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Current evidence on GnRH agonist pretreatment before frozen embryo transfer and pregnancy outcomes in women with adenomyosis: a systematic review and meta-analysis

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Article

Keywords: Adenomyosis, GnRH agonist pretreatment, frozen embryo transfers, infertility

Posted Date: November 18th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11527100/v1

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Additional Declarations: No competing interests reported.

Abstract

Adenomyosis is increasingly recognized as an important cause of infertility and reduced success rates in assisted reproductive technology (ART). Women with adenomyosis undergoing frozen embryo transfer (FET) have lower implantation and live birth rates compared to women without the disease. Gonadotropin-releasing hormone agonist (GnRH-a) pretreatment before FET has been proposed to improve reproductive outcomes by suppressing adenomyotic activity and enhancing endometrial receptivity; however, published studies have reported conflicting findings. The objective of this review was to evaluate the current evidence regarding the effectiveness of GnRH-a pretreatment before FET in women with adenomyosis.

A systematic search of MEDLINE, EMBASE, Cochrane Library, Web of Science, and SCOPUS was performed up to November 9, 2024. Ten eligible studies, including randomized controlled trials and retrospective cohort studies, were identified. Outcomes included live birth, clinical pregnancy, biochemical pregnancy, and miscarriage rates. Although none of the pooled analyses reached statistical significance, GnRH-a pretreatment showed a consistent trend toward improved live birth and clinical pregnancy outcomes. The odds ratio for live birth was 1.47 per cycle and 1.23 per patient, favouring pretreatment. Clinical pregnancy rates also tended to improve, while biochemical pregnancy and miscarriage rates remained similar between groups.

Current evidence suggests that GnRH-a pretreatment before FET may improve reproductive outcomes in women with adenomyosis, particularly live birth rates, although the quality of evidence remains limited by heterogeneity, retrospective study design, and inconsistent diagnostic criteria. These findings support the potential role of GnRH-a pretreatment in selected patients while highlighting the need for large, well-designed randomized controlled trials to establish clear clinical recommendations.

Introduction

Adenomyosis is a benign condition where the endometrium invades the myometrial layer of the uterus (1). This condition is frequently associated with pelvic pain, abnormal uterine bleeding, and infertility, making it a relevant concern in reproductive medicine (2). Establishing the prevalence of adenomyosis is challenging, as studies report a wide range of estimates, likely due to nonspecific symptoms and variations in diagnostic criteria. Histological evaluation of hysterectomy patients shows a prevalence of 8.8% to 61.5% - however, including only patients who required surgery inevitably leads to selection bias (3). Among infertile patients, the reported prevalence of adenomyosis ranges from 8% to 24% (3), and even with the use of assisted reproduction techniques (ART), these patients have a 31–43% lower pregnancy rate (4). This may be due to abnormal contractility, disrupted myometrial structure, or increased inflammation (2). To address this issue, several strategies have been explored to optimize ART outcomes, including medical pretreatment with hormonal agents such as levonorgestrel-releasing intrauterine systems (LNG-IUS) or gonadotropin-releasing hormone agonists (GnRH-a) (5). These treatments aim to suppress pituitary activity and create a receptive endometrial environment for implantation. However, existing studies on GnRH-a pretreatment before frozen embryo transfer (FET) in adenomyosis patients have shown conflicting results. Another important consideration is the high cost of GnRH-a products: one randomized clinical trial investigated pregnancy outcomes and the cost-effectiveness of GnRH-a pretreatment in PCOS patients. It found that ineffective treatment puts a substantial burden on the healthcare system: 7,799.2 Chinese yuan ($1,198) per FET cycle with pretreatment vs. 4,438.9 yuan without ($682; exchange rates from March 2021 averages). (6). In addition, unnecessary delay in embryo transfers is also undesirable in the case of an ineffective treatment. Therefore, we aimed to assess whether GnRH-a pretreatment improves pregnancy outcomes in women with adenomyosis undergoing FET.

Methods

We report our systematic review and meta-analysis based on the recommendation of the PRISMA 2020 guideline (7) (see Supplementary Table 1), while we followed the Cochrane Handbook (8). The protocol of the study was registered on PROSPERO (registration number CRD42024607049), and we fully adhered to it.

