

Systematic Review

Comparing Various GnRH Protocols to Improve Fertility Outcomes in Patients with Adenomyosis: A Qualitative Systematic Review

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Abstract

Introduction: Adenomyosis impairs fertility through chronic inflammation and endometrial damage. While IVF with GnRH modulation is used to improve outcomes, no universal protocol exists. This study compares long versus short GnRH agonist protocols for improving fertility in adenomyosis patients.

Methods: This qualitative systematic review [CRD420251272312] searched databases like PubMed and Semantic Scholar in November 2025. It included English-language observational studies or RCTs involving human samples, while excluding duplicates and incomplete manuscripts.

Results: From 858 abstracts, three studies were analyzed. No method significantly altered oocyte count or myometrial thickness. Ultra-long and long GnRH agonist protocols showed higher pregnancy rates and lower miscarriage risks, whereas antagonist and short agonist protocols had poorer outcomes.

Conclusions: Ultra-long and long GnRH agonist protocols are promising for adenomyosis, but these preliminary results from limited studies require validation through larger randomized controlled trials addressing confounding factors.

Keywords: Adenomyosis; assisted reproduction therapy; fertility; GnRH agonist; GnRH antagonist; In Vitro Fertilization

Perbandingan Variasi Protokol GnRH untuk Meningkatkan Hasil Kesuburan pada Pasien dengan Adenomyosis: Sebuah Tinjauan Sistematis Kualitatif

Abstrak

Pendahuluan: Adenomyosis mengganggu kesuburan melalui peradangan kronis dan kerusakan endometrium. Meskipun IVF dengan modulasi GnRH digunakan untuk meningkatkan hasil, tidak ada protokol universal yang ada. Studi ini membandingkan protokol agonis GnRH panjang versus pendek untuk meningkatkan kesuburan pada pasien adenomyosis.

Metode: Tinjauan sistematis kualitatif ini [CRD420251272312] mencari basis data seperti PubMed dan Semantic Scholar pada November 2025. Ini mencakup studi observasional atau RCT berbahasa Inggris yang melibatkan sampel manusia, sambil mengecualikan duplikat dan manuskrip yang tidak lengkap.

Hasil: Dari 858 abstrak, tiga studi dianalisis. Tidak ada metode yang secara signifikan mengubah jumlah oosit atau ketebalan miometrium. Protokol agonis GnRH ultra-panjang dan panjang menunjukkan tingkat kehamilan yang lebih tinggi dan risiko keguguran yang lebih rendah, sementara protokol antagonist dan agonis pendek memiliki hasil yang lebih buruk.

Kesimpulan: Protokol agonis GnRH ultra-panjang dan panjang menjanjikan untuk adenomyosis, tetapi hasil awal dari studi terbatas ini memerlukan validasi melalui uji coba terkontrol acak yang lebih besar yang membahas faktor-faktor perancu.

Kata kunci: Adenomyosis; GnRH Agonist; GnRH Antagonist; kesuburan; Pembuahan In Vitro Terapi Reproduksi Bantu

Introduction

Adenomyosis is defined as the pathologic presence of ectopic endometrial glands within the myometrium. It is postulated that a chronic hyperperistaltic state causes microtrauma to the endometrial layer, thereby triggering the Tissue Injury and Repair (TIAR) mechanism. Chronic injury leads to ectopic implantation of endometrial tissue within the myometrium, often accompanied by destruction of the basal membrane. The ectopic endometrial glands remain functional, inducing cyclical inflammation and granulation tissue formation. This enigmatic pathophysiology results in a range of symptoms that vary among patients, from dysmenorrhea and Abnormal Uterine Bleeding (AUB) to subfertility.¹⁻⁵

