of a direct effect of the agonist on the early embryo2,5; however a direct effect on the endometrium cannot be ruled out. Evidence from in-vitro studies suggests that GnRH agonist acts directly on preimplanted embryos, as the GnRH receptor is expressed extensively in human morula and blastocyst embryos6. Porcine and murine preimplantation embryo development is enhanced when embryos are incubated with GnRH agonists and diminished when incubated with an antagonist7,8.

Owing to the potential embryonic/fetal effects, adverse perinatal outcomes and congenital malformations are important safety outcomes, which have been scarcely reported. Although there is a lack of information regarding the fetal safety of GnRH agonist use in early pregnancy and an apparent inconsistency among results of clinical studies, three systematic reviews published previously concluded that there was a benefit from the intervention1,9,10. This intervention has been the subject of intensive study and new data are emerging highlighting the need for a comprehensive and judicious systematic review of the literature. The objective of this systematic review and meta-analysis was to identify, appraise and summarize the evidence from randomized controlled trials (RCTs), examining and weighing the efficacy and safety of using GnRH agonist during the luteal phase.

METHODS

Protocol registration

The protocol of this review was registered at the international prospective register of systematic reviews (PROSPERO): CRD42014014895.

Eligibility criteria

Parallel group and cross-over RCTs were considered eligible for the review. If a cross-over trial was included, only data from the first treatment of each participant were considered for analysis. We did not include pseudo-randomized studies or studies that randomized embryos or oocytes rather than women or couples. Studies that included women undergoing ART were eligible for inclusion in the review; studies examining women undergoing intrauterine insemination (IUI) or timed intercourse were not included. For study inclusion, the intervention was addition of GnRH agonist during luteal phase compared with standard luteal-phase support and no other relevant difference between intervention and control groups.

Search and study selection

We searched for published studies in the following electronic databases: Cochrane Central Register of Controlled Trials (CENTRAL), PubMed and Scopus; and searched for study protocols on the following databases: Current Controlled Trials (www.controlled-trials.com), ClinicalTrials.gov (http://clinicaltrials.gov/ct2/search) and the World Health Organization International Clinical Trials Registry Platform (WHO-ICTRP) search portal (http://apps.who.int/trialsearch/Default.aspx). We searched for conference abstracts on Web of Science.

The following terms were used, adjusting for each database as necessary: ((in vitro fertilization) OR (IVF) OR (intracytoplasmic sperm) OR (ICSI) OR (embryo) OR (blastocyst)) AND ((Agonist) OR (Buserelin) OR (Goserelin) OR (Leuprolide) OR (Nafarelin) OR (Triptorelin)) AND (luteal) AND (random* OR trial). In addition, we hand-searched the reference list of included studies and similar reviews in order to find potentially eligible studies. We did not impose any limitation on publication date or language.

Two authors (C.O.N and W.P.M) independently reviewed titles and abstracts by checking for duplicates and using the pre-established criteria for inclusion of articles, and retrieved full-text manuscripts of trials considered to be potentially eligible for inclusion and evaluated independently the eligibility of these trials. Disagreements were solved by consensus. We corresponded with study investigators as required, to clarify study eligibility.

Data collection process and items

Data extraction from included trials was performed independently in a standardized manner by two authors (C.O.N and W.P.M) using a data extraction form designed and pilot-tested by the authors. Disagreements between these authors were resolved by consensus. When a study with multiple records (e.g. publication, abstract, protocol registration) was identified, we used the main trial report as reference and supplementary details could be added from secondary sources. If there were any data queries, we tried to correspond with the study investigators.

