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Meta-Analysis on the Therapeutic Effectiveness of Dienogest plus GnRH Agonist in Treating Adenomyosis and Its Related Obstetric Risk Factors

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Abstract

Adenomyosis is a chronic gynecological disorder primarily affecting women of reproductive age, with its underlying causes remaining unclear. In clinical settings, gonadotropin-releasing hormone agonists (GnRH-a), often in combination with other medications, are employed to manage mild to moderate cases. This meta-analysis aimed to assess the therapeutic effectiveness of combining dienogest with GnRH-a in treating adenomyosis and to investigate associated obstetric risk factors. A comprehensive literature search identified relevant studies published up to 2024, resulting in 5 studies encompassing 520 patients included in the meta-analysis. Findings indicated that the combination therapy significantly improved visual analogue scale scores, hemoglobin levels, CA-125 levels, and uterine volume compared to monotherapy, without increasing adverse event rates. Furthermore, analysis of 11 studies including 15,015 participants on obstetric outcomes revealed that women with adenomyosis faced higher risks of spontaneous abortion, premature rupture of membranes, preterm birth, small-for-gestational-age infants, and cesarean delivery. These results suggest that dienogest combined with GnRH-a enhances treatment outcomes in adenomyosis while emphasizing the elevated obstetric risks associated with the condition.

Keywords: Risk factors, Adenomyosis, MA, Dienogest, GnRH-a

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Introduction

Adenomyosis is a benign uterine disorder characterized by the growth of endometrial stroma and glands into the myometrium, driven by multiple pathogenic factors [1]. It commonly affects women of reproductive age, presenting with symptoms such as menorrhagia, prolonged menstrual periods, dysmenorrhea, and infertility [2]. While hysterectomy offers a definitive treatment, fertility-preserving therapeutic strategies are essential for women seeking future pregnancies.

Clinically, gestrinone has been frequently used to treat adenomyosis by alleviating dysmenorrhea through estrogen suppression and modulation of cell survival within lesions [3]. However, its efficacy is limited, and side effects are common. Dienogest, a progestogen developed by Jenapharm (Germany), strongly inhibits ovulation and selectively binds to progesterone receptors, reducing endogenous estrogen production and limiting estrogen-driven stimulation of both normal and ectopic endometrial tissue [4, 5]. Peripheral in action and resembling natural progesterone, dienogest is beneficial to endometrial health. Clinical studies indicate that dienogest can effectively relieve dysmenorrhea and control uterine enlargement and endometrial thickening in adenomyosis patients [6]. Nonetheless, dienogest may cause irregular

bleeding, amenorrhea, prolonged menstruation, and mood changes.

GnRH-a, a synthetic decapeptide, binds efficiently to GnRH receptors, suppressing ovarian secretion of estrogen and luteinizing hormone via negative feedback, thereby maintaining a low, sustained estrogen level [7, 8]. This inhibition mitigates estrogen-driven adenomyotic lesions and can enhance endometrial receptivity for embryo implantation, supporting oocyte development and reducing recurrence risk [9, 10]. Prolonged GnRH-a therapy, however, may lead to perimenopausal symptoms, osteoporosis due to hypoestrogenism, and ovarian dysfunction.

In summary, both dienogest and GnRH-a demonstrate therapeutic potential in adenomyosis, yet each carries distinct side effects. To clarify the clinical value of their combination, this study systematically reviewed relevant literature and conducted a meta-analysis to evaluate the efficacy and safety of dienogest plus GnRH-a, while also examining obstetric risk factors associated with adenomyosis, thereby providing guidance for treatment strategies and improving pregnancy outcomes.

Materials and Methods

Selection criteria

This study was approved by the Ethics Committee of Shengzhou People's Hospital.

Inclusion criteria: Clinical controlled studies were considered regardless of allocation concealment or blinding; participants had a clinical diagnosis of adenomyosis, irrespective of race; interventions included dienogest or GnRH-a monotherapy, or dienogest combined with GnRH-a; outcome measures for efficacy analysis included dysmenorrhea VAS score, hemoglobin (Hb), CA-125, uterine volume (UV), and incidence of adverse events (AE); adverse pregnancy outcomes were used as outcome measures in risk factor analyses.

Exclusion criteria: Duplicate publications; literature reviews or meta-analyses; studies with small sample sizes; basic experimental studies; case reports or experience-based reports; studies with unavailable or unextractable data; and articles for which full text could not be obtained.

Search strategy

A combination of subject terms and free-text words was used to retrieve relevant literature. Databases including PubMed and EBbase were searched using terms such as "Dienogest," "Gonadotropin-releasing hormone agonist," "GnRH-a," "Adenomyosis," "Endometriosis," "Endometriose," and "Endometriomas," covering publications up to May 2024, with no language restrictions. Additional searches were conducted using Google Scholar, SCI-HUB, and other search engines.

Screening, data extraction, and quality assessment

Two researchers independently conducted literature screening, data extraction, and quality assessment, with discrepancies resolved through discussion or consultation with a third researcher. Titles and abstracts were first reviewed to exclude obviously irrelevant articles. Full texts of potentially eligible studies were then assessed to determine inclusion in the meta-analysis. Extracted data included study details (title, authors), participant characteristics (sample size), efficacy outcomes (dysmenorrhea VAS score, Hb, CA-125, UV, incidence of AE), and adverse pregnancy outcomes (abortion, premature rupture of membranes [PRM], preterm birth [PTB], small-for-gestational-age [SGA] infants, cesarean section [CS]). Methodological quality was assessed using the Cochrane Collaboration tool, evaluating random sequence generation, allocation concealment, blinding of participants/personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases, classified as "high," "low," or "unclear" risk.

Statistical analysis

Meta-analysis was conducted using RevMan 5.3. Continuous outcomes were expressed as mean difference (MD) with 95% confidence interval (CI), and categorical outcomes as odds ratio (OR) with 95% CI. For risk factor analysis, a random-effects inverse variance model was applied to summarize ORs; log(OR) and standard error (SE) were calculated and combined to obtain pooled OR with 95% CI. Heterogeneity was assessed using I^2 and subgroup analysis; when $I^2 > 50\%$ and $P < 0.10$, sources of heterogeneity were explored. If heterogeneity was statistical but not clinical, the random-effects model (REM) was used; otherwise, the fixed-effects model (FEM) was applied when $I^2 \leq 50\%$ and $P \geq 0.10$. Funnel plots were generated to assess publication bias. Statistical significance was set at $\alpha = 0.05$.

Results and Discussion

Literature screening

A total of 104 articles on dienogest plus GnRH-a for adenomyosis were retrieved. After removing 53 duplicates, 51 articles were screened, with 41 reviews, basic studies, case reports, and conference abstracts excluded, leaving 10 articles for full-text review. Five studies were further excluded due to small sample size, inaccessible full text, or low quality, resulting in 5 studies [11–15] included in the meta-analysis.

For obstetric risk factor analysis, 488 articles were initially retrieved, with 171 duplicates removed, leaving 317 for screening. After excluding 292 reviews, basic studies, case reports, and abstracts, 25 articles were reviewed in full. Fourteen studies were further excluded, and 11 studies

[16–26] were ultimately included for outcome comparison **(Figure 1)**.