Subfertility is one of the most clinically significant presentations in these individuals. Current epidemiological data suggest that adenomyosis affects approximately 20–30% of females under age 40 who experience infertility.⁶ The presence of adenomyosis is associated with a 26% reduction in clinical pregnancy rates and a 1.9-fold increase in miscarriage rates compared with age-matched controls, independent of oocyte quality.^{7,8} While hysterectomy is the definitive treatment for eradicating adenomyosis, it is an unreasonable option for individuals who wish to preserve their fertility. Hormonal therapy can be considered to reduce symptoms; however, it does not consistently improve fertility outcomes.^{1,2}

Assisted Reproductive Technology (ART) is a feasible management strategy for patients seeking to conceive; however, ART does not necessarily guarantee fertility success. Mouse models have shown that damage to the endometrial layer significantly impairs uterine architecture, thereby preventing embryo implantation.⁹ Previous studies have also reported that women with adenomyosis have a significantly

lower pregnancy rate (23.6%) than those without adenomyosis (44.6%). This problem underscores an imperative clinical question: whether optimizing ART protocols can improve fertility in patients with adenomyosis.¹⁰

The administration of Gonadotropin-Releasing Hormone (GnRH) can reduce the hyperestrogenic state in adenomyosis, thereby decreasing local inflammation and junctional zone hyperplasia, mitigating hyperperistalsis, and preventing disruption of critical implantation markers, such as HOXA10 and LIF, during the window of implantation. Therefore, GnRH therapy has been widely accepted to desensitize pituitary receptors, inducing a temporary hypoestrogenic state to improve conception success. Currently, there are four known GnRH therapy protocols: short-acting GnRH agonist, long-acting GnRH agonist, ultra-long-acting GnRH agonist, and GnRH antagonist.^{6,11}

This systematic review aims to critically evaluate the comparative efficacy of GnRH therapy protocols. We synthesize evidence on fertilization success, clinical pregnancy rates, miscarriage rates, and live birth outcomes to provide a robust, evidence-based framework for clinical decision-making in this challenging patient population.

Methods

Registration

This study was conducted in accordance with the PRISMA 2020 Guideline.¹² We registered this study protocol in PROSPERO under the number [CRD420251272312].

Screening

A literature search was conducted from November 21 to December 15, 2025, using databases including PubMed, Science Direct, Springer, BMJ, and an AI-powered

engine (Semantic Scholar). The search terms were: “Adenomyosis” AND “GnRH Long Protocol” AND “GnRH Short Protocol”. A filter for “original research” was applied across all databases where available. Three investigators (SS, AMS, SMP) searched different databases with the same terms and compiled the data in a Google Sheet accessible to all authors. Three investigators (SS, AMS, SMP) searched different databases with the same search terms and compiled the data in a Google Sheet accessible to all authors.

Eligibility Criteria

The eligibility criteria were based on the PICO framework, consisting of: Adenomyosis (Patient); GnRH Protocol (Intervention); Other GnRH Duration Protocols (Comparison); and Success Rate of IVF, Pregnancy Rate, or Live Birth Rate (Outcome). Our exclusion criteria included: review articles, commentaries, editorials, case reports, and articles not in English or Indonesian. If an article is ambiguous, the supervisors (IEBH, MY, and NPKS) will discuss it to determine whether to include it.

Data Extraction

We extracted data from the included studies, including: (1) authors' first names, (2) year of publication, (3) country, (4) number of participants, (5) age, (6) regimen duration and definition, (7) regimen description, (8) endometrial thickness, (9) oocyte count, (10) FSH level, (11) pregnancy rate, (12) live birth rate, and (13) abortion rate. Data extraction was performed by at least two authors; if disagreements arose, an open discussion with other authors and a vote were held.

Data Synthesis

The extracted data were analyzed qualitatively. The data were compared across trial groups

evaluating GnRH for adenomyosis, using outcomes such as endometrial thickness, oocyte count, FSH level, pregnancy rate, live birth rate, and abortion rate. A meta-analysis was not performed in this study due to the small number of included studies ($n = 3$) and the lack of homogeneity among the studies. For example, some compared four groups (ultra-long, long, antagonist, and short), while others compared fewer than four. Consequently, a meta-analysis would have yielded limited data and would, therefore, be of limited clinical value.