The following information was extracted from each included trial: authors; country; institution; funding sources; conflicts of interest; informed consent; ethical approval; study design; period of enrollment; eligibility criteria; number of participants in each group at each stage; age and body mass index (BMI) (mean ± SD) of participants; number of oocytes retrieved; number of embryos transferred per woman; and implantation rate. For primary outcomes, the live birth/ongoing pregnancy per randomized woman was extracted (birth of twins/triplets was counted as a single live birth). We preferentially used data for live birth; however, when live birth was not reported, we used data for ongoing pregnancy (intrauterine live fetus with a gestational

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age ≥ 12 weeks) as a surrogate for live birth, since the difference between ongoing pregnancy and live birth is often not large; fewer than 1% of the pregnancies will result in a stillbirth\textsuperscript{11,12}. Secondary outcomes included: clinical pregnancy per randomized woman (ultrasonographic visualization of one or more gestational sac or definitive clinical signs of pregnancy); miscarriage per clinical pregnancy (single fetal demise in twins or triplet pregnancies were not counted as a miscarriage); adverse perinatal outcome (gestational diabetes, pregnancy-induced hypertension, pre-eclampsia, large- or small-for-gestational age, preterm birth, acidosis, intensive care unit admission, pre- and perinatal mortality); and congenital malformations. When miscarriage was not reported but authors reported clinical pregnancy and ongoing pregnancy, the number of miscarriages was considered as the difference between the number of clinical pregnancies and ongoing pregnancies.

Risk of bias in individual studies

Two authors (C.O.N. and W.P.M.) assessed independently the risk of selection bias, performance bias, detection bias, attrition bias, reporting bias and other potential sources of bias (e.g. difference in the number of embryos transferred, age of participants, co-interventions, early stoppage of the trial). We did not consider blinding likely to influence the risk of performance and detection bias for the review outcomes. Disagreements were solved by consensus. To judge the risk of bias, we followed the Cochrane Collaboration’s criteria for judging risk of bias\textsuperscript{13}: the studies were classified as being at low, high or unclear risk of bias.

Summary measures

The effects of the intervention were summarized as the risk ratio (RR) and the precision of the estimates was evaluated by the 95% CI. We considered the clinical relevance of all comparisons taking into account the precision of the estimates, determining the number needed to treat for an additional beneficial outcome (NNTB) or an additional harmful outcome (NNTH) when a significant difference was observed.

Synthesis of results

All results were combined for meta-analysis using Review Manager 5.3 (The Cochrane Collaboration, Copenhagen, Denmark). Heterogeneity was assessed subjectively and by the $I^2$ statistic. An increase in the risk of a particular outcome, which may be beneficial (e.g. live birth) or detrimental (e.g. miscarriage), was displayed graphically in the meta-analyses to the right of the center line and a decrease in the risk of an outcome to the left of the center line.

Risk of bias across studies

In view of the difficulty of detecting and correcting for publication bias and other reporting biases, we tried to minimize their potential impact by ensuring a comprehensive search for eligible studies and by being alert for duplication of data. We planned to use a funnel plot only if 10 or more studies were included, to explore the possibility of small-study effects (a tendency for estimates of the intervention effect to be more beneficial in smaller studies). However, this was not employed as only seven studies were included.

Additional analyses

A sensitivity analysis was performed to verify whether the conclusions about the primary outcome measures would be different if eligibility was restricted to studies with low risk of bias and if data for ongoing pregnancy were not pooled with live birth.

In order to examine the observed heterogeneity, we performed two subgroup analyses, separating the studies according to the following categories: single vs multiple doses of GnRH agonist; agonist vs antagonist protocol.

Overall quality of the body of evidence: summary of findings table

A summary of findings table was created, evaluating the quality of evidence for the main review outcomes, using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group recommendation\textsuperscript{14}: we considered the study limitations, inconsistency of effect, imprecision, indirectness, and risk of publication bias. The judgments about evidence quality were justified, documented and incorporated into the reporting of results for each outcome.

The quality of the evidence (and its interpretation) was judged as follows:

- High quality: further research is very unlikely to change our confidence in the estimate of effect.
- Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- Very low quality: we are very uncertain about the estimate.