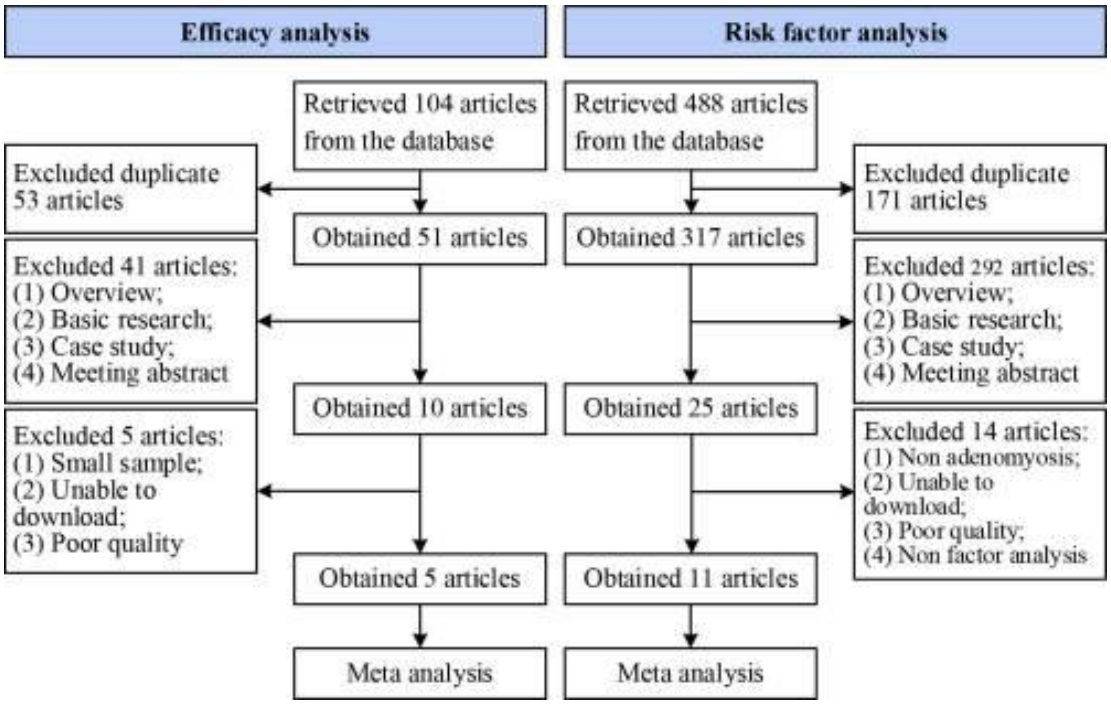

Figure 1. Literature Selection Process

Study characteristics

Table 1 details the characteristics of the five studies included in the meta-analysis, comprising a total of 520 participants, with 234 receiving either dienogest or GnRH-a alone and 286 receiving the combined therapy of dienogest with GnRH-a; outcomes assessed included VAS score for dysmenorrhea, hemoglobin (Hb) levels, CA-125, uterine volume (UV), and incidence of adverse events (AE).

Table 2 summarizes the characteristics of the 11 studies included for analyzing obstetric risk factors, covering 15,015 participants, including 1,481 women with adenomyosis and 13,534 without; all studies were cohort in design, and the evaluated obstetric outcomes included delivery, abortion, premature rupture of membranes (PRM), preterm birth (PTB), small-for-gestational-age (SGA) infants, and cesarean section (CS).

Table 1. Key characteristics of studies evaluating dienogest combined with GnRH agonists versus dienogest or GnRH agonist monotherapy for the treatment of adenomyosis

Author	Year	Combined therapy regimen (Dienogest + GnRH-a)	Control/Monotherapy regimen	Sample size (Combined)	Sample size (Control/Monotherapy)	Main outcome measures
Chan *et al.* [11]	2023	Dienogest 2 mg/day started after completion of 6 months of GnRH-a	Leuprolide 11.25 mg depot, single dose, 6-month duration	44	46	VAS, Hb, CA-125 uterine volume, adverse events
Matsushima *et al.* [12]	2020	Dienogest 2 mg/day initiated after 6 months of GnRH-a therapy	Leuprolide 1.88 mg subcutaneously every 4 weeks for 6 months	15	15	Hb, CA-125, uterine volume, adverse events
Miao *et al.* [13]	2022	Dienogest 2 mg/day started after 4 cycles of GnRH-a (3.75 mg every 4 weeks)	Dienogest 2 mg/day alone	71	52	CA-125, uterine volume, adverse events
Wang *et al.* [14]	2023	Dienogest 1 tablet/day commenced after GnRH-a treatment completion	Goserelin 3.6 mg subcutaneously for 6 cycles	60	60	VAS, CA-125

Zhu *et al*. [15]	2023	Dienogest 2 mg/day continuously + 3–6 injections of GnRH-a	Dienogest 2 mg/day alone	96	61	Hb, CA-125, uterine volume, adverse events

Abbreviations: CA-125 = cancer antigen 125; GnRH-a = gonadotropin-releasing hormone agonist; Hb = hemoglobin; VAS = visual analogue scale (pain score); uterine volume measured by ultrasound or MRI.

Table 2. Key characteristics of studies investigating risk factors associated with adenomyosis

Author	Year	Study design	Case group (with adenomyosis)	Control group (without adenomyosis)	Sample siz (Cases)	Sample size (Controls)	Reported risk factors
Exacoustos *et al.* [16]	2016	Cohort	Women diagnosed with adenomyosis	Healthy women	200	300	Abortion, preterm delivery, small for-gestational-age (SGA) fetuses, cesarean section
Genc *et al*. [17]	2015	Cohort	Adenomyosis	No adenomyosis	327	618	Prior deliveries, abortion
Güzel *et al*. [18]	2015	Cohort	Adenomyosis	Normal uterus	26	22	Prior deliveries, abortion
Hashimoto *et al*. [19]	2018	Cohort	Adenomyosis	No adenomyosis	49	245	Abortion, preterm delivery, SGA fetuses
Joachim *et al*. [20	2023	Cohort	Adenomyosis	No adenomyosis	386	323	Prior deliveries
Juang *et al*. [21]	2007	Cohort	Adenomyosis	No adenomyosis	35	277	Premature rupture of membranes (PROM), preterm birth
Mochimaru *et al* [22]	2015	Cohort	Adenomyosis	No adenomyosis	36	144	Prior deliveries, abortion, PROM, preterm delivery, SGA fetuses, cesarean section
Romanek *et al*. [23]	2010	Cohort	Adenomyosis (with or without other pathology)	Uterine leiomyoma only	135	176	Prior deliveries, abortion, cesarean section
Shin *et al*. [24]	2018	Cohort	Adenomyosis	No adenomyosis	47	8,057	Abortion, preterm delivery, cesarean section
Shinohara *et al*. [25]	2020	Cohort	Adenomyosis	No adenomyosis	61	244	PROM, preterm delivery, SGA fetuses, cesarean section
Trinchant *et al*. [26]	2022	Cohort	Adenomyosis	No adenomyosis	179	3,128	Prior deliveries, abortion, preterm delivery, cesarean section

Abbreviations: PROM = premature rupture of membranes SGA = small for gestational age.