Search strategy

We performed a systematic search of MEDLINE (via PubMed), EMBASE, Cochrane Library, Web of Science, and SCOPUS on the 9th of November 2024. We did not use language or other restrictions. The search key we used is shown in detail in Appendix 1. Both domains of the search key refer to the population: Domain 1 refers to the condition (adenomyosis), Domain 2 refers to the specific ART technique (frozen embryo transfers). Backward and forward reference chasing of the eligible articles was also screened on February 12, 2025 to find all potentially relevant trials.

Eligibility criteria, selection, and data collection

Studies reporting on infertile patients with adenomyosis undergoing frozen embryo transfers - P (Population) - were included in our analysis if they provided data on the use of GnRH-a pretreatment - I (Intervention), C (Comparator) - and the outcomes of the IVF treatment, such as live birth rate, clinical pregnancy rate, and biochemical pregnancy rate - O (Outcome). Two independent review authors (MSzB and BK) selected the records by title and abstracts, and then by full text after the duplicates were removed (first automatically, then manually). For duplicate removal and importing references, we used the EndNote X9 software (9), and for screening and resolving conflicts, the Rayyan web application (10). Cohen's kappa coefficient was calculated at the end of each selection phase. A third independent reviewer (LF) resolved the differences. Two authors (MSzB and BK) independently collected data from the eligible articles and entered them into a previously established data collection table. A third author (LF) resolved the disagreements. The following data were collected from each article in a predesigned Excel spreadsheet: the first author's name, publication year, DOI, study design, study period, study country, number of patients with adenomyosis, number of cycles, number of live births, number of ongoing pregnancies, number of clinical pregnancies, and number of biochemical pregnancies.

Risk of bias and study quality assessment

Two authors (MSzB and BK) performed the risk of bias assessment independently using the Revised Cochrane risk-of-bias tool (RoB 2) (11) for the randomized controlled trials, and the Risk Of Bias In Non-randomised Studies - of Interventions tool (ROBINS-I) (12) for the retrospective cohort studies. We used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) (13) method to evaluate the reliability of the evidence. Two independent reviewers (MSzB and BK) evaluated each outcome and comparison. A third reviewer resolved any disagreements (LF).

Statistical analysis

A minimum of three studies was required to perform a meta-analysis. We presented results using forest plots and conducted a meta-analysis to investigate the effect of GnRH-a pretreatment on women undergoing IVF with FET. Live birth rate, biochemical and clinical pregnancy rates between women receiving the pretreatment and the control group with no treatment were investigated. Odds ratios (OR) were used as an effect size measure with 95% confidence intervals (CI). To calculate study odds ratios and pooled odds ratios, the number of all patients and those with the event (live birth, biochemical, and clinical pregnancy) in each group was extracted or calculated from the studies. Furthermore, we calculated OR for the same outcomes, but calculated event rates per cycle instead of per patient. The results present the odds of an event in the treatment group compared to the odds of an event in the control group. Pooled ORs based on raw data were calculated by the Mantel-Haenszel method (14, 15). The Paule-Mandel method (16) was used with the Q profile method for confidence intervals to estimate the heterogeneity variance measure (tau-squared) as recommended by Veroniki et al. (17). The analysis was carried out with R (version 4.4.2) based on the recommendations from Harrer et al (18).

Results

Search and selection

Based on our search strategy, we identified 6,893 records. After rigorous selection, eight retrospective cohort studies (19–26) and two randomized controlled trials (27, 28) were found eligible for systematic review and meta-analysis. Cohen’s kappa coefficient for both the title and abstract selection and the full-text selection was 0.86. The PRISMA flowchart of the selection process is summarized in Fig. 1.

Basic characteristics of included studies

In total, 1,765 patients and 1,396 FET cycles were included; all patients underwent FET, but some studies reported either patient counts or completed cycle counts. There wasn’t sufficient data reported to assess event rates compared to the number of initiated IVF cycles. Pretreatment length differed not only across articles but also among individual studies. The shortest pretreatment duration a patient could’ve received was 21 days; the longest could be six months (20, 23)

The baseline characteristics of the selected studies are detailed in Table 1.