RESULTS

Study selection and characteristics

An electronic search was conducted on 22 March 2015, retrieving 882 records initially. Figure 1 summarizes the study inclusion process. Ten studies from 12 records were included in this review: two studies with two records each\textsuperscript{15–18} and eight studies with one record.

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Identification
Electronic search = 882 records
CENTRAL (n = 189)
PubMed (n = 216)
Scopus (n = 406)
ClinicalTrials.gov (n = 48)
Current Controlled Trials (n = 0)
WHO-ICTRP (n = 0)
Web of Science (n = 23)
Additional record identified through manual search (n = 1)

Screening by title and abstract (n = 883 records)

Assessed for eligibility (n = 22 records)

Included in review and quantitative analysis (n = 10 studies from 12 records)

Exclusions (n = 861)
334 duplicates
527 clearly did not meet eligibility criteria

Exclusions (n = 5 studies from 6 records)
3 studies (from 3 records) were not randomized or were pseudorandomized
1 study (from 1 record) examined only women undergoing IUI
1 study (from 2 records) had triggering performed with GnRH agonist in intervention group and with hCG in control group

Awaiting classification (n = 4 studies from 4 records)
3 ongoing studies
1 study with unknown status

Figure 1 Flowchart summarizing selection of studies comparing the use of gonadotropin releasing hormone (GnRH) agonist and standard luteal-phase support in women undergoing assisted reproductive techniques. CENTRAL, Cochrane Central Register of Controlled Trials; hCG, human chorionic gonadotropin; IUI, intrauterine insemination; WHO-ICTRP, World Health Organization International Clinical Trials Registry Platform search portal.

each19–26. At the time of writing, of the potentially eligible records/studies, five studies (from five records) were awaiting classification and were not included; four of these are ongoing studies27–30 and one has unknown status31. Five further studies (from six records) were excluded; three studies (from three records) were not randomized or were pseudorandomized4,5,32; one study (from one record) examined only women undergoing IUI33; in one study (from two records) triggering was performed with GnRH agonist in the intervention group and with hCG in the control group34,35.

The characteristics and eligibility criteria of the 10 studies included in this review are reported in Table S1. The following were included: eight studies reporting either live birth or ongoing pregnancy (three reported live birth17,21,22 and five reported ongoing pregnancy16,19,20,24,25); 10 studies reporting clinical pregnancy; eight studies from which data for miscarriage were retrieved (three reported miscarriage20,22,25 and in the other five we determined the number of miscarriages as being the difference between clinical pregnancy and ongoing pregnancy or live birth16,17,19,21,24). No study reported adverse perinatal outcomes or congenital malformations.

Risk of bias within studies
Five studies19,20,21,25,26 were considered to be at unclear risk of selection bias because, although they used computer generated randomization, there were no details regarding allocation concealment. The remaining five studies were considered to be at low risk of selection bias. Blinding was not considered to be relevant for the reproductive outcomes evaluated.

Three studies21,22,25 were considered to be at high risk of attrition bias: one study recruited 234 women, but analyzed only 120 without providing reasons22; one study lost 9.8% of participants in the intervention group and 2.4% in the control group to follow-up21; one lost 16% in one of the study arms and of 5% of the control group to follow-up25; the remaining seven studies were considered to be at low risk of attrition bias.

All 10 studies were considered to be at low risk of performance, detection, reporting and other source of bias. One study19 was judged to be at unclear risk of other bias, as women in the control group had slightly higher age and BMI than those in the study cohort.

Synthesis of results
The results for the individual studies are reported in the forest plots (Figures 2–4). For the probability of live birth or ongoing pregnancy (Figure 2), evidence from eight studies examining 2776 women showed a relative risk (RR) of 1.26 (95% CI, 1.04–1.53; I² = 58%). Sensitivity analysis, excluding the studies that did not report live birth and those at high risk of bias, resulted in one study examining 181 women with an RR of 1.07
(95% CI, 0.73–1.58). Subgroup analysis according to agonist and antagonist cycles was unable to explain the observed heterogeneity; however, the studies that did not observe any benefit of using GnRH agonist during the luteal phase were those that used an agonist protocol for COS, while the two studies that used a GnRH antagonist for the intervention protocol observed more ongoing pregnancies in the intervention group (Figure S1). Subgroup analysis of the studies, separated according to single or multiple doses of GnRH agonists, was unable to explain the observed heterogeneity (Figure S2).