Assessment

Out of the five included studies, one demonstrated selective reporting of outcome measures and was therefore rated as "high risk," while the remaining studies were assessed as having either "low" or "unclear" risk for the evaluated criteria **(Figure 2)**.

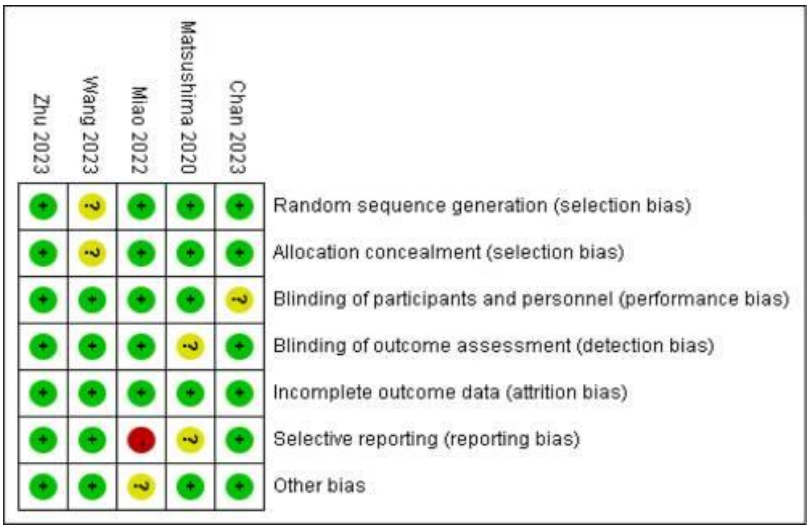

Figure 2. Risk of bias assessment.

Meta-analysis results of dienogest plus GnRH-a in adenomyosis

VAS score

Two to three studies reported VAS scores following treatment with either a single drug or the combination of both drugs. Significant heterogeneity was observed among the studies (I^2 = 100 percent, P < .00001), leading to the use of a random-effects model (REM) for analysis. Subgroup analysis indicated that at 6 months, the VAS score for the combination therapy was significantly lower than that for the single drug (MD = −4.02, 95 percent CI: −6.62 to −1.43, P = .002), whereas no significant difference was found at twelve and eighteen months (P > .05). Overall, the combination therapy resulted in a significantly lower VAS score compared to the single drug (MD = −3.00, 95% CI: −4.47 to −1.52, P < .0001) **(Figure 3)**.

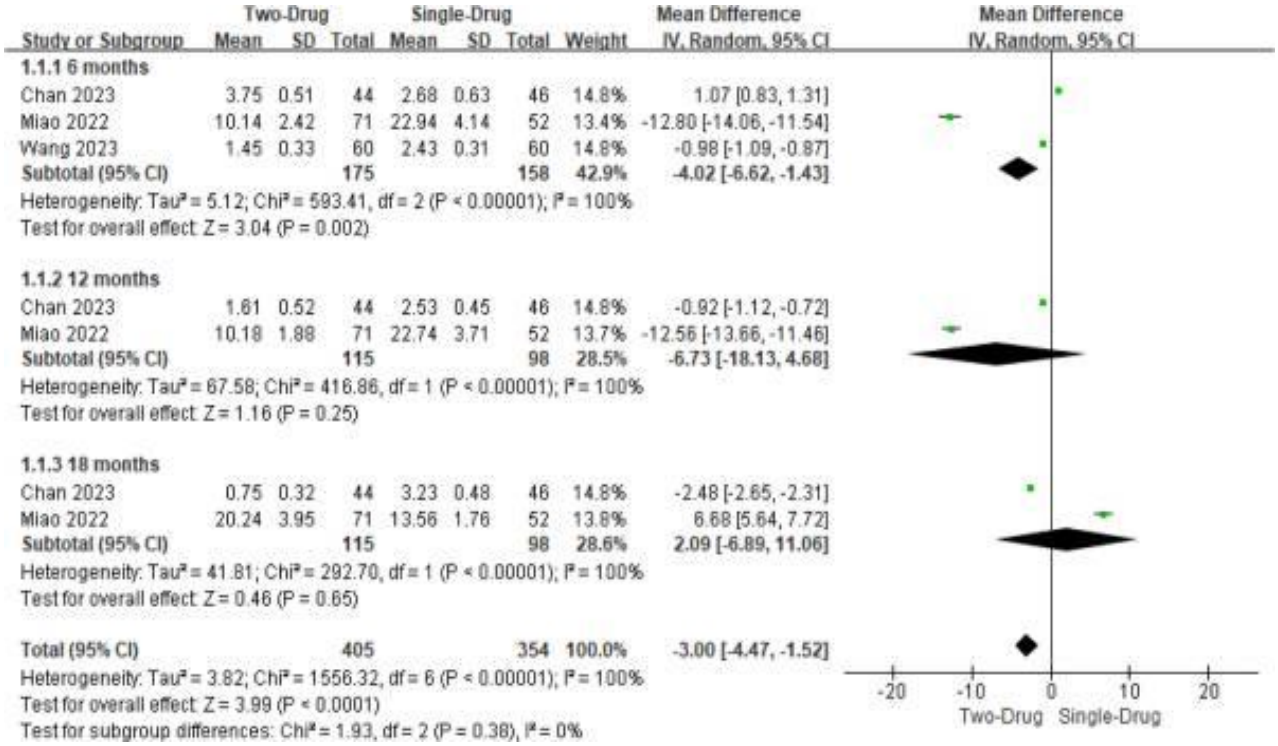

Figure 3. Meta-analysis forest plot (FOP) comparing VAS scores after treatment. MA = meta-analysis, VAS = visual analogue scale.

Hb

Two to three studies reported hemoglobin (Hb) levels following treatment with either a single drug or the combination of both drugs. Moderate heterogeneity was detected (I^2 = 71 percent, P = .001), so a random-effects model (REM) was applied. The analysis showed that at 18 months, Hb levels in the combination therapy group were significantly higher than those in the single-drug group

(MD = 0.74, 95 percent CI: 0.41 to 1.07, P < .0001), whereas no significant differences were observed at 6 and 12 months (P > .05). Overall, there was no significant difference in Hb levels between the two treatment groups (MD = 0.28, 95% CI: −0.20 to 0.76, P = .26) **(Figure 4)**.