Table 1
Baseline characteristics of the included studies

Number	First Author	Year of publication	Study Type	Study period	Population details	Reported total patient or cycle number	Population number	Intervention	Control	Re ou
1	Li et al.	2021	retrospective cohort study	2013 and 2018	patients diagnosed with adenomyosis unfergoing FET	both	341	GnRH-a downregulation + HRT	HRT alone	liv cl pr bi pr
2	Niu et al.	2013	retrospective cohort study	February 2009 and May 2012	patients undergoing FET cycles with adenomyosis	patient	339	GnRH-a downregulation + HRT	HRT alone	cl pr
3	Li et al.	2023	retrospective cohort	January 2016 and December 2020	patients undergoing FET or fresh ET cycles with adenomyosis	cycle	305	1 2 3 month pretreatment	no pretreatment	liv cl pr bi pr
4	Zhang et al.	2022	retrospective cohort	January 2009 to December 2019	adenomyosis patients undergoing FET	cycle	263	GnRh pretreatment	no pretreatment	liv cl pr
5	Ansaripour et al.	2024	RCT	NA	patients undergoing FET cycles with adenomyosis	both	64	ultra long downregulation	standard downregulation	cl pr bi pr
6	Moayed et al.	2023	RCT	May 2020 to March 2021	patients undergoing FET cycles with adenomyosis	both	130	gnrh-a + HRT	HRT alone	liv cl pr bi pr
7	Göktürk et al.	2022	retrospective cohort study	2011 to 2021	Patients with adenomyosis undergoing a FET cycle	both	144	GnRH agonist pre-treatment for minimum 2 and maximum 6 months	no pretreatment	liv cl pr
8	Guo et al.	2016	retrospective cohort study	January 2011 to December 2014	Patients with adenomyosis undergoing a FET cycle	cycle	120	adenomyosis patients who received pituitary down-regulation therapy and HRT	adenomyosis patients who received pure HRT	liv cl pr
9	Yu et al.	2024	retrospective cohort study	January, 2011 to November, 2022	adenomyosis patients with thin endometrium undergoing FET	both	122	(GnRH-a) + HRT group	HRT only	liv cl pr bi pr
10	X. Li et al.	2024	retrospective cohort study	January 2015 and October 2023	women with adenomyosis who underwent ETs or FETs	both	276	(GnRH-a) + HRT group	HRT only	liv cl pr pr

Live births

We analysed seven studies that reported cycle numbers (n = 1,396). The OR for live births was 1.47 in favour of patients receiving pretreatment (95% CI 0.91–2.38). Heterogeneity: (I^2) was 53% (95% CI 0%-80%). In five studies, the total number of patients was reported (n = 983); in this case, the OR for live births was 1.23 (95% CI 0.64–2.37). Heterogeneity (I^2) was 52% (95% CI 0%-82%). (Fig. 2).

Clinical pregnancy rates

All 10 studies reported clinical pregnancy numbers. For eight studies, the total number of cycles was assessed (n = 1460). OR for clinical pregnancies was 1.22 (95% CI 0.83–1.78). Heterogeneity: (I^2) was 42% (95% CI 0%-75%). In seven studies, we analysed the events in relation to the total patient numbers (n =

1,386). OR of clinical pregnancy was 1.32 (95% CI 0.71–2.44). Heterogeneity (I^2) was 78% (95% CI 55%-90%). (Fig. 3).

Biochemical pregnancy rates

Four studies reported biochemical pregnancies. In this case, the pooled OR was 0.95 (95% CI 0.63–1.43) Heterogeneity (I^2) was 0% (95% CI 0%-85%). (Fig. 4).

Miscarriage rates

For seven studies we calculated the number of miscarriages based on the total number of cycles (n = 1,396). OR for miscarriage was 1.04 (95% CI 0.73–1.48). Heterogeneity: (I^2) was 0% (95% CI 0%-71%). (Supplementary Fig. 8).