For the probability of clinical pregnancy (Figure 3), evidence from 10 studies examining 3056 women showed an RR of 1.28 (95% CI, 1.08–1.52; $I^2 = 61\%$). Sensitivity analysis, excluding the studies at high risk of bias, resulted in seven studies examining 2503 women with an RR of 1.15 (95% CI, 0.98–1.34; $I^2 = 49\%$).

For the probability of miscarriage (Figure 4), evidence from eight studies examining 1077 clinical pregnancies showed an RR of 0.82 (95% CI, 0.60–1.10; $I^2 = 26\%$). Sensitivity analysis excluding the studies at high risk of bias resulted in five studies examining 892 clinical pregnancies with an RR of 0.92 (95% CI, 0.72–1.19; $I^2 = 0\%$).

Risk of bias across studies

A small-study effect was suspected among the included studies because those suggesting a benefit of the intervention were the most imprecise, while the most precise studies suggested no effect; there was no imprecise study suggesting ‘harm’ from the intervention (Figure S3). The funnel plot analysis for the only outcome reported by all 10 studies (clinical pregnancy) showed clear asymmetry, highly suggestive of publication bias.

DISCUSSION

Summary of the evidence

Despite the relatively large number of studies and participants included in the systematic review and meta-analysis, we remain uncertain about the estimate of the effect and its precision (Table 1). The results of the individual studies are inconsistent, which translates into both substantial heterogeneity and a large confidence interval. We suspected that the dissemination of research findings could have been influenced by the nature and direction of results. The included studies only partially answered the review question, as no data regarding fetal safety were identified.

Quality of the evidence

The quality of the evidence for live birth/ongoing pregnancy and clinical pregnancy was downgraded for four reasons. First, the RCTs included in this review had serious limitations and only two of the 10 included studies were deemed at low risk of bias in every domain. Only one study reporting live birth was considered to be at low risk of bias, and the estimate of this single study suggested no effect, compared with a beneficial effect of the intervention when considering data from all studies. The estimate for clinical pregnancy when considering only the studies not at high risk of bias suggested no effect, compared with a beneficial effect of the intervention when considering data from all studies. Second, the quality was downgraded one level due to imprecision: although there are a relatively large number of participants and events, the 95% CI of the RR and of the NNTB are wide (Table 1), not being sufficiently precise to ascertain whether the benefit would be clinically irrelevant or large. The third reason for downgrading was the unexplanable inconsistency across studies: some larger
studies observed no effect while others observed a benefit of the intervention. Lastly, the quality was downgraded because of a strong suspicion of publication bias.

The quality of the evidence for miscarriage was downgraded one level because of limitations of the included studies and one level because of imprecision: <300 events considering both groups and the 95% CI of RR (0.60–1.10) was wide, not being sufficiently precise to ascertain whether intervention confers benefit or has no effect.

Agreement with other reviews and studies

We found three other reviews on this subject published a few years ago.1-9,10 Overall, we adopted more strict eligibility criteria to obtain a meaningful conclusion, allowing the inclusion of only truly randomized studies on the luteal phase only. Evidence in this field is emerging quickly, and the four new RCTs we found is emerging quickly, and the four new RCTs we found.

Figure 3 Forest plot of relative risk for miscarriage, comparing use of gonadotropin releasing hormone (GnRH) agonist and standard luteal-phase support (LPS) in women undergoing assisted reproductive techniques. Only first author of each study is given. Risk of bias (low (+), high (−) or unclear (?)): A, random sequence generation (selection bias); B, allocation concealment (selection bias); C, blinding of participants and personnel (performance bias); D, blinding of outcome assessment (detection bias); E, incomplete outcome data (attrition bias); F, selective reporting (reporting bias); G, other bias. M-H, Mantel–Haenszel.