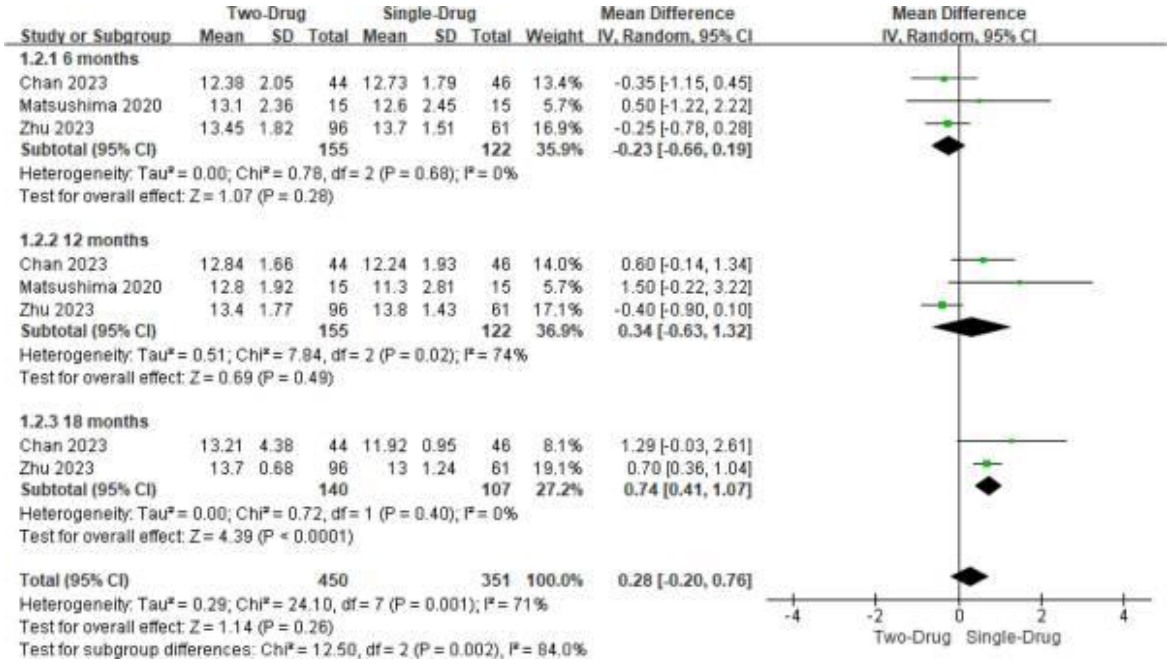

Figure 4. Forest plot (FOP) of meta-analysis comparing Hb levels after treatment. MA = meta-analysis.

CA-125

Two to four studies reported CA-125 levels following treatment. Significant heterogeneity was observed (I^2 = 100 percent, P < .00001), so a random-effects model (REM) was applied. The analysis indicated that at twelve and eighteen months, CA-125 levels in the combination therapy group were significantly lower than in the single-drug group (MD = −12.39, 95 percent CI: −22.53 to −2.25, P = .002; MD = −23.54, 95% CI: −41.27 to −5.80, P = .009), whereas no significant difference was found at 6 months (P > .05). Overall, CA-125 levels did not show a significant difference between the two groups across all time points (MD = −7.68, 95% CI: −16.39 to 1.02, P = .08) **(Figure 5)**.

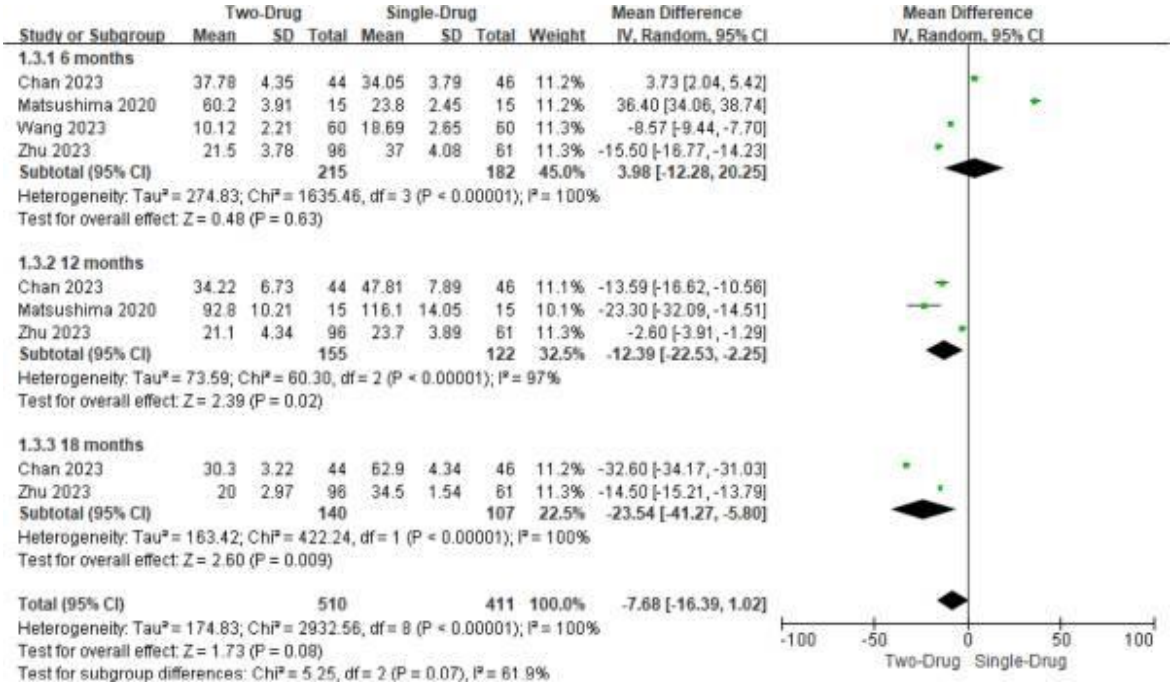

Figure 5. Meta-analysis forest plot (FOP) comparing CA-125 levels after treatment. CA-125 = cancer antigen 125, MA = meta-analysis.

Uterine volume (UV)

Three to four studies reported uterine volume (UV) following treatment. Significant heterogeneity was observed (I^2 = 99 percent, P < .00001), so a random-effects model (REM) was applied. The analysis showed that at 18 months, UV in the combination therapy group was significantly smaller than in the single-drug group (MD = −31.04, 95 percent CI: −48.78 to −13.30, P = .0006), whereas no significant differences were observed at 6 and 12 months (P > .05). Overall, there was no significant difference in UV between the two treatment groups across all time points (MD = −6.91, 95% CI: −33.76 to 19.95, P = .61) **(Figure 6)**.