In six studies, we calculated the odds for miscarriage per the total patient numbers (n = 1,322). OR for miscarriage was 0.91 (95% CI 0.65–1.27). Heterogeneity (I^2) was 0% (95% CI 0%-75%). (Supplementary Fig. 9).

Controlling for bias

We excluded one study from our final analysis due to selection bias. This was explained by the different severities of adenomyosis in the patient population (21). In this study, only 35% of patients had moderate to severe dysmenorrhea in the non-downregulation group, and the 1, 2, and 3-month pretreatment groups had 54%, 68%, and 79%, respectively. The initial mean diameter of the uterus was 5.50cm in the control group, and 6.10, 6.55, and 7.20cm in the three intervention groups. These differences indicate that GnRH-a pretreatment was applied in the more severe cases of adenomyosis. We provided the initial analysis and the leave-one-out analysis in the supplementary material (Supplementary Figs. 1–9). Although the evidence is limited, one study suggests that the severity of adenomyosis significantly affects both pregnancy outcomes and the effectiveness of GnRH-a pretreatment. Notably, this study excluded the most severe cases, resulting in a more homogeneous population, and reported the largest increase in live birth rate among the included studies (22).

Risk of bias assessment

The findings of the evaluation of the risk of bias are reported in Fig. 5. Most of the studies reported low or moderate risk of bias, but two studies resulted in serious risk of bias, because of serious uncontrolled confounding (21, 23).

Heterogeneity and quality of evidence

The figures corresponding to the evaluated outcomes (Figs. 2–4) display the findings of heterogeneity. The quality of evidence across outcomes was downgraded partly because of the risk of bias and inconsistency in the included studies. We describe the quality of evidence in detail in Supplementary Table 2 and summarize the results for each outcome in Figs. 2–4.

Discussion

Summary of findings

This study aimed to assess the efficacy of GnRH-a pretreatment in patients with adenomyosis undergoing frozen embryo transfers. We analysed each outcome based on either IVF cycle numbers or total patient numbers, since some studies reported only one or both numbers. Our most notable result was the increase in live births per IVF cycles: we saw a 47% increase in the odds for live birth in favour of GnRH-a pretreatment, however the association was not statistically significant possibly due to the low case number studies and high heterogeneity.

Existing literature, cause of heterogeneity, and pathophysiology

Multiple studies showed the association of adenomyosis with infertility.

A recent Swedish publication showed that adenomyosis lowers the success rate of frozen embryo transfers by more than 40% (29).

Adenomyosis can affect fertility in multiple ways. The invasion of endometrial tissue into the myometrium leads to an abnormal inflammatory response, local hyperestrogenism, and distorted myometrial structure (30). These changes can lead to uterine hyperperistalsis, which can disrupt sperm transport and embryo implantation (31). Additionally, adenomyosis is associated with increased expression of inflammatory cytokines and oxidative stress markers, which may contribute to early pregnancy loss (32).

There is significant heterogeneity in the diagnosis of adenomyosis across studies. All studies used transvaginal ultrasound (TVUS), but not all adopt standardized criteria such as those proposed by the Morphological Uterus Sonographic Assessment (MUSA) group (33). The number and combination of diagnostic features (e.g., myometrial cysts, asymmetrical wall thickening, hyperechoic islands) vary between studies, as does the threshold for diagnosis. Furthermore, few studies stratify patients by severity or type of disease (diffuse, focal, mixed), which likely have different clinical manifestations, therefore contributing to conflicting results across the literature (34).

Retrospective studies on ART outcomes in adenomyosis are prone to several confounders. Factors such as patient age, ovarian reserve (e.g., AMH, AFC), embryo quality, and the presence of coexisting conditions like endometriosis or fibroids can strongly influence success rates but are not consistently adjusted for (35), (36), (37), (38). Importantly, in one retrospective study, GnRH-a pretreatment was more frequently offered to patients with more severe disease, introducing selection bias (21). Differences in stimulation protocols, embryo transfer timing, and luteal phase support further limit comparability between studies.