Figure 4 Forest plot of relative risk for miscarriage, comparing use of gonadotropin releasing hormone (GnRH) agonist and standard luteal-phase support (LPS) in women undergoing assisted reproductive techniques. Only first author of each study is given. Risk of bias (low (+), high (−) or unclear (?)): A, random sequence generation (selection bias); B, allocation concealment (selection bias); C, blinding of participants and personnel (performance bias); D, blinding of outcome assessment (detection bias); E, incomplete outcome data (attrition bias); F, selective reporting (reporting bias); G, other bias. M-H, Mantel–Haenszel.
when GnRH agonist was inadvertently administrated during early pregnancy\textsuperscript{35}, the use during pregnancy is contraindicated by the manufacturer’s laboratory.

The evidence available at present does not allow us to ascertain what the most likely mechanism of action of GnRH during the luteal phase would be. When observing the subgroup analysis of live birth/ongoing pregnancy according to GnRH agonist or antagonist (Figure 2), although a marginally significant benefit was seen in the antagonist-protocol subgroup, this was not statistically different from the benefit seen in the agonist-protocol subgroup ($P = 0.20$). However, only two small studies used the antagonist protocol for COS. Considering that premature luteolysis may be an important issue to overcome, cycles in which the pituitary function is blocked by GnRH antagonists would be more likely to benefit from a GnRH agonist in the luteal phase than cycles in which the pituitary function is blocked by a GnRH agonist.

Nevertheless, the hypothesis of a direct effect of GnRH agonist on the embryo is supported by in-vitro\textsuperscript{6--8} and clinical findings\textsuperscript{5}. Evidence compiled in this meta-analysis does not allow us to either corroborate or undermine such a hypothesis, which brings about the need for evaluating safety outcome before using the intervention in clinical practice.

**Conclusions**

There is very low-quality evidence that administering GnRH agonist during the luteal phase in women undergoing ART improves ongoing and clinical pregnancy, particularly in antagonist cycles. Nevertheless, there is no evidence about its safety, considering both adverse perinatal outcome and congenital malformations. Given the biological rationale, future studies could focus on establishing the effect of the intervention in cycles that use antagonist protocols for COS. We therefore believe that including this intervention in clinical practice without further study would be premature. This review should be updated in the near future as there are ongoing studies examining this intervention.

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**REFERENCES**


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GnRH agonist during luteal phase support

SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Figure S1  Forest plot of relative risk for live birth or ongoing pregnancy, comparing use of gonadotropin releasing hormone (GnRH) agonist and standard luteal-phase support (LPS) in women undergoing assisted reproductive techniques, with studies separated according to GnRH agonist vs antagonist protocol.

Figure S2  Forest plot of relative risk for live birth or ongoing pregnancy, comparing use of gonadotropin releasing hormone (GnRH) agonist and standard luteal-phase support (LPS) in women undergoing assisted reproductive techniques, with studies separated according to single vs multiple GnRH agonist dose.

Figure S3  Funnel plot for clinical pregnancy in randomized controlled trials comparing use of gonadotropin releasing hormone agonist and standard luteal phase support in women undergoing assisted reproductive techniques.

Table S1  Characteristics of included studies comparing the use of gonadotropin releasing hormone (GnRH) agonist in the luteal phase and standard luteal-phase support in women undergoing assisted reproductive techniques (ART)

This article has been selected for Journal Club.
A slide presentation, prepared by Dr Joel Naftalin, one of UOG's Editors for Trainees, is available online.
Chinese translation by Dr Yang Fang.