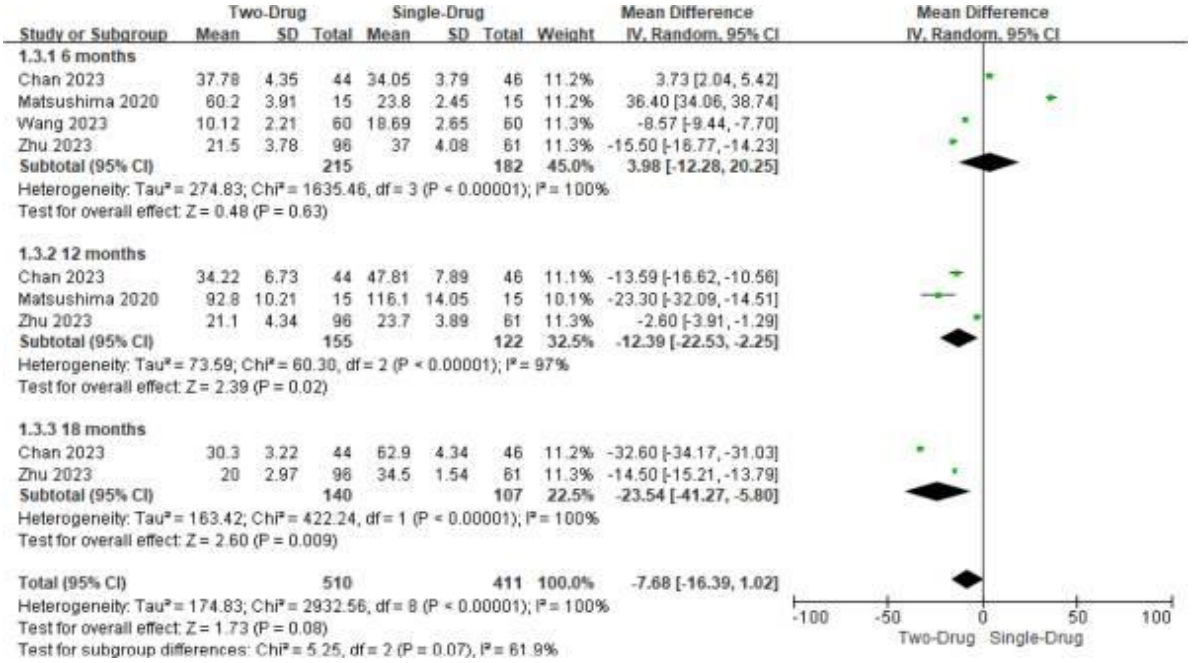

Figure 6. Forest plot (FOP) of meta-analysis comparing uterine volume (UV) after treatment. MA: meta-analysis.

Adverse event rate

Three studies reported adverse events (AEs) after treatment. Moderate heterogeneity was present (I^2 = 56 percent, P = .03), so a random-effects model (REM) was applied. Both subgroup and overall analyses indicated no significant difference in AE occurrence between the combination therapy and single-drug groups (OR = 0.99, 95 percent CI: 0.55–1.78, P = .98) **(Figure 7)**. The most commonly observed AEs were irregular vaginal bleeding, amenorrhea, hot flashes, and mood changes, which are consistent with the known safety profiles of dienogest and GnRH-a, and no serious or unexpected AEs were reported.

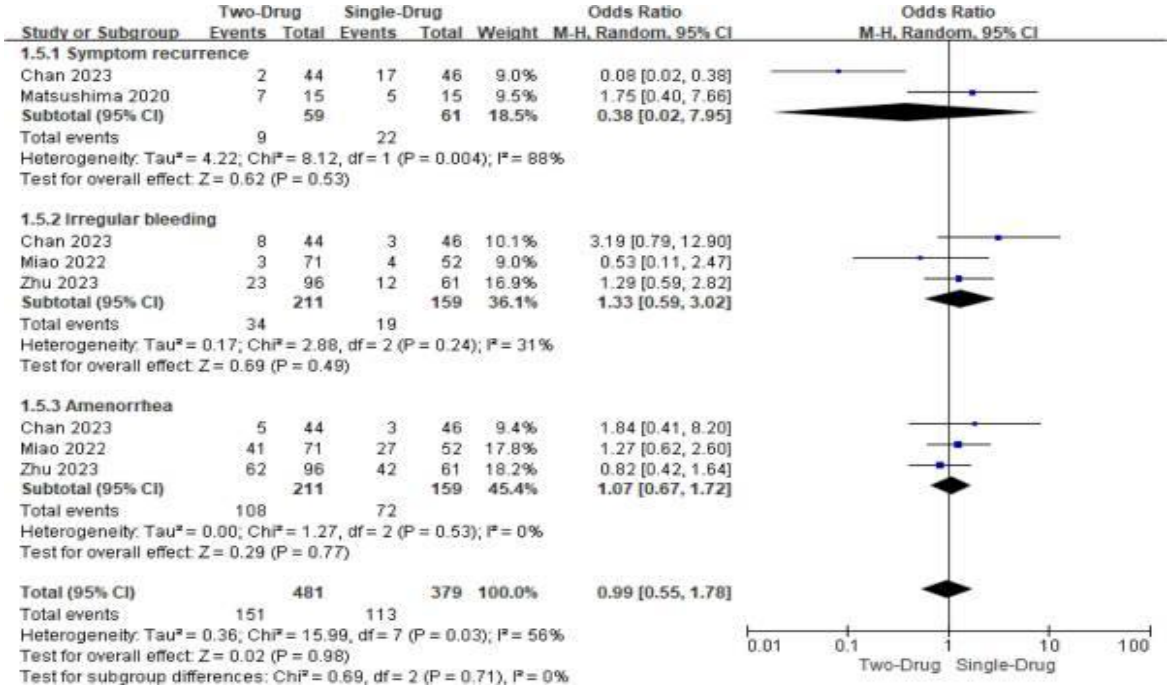

Figure 7. Forest plot (FOP) of meta-analysis comparing adverse event (AE) rates after treatment. AE = adverse event, MA = meta-analysis.

Meta-analysis of risk factors associated with adenomyosis

Delivery history

Six studies examined the association between having a normal delivery and the presence of adenomyosis. Considerable heterogeneity was observed (I^2 = 85 percent, P < .00001), prompting the use of a random-effects model (REM). The meta-analysis indicated no significant difference in the rate of normal deliveries between individuals with adenomyosis and those without (OR = 1.25, 95 percent CI: 0.60–2.63, P = .55) **(Figure 8)**.

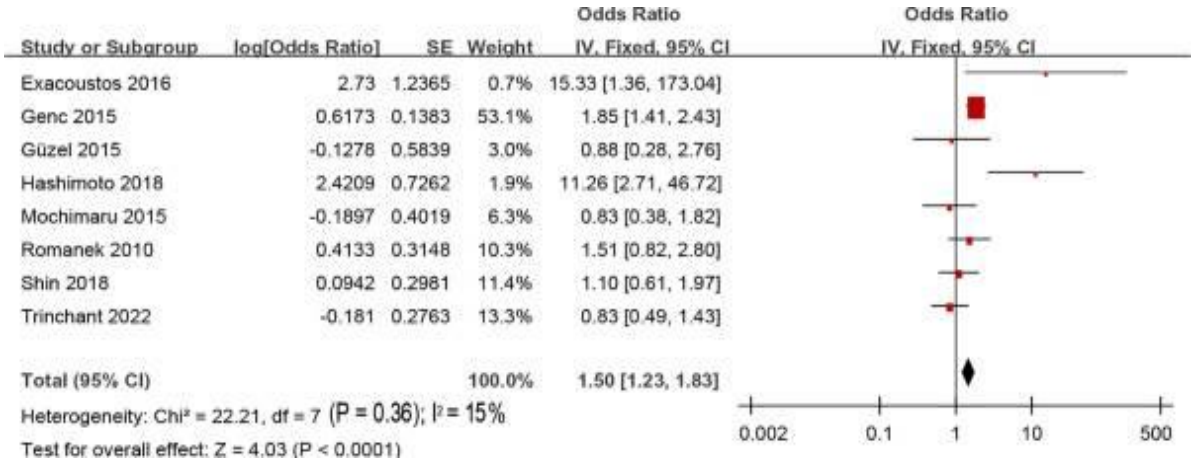

Figure 8. Forest plot (FOP) of meta-analysis examining the association between adenomyosis and normal delivery

Abortion history

Eight studies assessed the link between abortion and adenomyosis, showing low heterogeneity across studies (I^2 = 15 percent, P = .36). Therefore, a fixed-effects model (FEM) was applied. The meta-analysis indicated that individuals with adenomyosis had a significantly higher abortion rate compared to those without adenomyosis (OR = 1.50, 95 percent CI: 1.23–1.83, P < .0001) **(Figure 9)**.