Risk of Bias

We conducted a risk-of-bias assessment using the JBI cohort questionnaire. The questionnaire consists of 11 questions, and each article was reviewed by at least two investigators. Any disagreements were resolved by consensus. Results were presented in a comparison table for each included study. The score was calculated by dividing the total number of “Yes” responses by the total number of questions; scores $>75\%$ were considered Low Risk, $50\%-75\%$ were considered Moderate Risk, and $<50\%$ were considered High Risk of bias.

Result

Screening Result

A total of 858 articles were identified, and 23 were immediately excluded for duplication. We included 9 articles that met the eligibility criteria, and 6 were excluded after a full-text review for various reasons (Fig. 1). Ultimately, we included 3 studies for further analysis.¹³⁻¹⁵

Characteristics of Included Studies

Three studies¹³⁻¹⁵ were included: one RCT conducted in Iran¹⁴ and two cohort studies^{13,15} conducted in China. Ge et al. had the largest

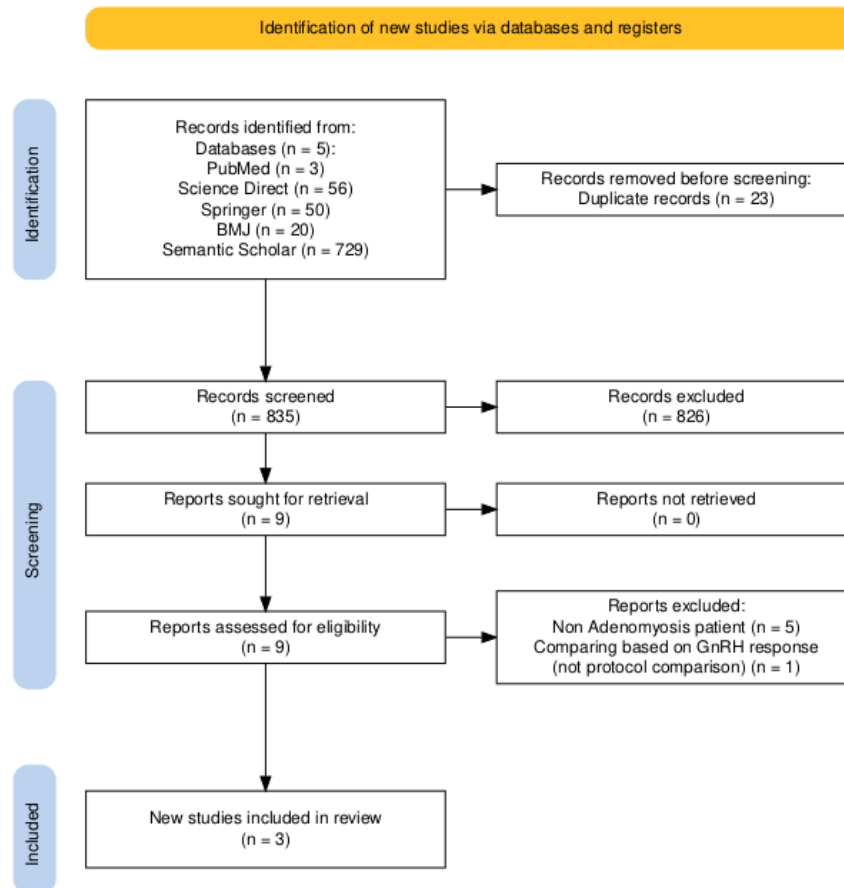


Figure 1 PRISMA Flowchart

sample size, with 257 participants, followed by Firouzabadi et al. (210) and Zhang et al. (143). This brought the total number of included patients to 710. Firouzabadi et al.¹⁴ compared a protocol without desensitization to a long protocol; Zhang et al.¹⁵ compared an antagonist protocol to an ultra-long GnRH protocol; and Ge et al.¹³ provided the widest range of comparisons, including long, antagonist, short, and ultra-long protocols.