GnRH-a works by desensitising the pituitary gland, leading to suppression of gonadotropin secretion and a hypoestrogenic state. This hormonal downregulation reduces the size and activity of adenomyotic lesions and may reduce inflammatory and angiogenic responses (39), (40). In adenomyosis, GnRH-a pretreatment has been associated with decreased uterine volume (41). One mouse model showed improved endometrial receptivity after GnRH-a treatment by increased expression of “Hoxa10”, “Hoxa11”, and Leukaemia Inhibitory Factor (LIF) mRNA and protein, which play an important role in implantation (42). These changes may collectively enhance the chance of embryo implantation in ART cycles.

The literature shows conflicting evidence regarding the benefit of GnRH-a pretreatment before ART in patients with adenomyosis. For example, one study included in our meta-analysis (22) showed that GnRH-a pretreatment before frozen embryo transfer significantly improved live birth rates in women with moderate adenomyosis. In contrast, some included studies did not find any significant improvement in pregnancy outcomes (19), (28), (25). One study reported that in adenomyosis patients undergoing fresh embryo transfers, improvements in implantation, biochemical pregnancy, and clinical pregnancy rates were observed only among those receiving at least three months of GnRH-a pretreatment, suggesting that treatment duration may be a critical factor (21). However, inconsistent reporting of pretreatment duration across the available studies prevents subgroup analysis in this meta-analysis.

To summarize, these discrepancies likely stem from differences in diagnostic methods, patient selection, treatment duration, and severity of disease. Overall, the lack of uniform protocols limits the comparability of results.

Implications for clinical practice, future research directions, strengths, and limitations

Regarding the strengths of our analysis, we followed our protocol, which was registered in advance, and we made no deviations from it. A rigorous methodology was applied, with two independent investigators conducting each step of the process. This study is the first meta-analysis investigating the efficacy of this exact intervention, and while the results did not reach statistical significance, a tendency towards improved pregnancy outcomes was observed.

A low number of included studies and patients can be considered a serious limitation of this study. Most studies didn’t compare the severity of adenomyosis between the intervention and the control groups. Only two randomized controlled trials could be included; the different design of retrospective studies (lack of randomization) may also cause bias

The generalization of our result is challenging, since in retrospective studies, patients who received pretreatment probably had the more severe cases of adenomyosis. The presence of moderate and high risk of bias in some of the domains is another limitation.

Implementing scientific findings in practice is crucial (43), (44), therefore, with our research, we would like to draw the attention of clinicians and researchers working in the field of reproductive medicine to this therapeutic method, which, based on our results, may increase the live birth rate of FETs performed on patients with adenomyosis by nearly one and a half times, although not yet significantly. Therefore, in our opinion, until further well-designed, high patient-number, randomised trials provide data confirming the true significance of these results, GnRH agonist pretreatment still has a place in ART practice, with appropriate critical thinking and caution.

Conclusions

GnRH agonist pretreatment before frozen embryo transfer showed a potential but non-significant improvement in reproductive outcomes among women with adenomyosis. Further high-quality randomised trials are required.

Abbreviations

GnRH
gonadotropin-releasing hormone
GnRH-a
gonadotropin-releasing hormone agonist
ART
assisted reproduction technique
FET
frozen embryo transfer
OR
odds ratio
PCOS
polycystic ovarian syndrome
LIF
leukaemia inhibitory factor
IVF
in vitro fertilization
PRISMA
Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RoB 2
Revised Cochrane risk-of-bias tool for randomized trials

ROBINS-I
Risk Of Bias In Non-randomised Studies - of Interventions
GRADE
Grading of Recommendations Assessment, Development, and Evaluation
TVUS
Transvaginal ultrasound
MUSA
Morphological Uterus Sonographic Assessment
AMH
Anti-Müllerian hormone
AFC
Antral follicle count

Declarations

Declarations

Ethics approval and consent to participate

Not applicable.

Consent to Publication

declaration

Competing interests

All authors declare no competing interest.