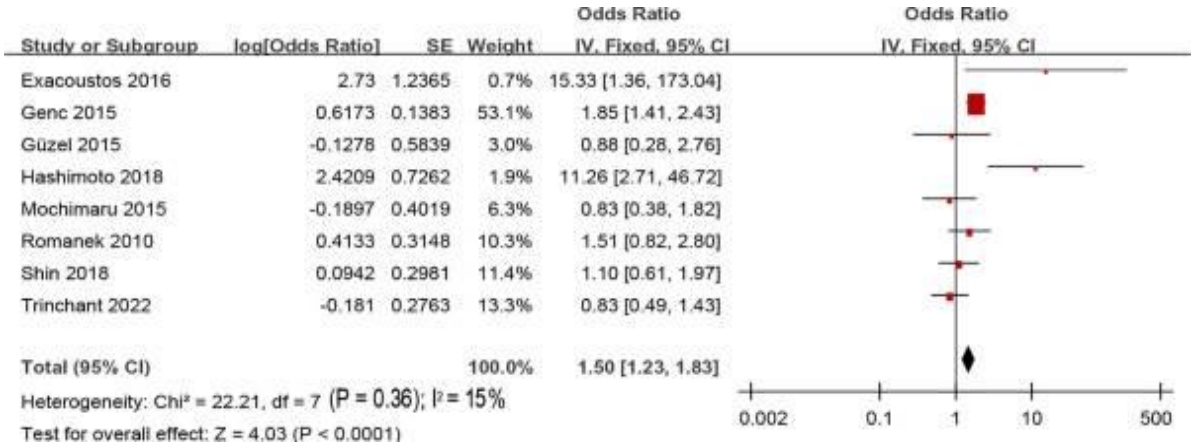

Figure 9. Forest plot (FOP) of meta-analysis examining the association between adenomyosis and abortion.

History of PRM

Three studies investigated the relationship between previous pelvic or reproductive morbidities (PRM) and adenomyosis, with low heterogeneity observed across studies (I^2 = 28 percent, P = .25). A fixed-effects model (FEM) was therefore applied. The meta-analysis demonstrated that individuals with adenomyosis had a significantly higher rate of PRM compared to those without adenomyosis (OR = 2.44, 95 percent CI: 1.30–4.59, P = .005) **(Figure 10)**.

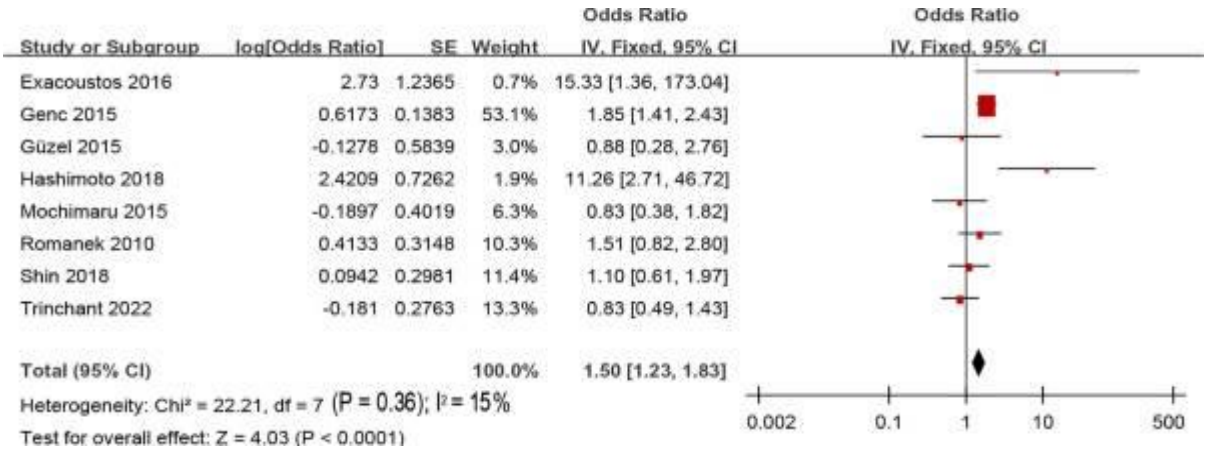

Figure 10. Forest plot (FOP) of meta-analysis exploring the association between adenomyosis and premature rupture of membranes (PRM)

History of PTB

A total of seven studies investigated the connection between adenomyosis and prior occurrences of preterm birth (PTB), revealing substantial variability among results (I^2 = 79 percent, P < .0001). Using a random-effects model to account for this heterogeneity, the analysis showed that individuals diagnosed with adenomyosis had a significantly higher likelihood of having experienced PTB compared with those without the condition (OR = 2.34, 95 percent CI: 1.22–4.50, P = .01) **(Figure 11)**.

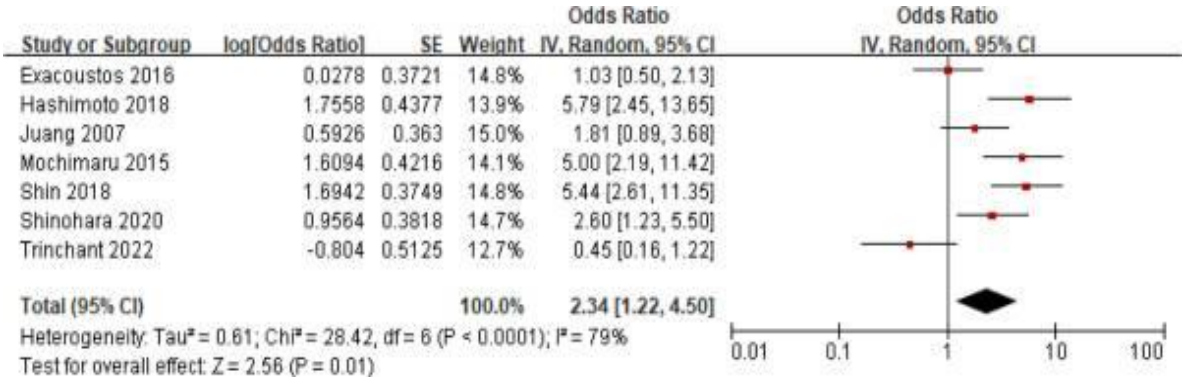

Figure 11. Forest plot (FOP) of meta-analysis assessing the association between adenomyosis and preterm birth (PTB).