All included studies used a GnRH antagonist intervention, and the protocols were identical across studies. All studies provided 0.25 mg of a GnRH antagonist daily to included patients. Firouzabadi et al. and Ge et al. identified the drug as ganirelix acetate, whereas Zhang et al. did not specify the medication used. Only Ge et al. used a short GnRH agonist protocol, administering 0.05–0.1 mg of triptorelin acetate.

Two studies used a long GnRH agonist protocol: Firouzabadi et al. and Ge et al. However, they used different methodologies: Firouzabadi et al. used a 500 ug buserelin injection, while Ge et al. used a 0.05–0.1 mg triptorelin acetate injection. Two studies used the ultra-long GnRH agonist protocol: Ge et al. and Zhang et al. Both employed a similar approach, injecting 3.75 mg of a GnRH agonist. Ge et al. reported using triptorelin acetate, but Zhang et al. did not specify the drug.

Baseline Characteristic

There was variation in the average age across the included studies. The average ages for patients in the GnRH antagonist groups were 28.36, 32, and 33.5 years, as reported by Firouzabadi et al., Zhang et al., and Ge et

Table 1 Characteristics of Included Studies

Characteristics	Ge <i>et al.</i> , 2023	Zhang <i>et al.</i> , 2022	Firouzabadi <i>et al.</i> , 2010
Age	33.5*	32*	28.36*
BMI	27.54*	22.23*	27.54*
Protocols Involved	Ultra-long; Long; Antagonist; and Short	Antagonist; Long Acting	Long; Antagonist

*Average

al., respectively. The average age in the short GnRH agonist group was 37 years, reported by Ge *et al.* For the long GnRH agonist groups, the average ages were 28.71 and 32.5 years, reported by Firouzabadi *et al.* and Ge *et al.*, respectively. For the ultra-long GnRH agonist groups, the average ages were 32 and 34 years, reported by Zhang *et al.* and Ge *et al.*, respectively.

The average BMI was similar across groups. According to Firouzabadi *et al.*, Zhang *et al.*, and Ge *et al.*, the average BMIs for patients in the GnRH antagonist groups were 27.54, 22.23, and 25.7, respectively. The average BMI in the short GnRH agonist group was 23.95, reported by Ge *et al.* For the long GnRH agonist groups, the average BMIs were 23.1 and 23.37, reported by Firouzabadi *et al.* and Ge *et al.*, respectively. The average BMI for the ultra-long GnRH agonist group was 22.18 and 24.4, reported by Zhang *et al.* and Ge *et al.*, respectively. Baseline characteristics are compiled in Table 1. The diversity of the protocols used resulted in only about two studies per protocol. Consequently, the limited availability of data rendered a meta-analysis unsuitable.

Endometrial Thickness and FSH Level

Endometrial thickness after stimulation was reported by only two studies: Firouzabadi *et al.* and Ge *et al.* There were no significant differences in endometrial thickness among the study groups. The average endometrial thickness for the GnRH antagonist group was 9.6 ± 0.8 mm and 10 mm, respectively. The

average endometrial thickness in the short GnRH agonist group was 9 mm, as Ge *et al.* reported. For the long GnRH agonist group, it was 9.6 ± 0.8 mm and 11 mm, and for the ultra-long GnRH agonist group, it was 11 mm.

Moreover, Firouzabadi *et al.* and Ge *et al.* also reported FSH levels after stimulation. There were slight differences in FSH levels between the groups. The average FSH level for the GnRH antagonist group was 5.54 ± 1.1 IU/L and 6.76 IU/L. For the short GnRH agonist group, it was 7.6 IU/L. For the long GnRH agonist group, it was 5.77 ± 1.2 IU/L and 6.5 IU/L; for the ultra-long GnRH agonist group, it was 6.45 IU/L. The statistical significance of these differences could not be reliably assessed.