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RESUMEN

Objetivo Identificar, evaluar y resumir la evidencia disponible sobre la eficacia y la seguridad de la administración de hormona liberadora de gonadotropina (GnRH) durante la fase luteínica en mujeres sometidas a técnicas de reproducción asistida.

Métodos En esta revisión sistemática y metaanálisis se realizó una búsqueda de ensayos controlados y aleatorizados, cuyo objetivo haya sido comparar la adición de un agonista de la GnRH durante la fase luteínica, con el apoyo estándar de la fase lútea. Se realizó una búsqueda de referencias de los estudios incluidos y las revisiones relacionadas en siete bases de datos electrónicas y manualmente. El resultado principal fue o nacimientos vivos o embarazos en curso, por cada mujer asignada al azar. Los resultados secundarios fueron embarazo confirmado ecográficamente por cada mujer asignada al azar, aborto en embarazos previamente confirmados, resultado perinatal adverso y malformaciones congénitas.

Resultados La evidencia de ocho estudios que incluyeron 2776 mujeres mostraron un riesgo relativo (RR) para los nacimientos vivos o embarazos en curso de 1,26 (IC del 95%, 1,04-1,53; I² = 58%). El análisis de sensibilidad, una vez excluidos los estudios que no reportaron nacimientos vivos y aquellos con un alto riesgo de sesgo, dio lugar a un estudio que examinó a 181 mujeres con un RR de 1,07 (IC del 95%, 0,73-1,58). El análisis de subgrupos, que separó los estudios por dosis individuales/múltiples de los agonistas de la GnRH o por la estimulación ovárica con un agonista/antagonista de la GnRH, fue incapaz de explicar la heterogeneidad observada. La calidad de las pruebas se consideró muy baja: se rebajó debido a la limitación de los estudios incluidos, la inexactitud, la inconsistencia entre los resultados de los estudios, y la sospecha de sesgos de publicación. Ninguno de los estudios incluidos reportó resultados perinales adversos o malformaciones congénitas.

Conclusiones Existe evidencia de que la adición de un agonista de la GnRH durante la fase luteínica mejora la probabilidad de embarazo en mujeres sometidas a técnicas de reproducción asistida. Sin embargo, esta evidencia es de muy baja calidad y no hay evidencia de resultado perinatal adverso y malformaciones congénitas. Por tanto, se cree que la inclusión de esta intervención en la práctica clínica sería prematura.

目的：查找、评估、总结关于接受辅助生殖技术的女性在黄体期应用促性腺激素释放激素（gonadotropin releasing hormone, GnRH）激动剂的有效性和安全性的现有证据。

方法：在本篇系统综述和荟萃分析中，我们检索了黄体期应用GnRH激动剂与标准黄体期支持进行比较的随机对照试验（randomized controlled trials, RCTs）。我们检索了7个电子数据库，并手工检索了纳入研究和相关综述的参考文献列表。主要结局为每例随机选择的女性活产或继续妊娠。次要结局为每例随机选择的女性临床妊娠、每例临床妊娠流产、不良围产结局和先天畸形。

结果：从8项研究、共2776例女性得到的证据显示，活产或继续妊娠的相对危险度（relative risk, RR）为1.26（95%CI, 1.04–1.53；I²=58%）。排除未报道活产情况和偏倚风险较高的研究，对一项检测了181例女性的研究进行敏感性分析，RR为1.07（95% CI, 0.73–1.58）。根据应用单剂量/多剂量GnRH激动剂或根据应用GnRH激动剂/拮抗剂进行卵巢刺激将研究分组进行亚组分析，未能解释研究观察到的异质性。证据质量极低是由于纳入研究的局限性、不准确、研究结果不一致以及怀疑存在发表偏倚所导致。纳入研究均未报道不良围产结局或先天畸形。

结论：证据表明，黄体期应用GnRH激动剂能够提高继续妊娠的可能性。然而该证据质量极低，且缺乏不良围产结局和先天畸形的证据。因此我们认为，将这种干预用于临床实践还为时过早。