CRediT author contribution

MSzB: Writing – original draft, Visualization, Project administration, Investigation, Data curation, Conceptualization. BK: Writing – review & editing, Investigation, Data curation. LF: Writing – review & editing, Validation, Project administration, Data curation, Conceptualization, Methodology. AR: Writing – review & editing, Validation, Investigation, Data curation, Methodology. BLSz: Writing – review & editing, Statistical analysis. AH: Writing – review & editing, Statistical analysis. PH: Writing – review & editing, Validation, Funding acquisition, Conceptualization. SV: Validation, Supervision, Conceptualization. NÁ: Validation, Supervision, Conceptualization. MS: Writing – original draft, Validation, Supervision, Conceptualization.

All authors certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing, or revision of the manuscript.

Funding

declaration

Funding was provided by the Centre for Translational Medicine, Semmelweis University.

Sponsors had no role in the design, data collection, analysis, interpretation, and manuscript preparation.

Author Contribution

MSzB: Writing – original draft, Visualization, Project administration, Investigation, Data curation, Conceptualization. BK: Writing – review & editing, Investigation, Data curation. LF: Writing – review & editing, Validation, Project administration, Data curation, Conceptualization, Methodology. AR: Writing – review & editing, Validation, Investigation, Data curation, Methodology. BLSz: Writing – review & editing, Statistical analysis. AH: Writing – review & editing, Statistical analysis. PH: Writing – review & editing, Validation, Funding acquisition, Conceptualization. SV: Validation, Supervision, Conceptualization. NÁ: Validation, Supervision, Conceptualization. MS: Writing – original draft, Validation, Supervision, Conceptualization. All authors certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing, or revision of the manuscript.

Acknowledgement

None to declare.