Oocyte Count

Successful GnRH therapy yields multiple viable oocytes, which serve as an indicator of IVF success. We compiled this data in Table 2. There were minor differences in oocyte counts between the groups. The average oocyte count for the GnRH antagonist group was 7.15 ± 3.2 , 8, and 6, as reported by Firouzabadi *et al.*, Zhang *et al.*, and Ge *et al.*, respectively. For the short GnRH agonist group, it was 9. For the long GnRH agonist group, it was 7.86 ± 3.4 and 10, and for the ultra-long GnRH agonist group, it was 9 and 7.

Pregnancy and Live Birth Rate

Table 2 Outcome of Included Studies

Author, year	Protocol	Oocyte Count	Pregnancy Rate	Live Birth Rate	Miscarriage Rate
Ge <i>et al.</i> , 2023	Ultra Long	7*	57.4%	39.8%	30.6%
	Long	10*	64.3%	48.2%	25%
	Antagonist	6*	38.2%	26.5%	30.8%
	Short	4*	35.6%	20.3%	42.9%
Zhang <i>et al.</i> , 2022	Antagonist	7*	49.4%	36.9%	12.5%
	Long Acting	10*	64.04%	45.61%	17.54%
Firouzabadi <i>et al.</i> , 2010	Agonist	7.86 ± 3.4	30%	27.6%	NA
	Antagonist	7.15 ± 3.2	34.5%	33.3%	NA

*Median; NA, Not Available

Clinical pregnancy rate indicates whether GnRH therapy successfully reduces the clinical manifestations of adenomyosis, thereby accelerating implantation success. The ultra-long GnRH agonist group had the highest pregnancy rate. Ge *et al.* and Zhang *et al.* reported pregnancy rates of 57.4% and 60.56%, respectively. Pregnancy success followed the long GnRH group, with rates of 64.3% and 27.6%, reported by Firouzabadi *et al.* and Ge *et al.*, respectively. Although Ge *et al.* report that the long GnRH agonist protocol has the highest pregnancy rate among all groups, the marked difference with Firouzabadi's findings (64.3% vs 27.6%) raises questions about the consistency of the results. The GnRH antagonist group had a success rate of 33.3%, 46.48%, and 38.2%, reported by Firouzabadi *et al.*, Zhang *et al.*, and Ge *et al.*, respectively. The short GnRH agonist group had the lowest pregnancy success rate, with a rate of 35.6% reported by Ge *et al.*

The live birth rate is reported only by Zhang *et al.* and Ge *et al.*, and not by Firouzabadi *et al.* Successful delivery aligns with the successful pregnancy rate findings, with the long and ultra long GnRH agonist

groups having the highest live birth rates. In the long GnRH agonist group, the live birth rate was 48.2%, reported by Ge *et al.* In the ultra-long GnRH agonist group, the live birth rate was 45.07% and 39.8%, reported by Zhang *et al.* and Ge *et al.*, respectively. The success rate is followed by the GnRH antagonist group, with the live birth rate reported as 32.39% and 36.5% by Zhang *et al.* and Ge *et al.*, respectively. The group with the lowest live birth rate was the short GnRH agonist group, with a live birth rate of 20.3% reported by Ge *et al.*

Miscarriage Rate

The miscarriage rate indicates whether GnRH therapy can preserve the pregnancy until term. As adenomyosis increases local inflammation and uterine peristalsis, miscarriage is likely to occur. Early miscarriage is defined as pregnancy loss before 12 weeks of gestational age, and late miscarriage is defined as pregnancy loss between 13 and 28 weeks of pregnancy.