History of SGA fetuses

Four studies evaluated the link between adenomyosis and the occurrence of small-for-gestational-age (SGA) fetuses, with low heterogeneity across the studies (I^2 = 21 percent, P = .28). A fixed-effects model (FEM) was applied for analysis. The pooled results indicated that women with adenomyosis had a significantly higher risk of delivering SGA fetuses compared to women without the condition (OR = 2.44, 95 percent CI: 1.54–3.87, P = .0001) **(Figure 12)**.

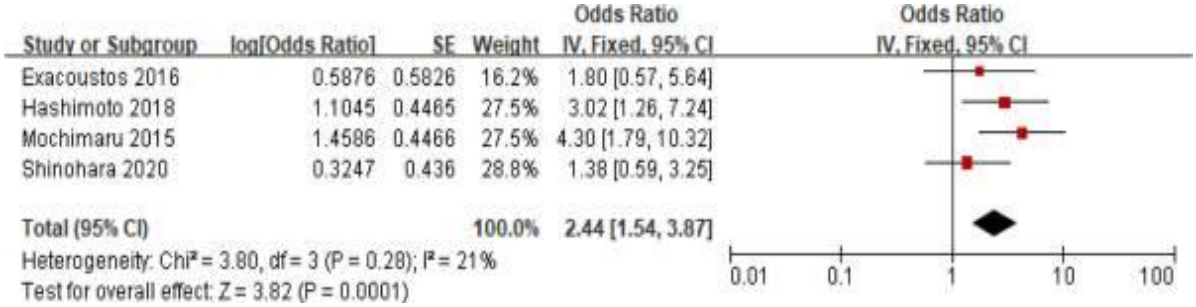

Figure 12. Forest plot (FOP) of meta-analysis examining the association between adenomyosis and SGA fetuses. MA: meta-analysis, SGA: small for gestational age.

History of cesarean section (CS)

Six studies explored the relationship between adenomyosis and cesarean section (CS), with no substantial heterogeneity detected across studies (I^2 = 48 percent, P = .11). A fixed-effects model (FEM) was employed. The analysis showed that women with

adenomyosis had a significantly higher likelihood of having undergone CS compared to women without adenomyosis (OR = 1.37, 95 percent CI: 1.09–1.72, P = .007) **(Figure 13)**.

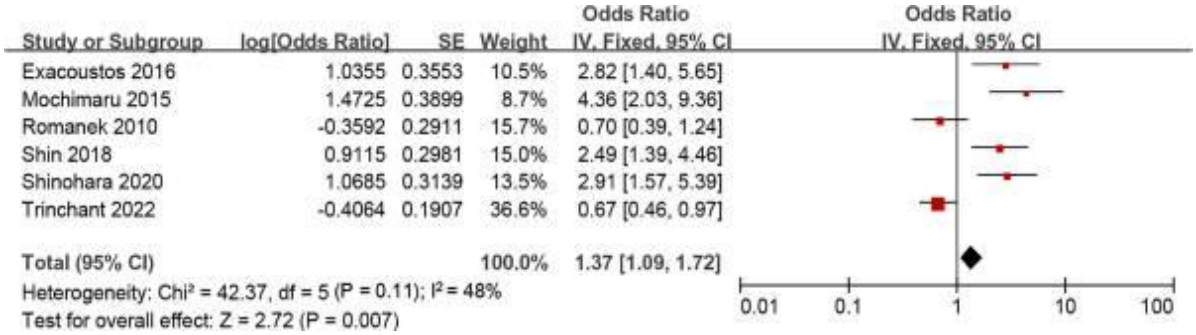

Figure 13. Forest plot (FOP) of meta-analysis assessing the association between adenomyosis and cesarean section (CS). CS: cesarean section

Publication bias (PB)

To evaluate publication bias, funnel plots were generated for selected outcomes, including adverse events (AEs) following dienogest plus GnRH-a treatment in adenomyosis and the association between PTB and adenomyosis. The standard errors (SEs) of the included studies were relatively low, and the data points were symmetrically distributed around the vertical line, with only a few studies falling outside the 95% confidence interval. These observations suggest that the included studies exhibited minimal publication bias **(Figures 14 and 15)**.

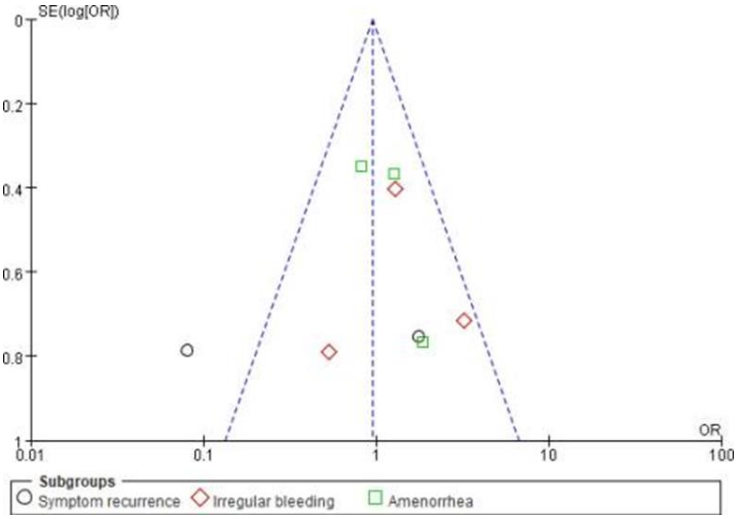

Figure 14. Funnel plot (FUP) from the meta-analysis assessing adverse events (AE) after treatment.

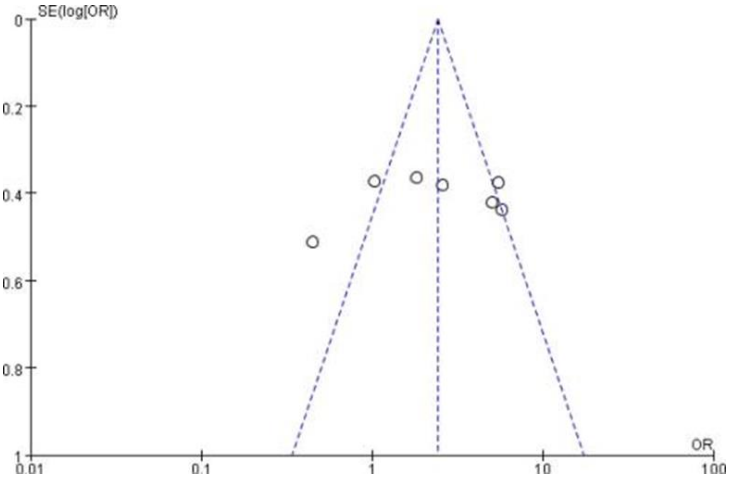

Figure 15. Funnel plot (FUP) from the meta-analysis evaluating preterm birth (PTB)

Adenomyosis is a benign uterine disorder characterized by the invasion of endometrial glands and stroma into the myometrium, often accompanied by smooth muscle hyperplasia [27, 28]. Its precise etiology remains unclear, and the condition is increasingly observed in younger women, highlighting the importance of effective treatment strategies. Although both dienogest and GnRH-a are used in clinical practice, the added benefit of combining these two agents requires further evidence. To address this, the present meta-analysis systematically evaluated the efficacy and safety of dienogest plus GnRH-a in patients with adenomyosis.