Data Availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Figures

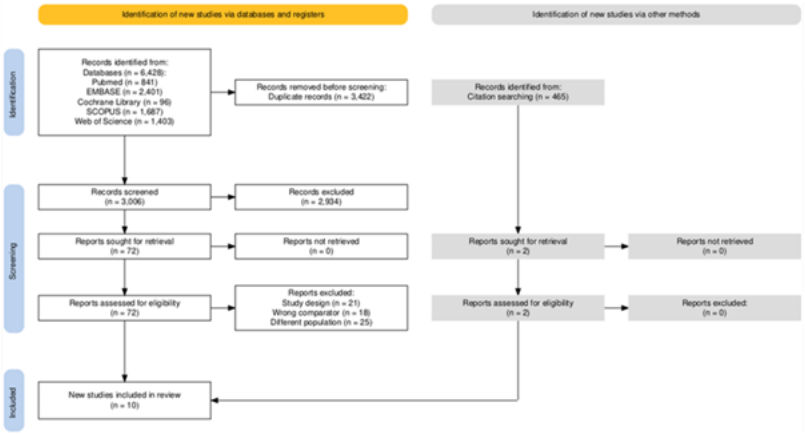


Figure 1

PRISMA flow diagram of selection

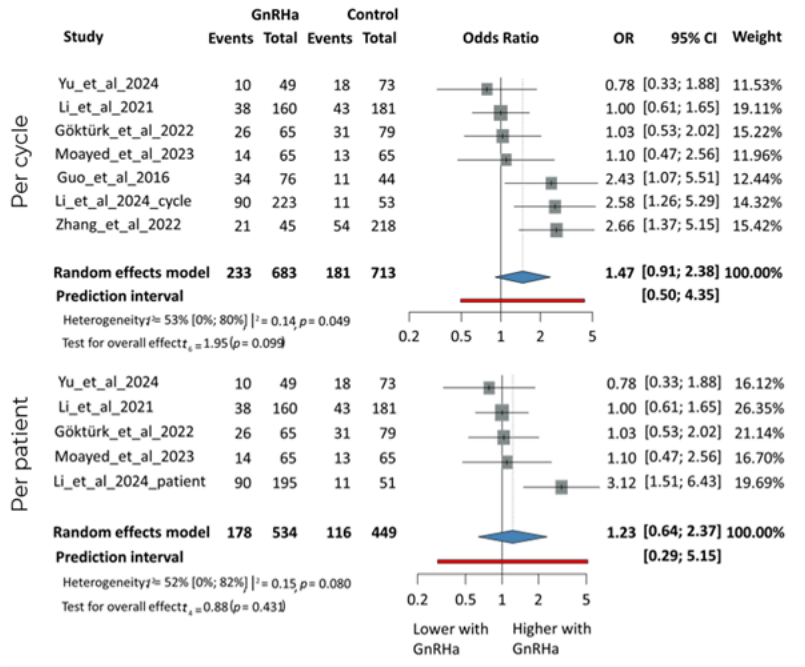


Figure 2

Forest plot showing OR for live births

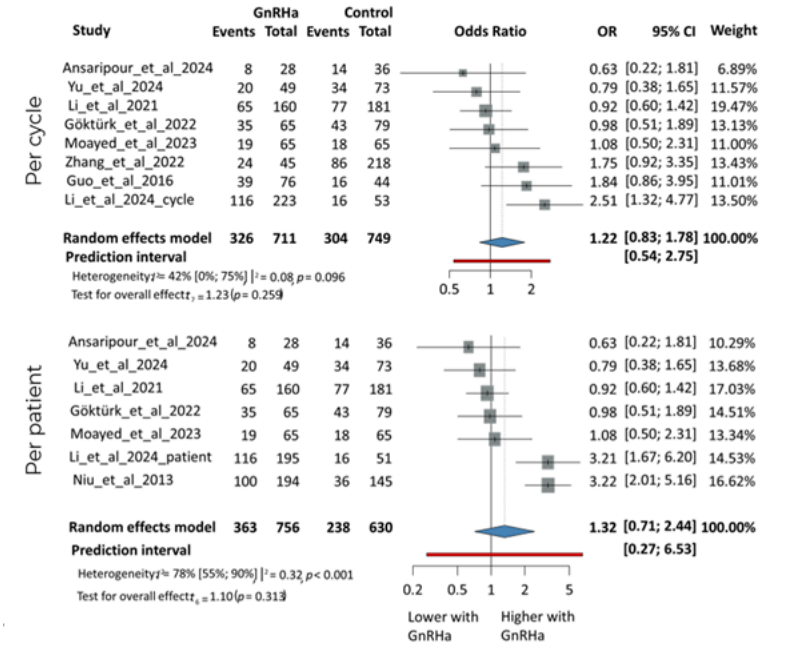


Figure 3

Forest plot showing OR for clinical pregnancies

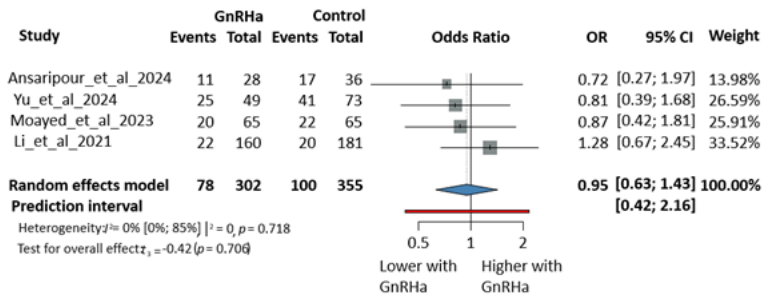


Figure 4

Forest plot showing OR for biochemical pregnancies

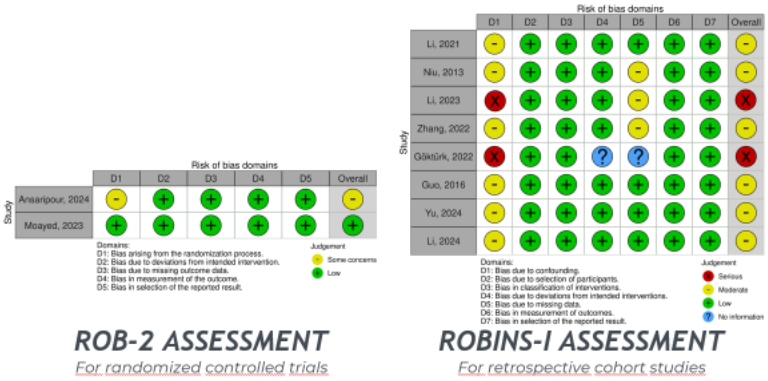


Figure 5

Risk of bias assessment charts

Supplementary Files

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