The highest miscarriage risk was observed in the Short GnRH agonist protocol, with a miscarriage rate of 42.9%. The early

Table 3 Risk of Bias using JBI

Author, Year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Score	Risk of Bias
Firouzabadi, 2010¹⁴	Y	N	Y	N	N	Y	Y	Y	Y	Y	Y	72.7%	Moderate
Zhang L, 2022¹⁵	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100%	Low Risk
Ge, 2023¹³	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	90.9%	Low Risk

*Y, Yes; N, No; NA, Not Available

*Q1: Were the two groups similar and recruited from the same population? Q2: Were the exposures measured similarly to assign people to both the exposed and unexposed groups? Q3: Was the exposure measured in a valid and reliable way? Q4: Were confounding factors identified? Q5: Were strategies to deal with confounding factors stated? Q6: Were the groups/ participants free of the outcome at the start of the study (or at the moment of exposure)? Q7: Were the outcomes measured in a valid and reliable way? Q8: Was the follow-up time reported and sufficient to be long enough for outcomes to occur? Q9: Was follow-up complete, and if not, were the reasons for loss to follow-up described and explored? Q10: Were strategies to address incomplete follow-up utilized? Q11: Was an appropriate statistical analysis used?

miscarriage rate was 38.1%, and the late miscarriage rate was 4.8%. The GnRH Antagonist and ultra-long GnRH agonist groups had similar overall miscarriage rates; however, the ultra-long group had the highest miscarriage rate later in pregnancy. In the ultra-long GnRH agonist group, the total miscarriage rate was reported as 15.49% and 30.6% by Zhang et al. and Ge et al., respectively. The early miscarriage rate was 14.91% and 16.1%, respectively, and the late miscarriage rate was 2.63% and 14.5%, respectively.

In the GnRH antagonist group, the total miscarriage rate was 14.08% and 30.8%, reported by Zhang et al. and Ge et al., respectively. The early miscarriage rate was 10.12% and 23.1%, respectively, and the late miscarriage rate was 2.38% and 7.7%, respectively. In the Long GnRH Agonist group, the miscarriage rate was 25%, reported by Ge et al. The early miscarriage rate was 22.2%, and the late miscarriage rate was 2.8%.

Complication

None of the research reports complication incidence, except for OHSS reported by Firouzabadi et al. This research reports 12%

OHSS in the long GnRH agonist group, compared with 2.7% OHSS in the GnRH antagonist group.

Risk of Bias

Three articles were assessed for risk of bias, and all were considered low risk. Firouzabadi et al.¹⁴ had the lowest score among the others due to unclear allocation concealment and the absence of blinding procedures. Ge et al.¹³ had groups that differed significantly in size (108 vs 56 vs 34 vs 59). The risk of bias is presented in Table 3.

Discussion

GnRH is produced by the hypothalamus and acts as a messenger in the anterior pituitary cells to regulate Follicle-Stimulating Hormone (FSH) and Luteinizing Hormone (LH). GnRH is secreted in pulses, with intervals ranging from every 71 to 216 minutes depending on the menstrual phase. Hypersecretion of GnRH causes a failure to secrete FSH and LH, thus preventing ovulation. In clinical practice, GnRH therapy is used to augment multifollicular development, aiming to increase the percentage of high-quality oocytes.¹⁶

Both GnRH agonists and antagonists inhibit premature LH surges, aiming to facilitate multifollicular development. GnRH agonists work by binding to GnRH receptors, initially increasing LH secretion (the “flare” effect) but subsequently reducing LH secretion due to downregulation. As a result, GnRH agonists carry a risk of inducing Ovarian Hyperstimulation Syndrome (OHSS). In contrast, GnRH antagonists competitively bind to GnRH receptors, suppressing LH secretion signals without inducing an initial LH surge. GnRH therapy can be administered as injections, sustained-release implants, or sprays.¹⁶

GnRH agonist protocols are further classified as ultra-long, long, and short. The long protocol induces prolonged stimulation by initiating GnRH injections during the midluteal phase and continuing until 10 days after the first menstrual day. Downregulation begins when estrogen, LH, progesterone, and endometrial thickness are suppressed; the GnRH dose is then reduced to 150–200 ug daily. Although associated with better fertility outcomes, this protocol is time-consuming and significantly more expensive. The short protocol uses three days of GnRH therapy starting on the first menstrual day. The dose is then halved and combined with FSH therapy until the desired follicular size is achieved. This method is preferred for poor responders and older patients due to a lower risk of OHSS.¹⁶