Dysmenorrhea is the predominant symptom of adenomyosis, typically manifesting as progressively worsening menstrual pain, heavier menstrual flow, and prolonged periods [29]. This meta-analysis demonstrated that combination therapy with dienogest and GnRH-a significantly reduced dysmenorrhea scores compared to monotherapy, indicating a more effective alleviation of pain. Dienogest, acting similarly to endogenous progestogens, stabilizes endometrial tissue by interacting with progesterone derivatives and ethylene nortestosterone, thereby mitigating pain and improving clinical symptoms [30]. GnRH-a contributes by suppressing cytokine and immune factor release in the peritoneal environment, further reducing dysmenorrhea [31].

Additionally, this meta-analysis found that 18 months of combination therapy led to a significant increase in hemoglobin (Hb) levels and a decrease in CA-125 compared to single-agent treatment. Severe adenomyosis often results in dysfunctional endometrium, excessive menstrual bleeding, and anemia, reflected by low Hb. CA-125, a mucin-like glycoprotein primarily found in mesothelial tissues, is abnormally elevated in the peripheral blood of patients with adenomyosis and can be used to assess uterine volume (UV) and residual lesions after surgery [32, 33]. The reduction of CA-125 by combined therapy may help limit lesion progression and lower recurrence risk.

Adenomyosis also causes uterine enlargement and disrupts contractility due to invasion of endometrial tissue into the myometrium [34, 35]. Previous studies suggested that dienogest alone alleviates dysmenorrhea and pelvic pain but has limited effect on UV [36]. In contrast, our findings indicate that combining dienogest with GnRH-a significantly reduces UV after 18 months, likely due to GnRH-a's modulation of the hypothalamic-pituitary-gonadal axis [37, 38]. This reduction in UV can improve dysmenorrhea and enhance the likelihood of successful embryo implantation.

Regarding safety, overall adverse event (AE) rates did not differ between combination therapy and monotherapy. Reported AEs were generally mild to moderate, including irregular bleeding, amenorrhea, vasomotor symptoms, and mood changes, consistent with the known pharmacology of the drugs. These findings suggest that adding GnRH-a does not increase toxicity; however, the small number of studies and limited AE reporting prevent definitive conclusions, highlighting the need for larger trials with standardized safety assessments.

Adenomyosis is also associated with reproductive challenges. In this meta-analysis, patients with adenomyosis had higher rates of abortion, PRM, PTB, and SGA fetuses compared to women without adenomyosis. These results align with prior findings showing increased miscarriage risk in affected women [39]. Impaired myometrial function, increased thickness and rigidity, and elevated intrauterine pressure can contribute to PRM or spontaneous PTB, while uterine enlargement and elevated prostaglandin secretion may further promote premature contractions [40, 41]. The higher incidence of SGA fetuses may result from factors such as uterine wall damage, placental insufficiency, hormonal imbalances, gestational diabetes, hypertension, multiple pregnancies, or prior abortions, with increased uterine volume potentially restricting fetal growth. Additionally, cesarean section (CS) scars may facilitate endometrial invasion into the myometrium, promoting adenomyosis development [42]. These findings underscore the need for careful consideration of reproductive history, including abortion, PTB, and CS, in future clinical research on adenomyosis.

Adenomyosis has been linked to adverse pregnancy outcomes through multiple pathophysiological pathways. The condition is marked by endometrial glands and stroma infiltrating the myometrium, along with smooth muscle proliferation and persistent inflammation. These changes can compromise the uterine lining's receptivity, alter normal myometrial contractions, and raise intrauterine pressure, which may lead to cervical insufficiency, premature membrane rupture, preterm contractions, and abnormal placental implantation, ultimately increasing the risk of miscarriage, preterm delivery, and growth-restricted infants. Structural remodeling and uterine wall injury associated with adenomyosis may also predispose women to cesarean sections. Treatment combining dienogest and GnRH-a may counter some of these effects by suppressing estrogen-driven tissue proliferation, shrinking uterine lesions, enhancing endometrial receptivity, and reducing local inflammation, suggesting potential benefits for fertility and pregnancy outcomes, though mechanistic and prospective clinical studies are still needed to confirm this.

Beyond statistical results, the clinical implications are noteworthy. Combination therapy produced a meaningful reduction in dysmenorrhea, which could translate into less reliance on pain medication and better daily function. Small improvements in hemoglobin may alleviate anemia-

related fatigue and decrease the need for iron therapy. Long-term reductions in CA-125 and uterine size indicate not only regression of disease activity but also potential improvements in fertility and lower recurrence risk. These advantages were achieved without a rise in adverse events, demonstrating a favorable balance of efficacy and safety and suggesting that dienogest plus GnRH-a can reduce treatment burden while improving quality of life.

Several limitations should be considered. Most included studies were observational, single-center, non-randomized, and limited in sample size; only five studies with 520 participants contributed to efficacy analysis. The lack of large-scale RCTs weakens causal inference and increases susceptibility to selection and publication bias. Study designs, treatment regimens (dosage, sequence, and duration), follow-up periods, and patient characteristics varied considerably, contributing to heterogeneity and limiting the generalizability of the findings. Outcome measures such as VAS, hemoglobin, CA-125, and uterine volume mainly reflect pain and biological changes, but they do not fully capture overall therapeutic benefit or patient-reported outcomes, which were inconsistently reported. Additionally, the small number of studies reduces the reliability of publication bias detection.

Considering these limitations, the results provide theoretical guidance but are not universally applicable to clinical practice. They may be most relevant for women with adenomyosis seeking fertility preservation, experiencing moderate-to-severe symptoms, or presenting with larger uterine volumes and elevated CA-125, where longer treatment may offer greater benefit. Conversely, caution is advised in women planning pregnancy, perimenopausal patients, or those with comorbidities, as the risk–benefit profile remains unclear. Future multicenter, randomized trials with standardized treatment protocols, longer follow-up, and inclusion of patient-reported outcomes are necessary to confirm these findings and determine their broader applicability.

Conclusion

The evidence indicates that combining dienogest with GnRH-a can reduce dysmenorrhea, improve hemoglobin levels, and decrease uterine size in adenomyosis patients. Prior miscarriage, preterm birth, and cesarean delivery emerged as disease-associated risk factors for adverse pregnancy outcomes. Nonetheless, evidence regarding long-term safety and efficacy is limited due to short follow-up periods and inconsistent reporting of side effects. These findings should therefore be interpreted cautiously, and future large-scale studies with extended follow-up are needed to establish sustained benefits and clarify potential long-term risks.

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