This study analyzed outcomes of four GnRH protocols: GnRH antagonist, short GnRH agonist, long GnRH agonist, and ultra-long GnRH agonist. We evaluated therapeutic outcomes, including pre-fertilization factors (oocyte count, endometrial thickness), fertility success (pregnancy rate, live birth rate), and complications (miscarriage and OHSS). Baseline characteristics (age and BMI) were similar across all groups, reducing the risk of selection bias. For pre-fertilization parameters (endometrial thickness, FSH level,

and oocyte count), all four protocols yielded similar outcomes. This finding suggests that the specific type of GnRH therapy does not substantially alter the baseline morphological quality of oocytes or the endometrium during IVF.

However, our preliminary data suggest that the highest pregnancy and birth rates were associated with the ultra-long GnRH agonist groups. We postulate that longer stimulation may create a more favorable environment for fertility success. Patients with adenomyosis experience chronic inflammation and granulation tissue formation. GnRH stimulation induces a hypoestrogenic state. While this allows for multifollicular development, it also exerts an additional therapeutic effect on adenomyotic lesions. Reduced estrogen activity dampens inflammation, likely promoting cellular rehabilitation. We theorize that longer stimulation protocols induce a more stable rehabilitative period, fostering consistent regeneration of endometrial structures, thereby providing a more favorable base for zygotic implantation.

This postulate is supported by findings on abortion rates. Shorter stimulation protocols (short GnRH agonist) were associated with higher early and late abortion rates. This aligns with our hypothesis: shorter stimulation may be insufficient to suppress local inflammation and adequately induce endometrial regeneration, leading to implantation failure. Endometrial tissue migrating into the myometrium increases myometrial peristalsis, which is unfavorable during pregnancy. Prolonged GnRH stimulation may induce regression of adenomyotic lesions, thereby reducing myometrial peristalsis and excessive angiogenesis. However, because we could not extract specific data on the reduction in adenomyosis size after GnRH stimulation, this hypothesis remains speculative.

Overall, we conclude that longer

GnRH stimulation with ultra-long or long GnRH agonist therapy appears to yield better fertility outcomes in patients with adenomyosis. Consistent endometrial suppression likely reduces local inflammation and induces multifollicular development. Nonetheless, selecting a GnRH protocol must be individualized. Older patients, poor responders, and those at high risk for OHSS might not be ideal candidates for longer stimulation therapies. Shorter therapy should be considered in these circumstances, and further research is needed to evaluate its efficacy in patients with specific complications.

This systematic review provides a structured understanding of GnRH protocol preferences for patients with adenomyosis. It can serve as a foundation for evidence-based medicine in fertility practices, though it carries several limitations.

First, the inclusion of only three studies limits the available clinical data. This small sample size inherently increases the risk of bias. Furthermore, the geographic restriction of these studies (Iran and China) introduces potential racial and cultural biases that may affect generalizability. Second, not all included studies used identical GnRH protocols for direct comparison. While all included a GnRH antagonist protocol, only two used long and ultra-long protocols, and only one evaluated the short protocol. This discrepancy, along with variations in sample sizes, hinders definitive cross-group comparisons. Finally, we could not definitively conclude whether GnRH therapy directly improved the underlying physical symptoms of adenomyosis. Theoretically, a hypoestrogenic state reduces lesion development. However, none of the included studies quantified adenomyosis metrics (clinical symptoms, myometrial thickness, lesion count, junctional zone thickness) before and after therapy, nor did they comprehensively detail patient management

histories. Thus, we cannot definitively state that the IVF intervention served as primary adenomyosis therapy.

Conclusion

Based on a limited analysis of only three included studies, the Ultra Long GnRH Protocol tentatively suggests a potential therapeutic modality to improve outcomes in patients with adenomyosis. Confirmation through more extensive randomized controlled trials is necessary, especially given the potential for complementary therapies and confounding factors.

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