Effect of GnRH-a pretreatment before frozen-thawed embryo transfer on pregnancy outcome of adenomyosis-associated infertile patients with 56 cm^3 ≤ uterine volume ≤100 cm^3

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Background: Whether gonadotrophin-releasing hormone agonist (GnRH-a) pretreatment before transferring frozen-thawed embryos (FETs) could improve the clinical outcome of adenomyosis-associated infertile patients with 56 cm^3 ≤ uterine volume ≤100 cm^3 is unclear.

Methods: Adenomyosis patients who underwent *in vitro* fertilization and frozen embryo transfers from January 2009 to December 2019 with 56 cm^3 ≤ uterine volume ≤100 cm^3 were included in this retrospective cohort study. The subjects were divided into two groups (GnRH-a treatment group *vs.* GnRH-a-free group). The effect of GnRH-a treatment before FET on pregnancy outcomes was explored by univariate and multivariate analysis. In the GnRH-a treatment group, uterine volume before and after GnRH-a pretreatment was also compared by *t*-tests.

Results: A total of 186 patients undergoing 263 cryopreserved embryo transfer cycles were included. There was no significant difference in terms of the clinical pregnancy rate between patients in the GnRH-a treatment group (24/45, 53.3%) and the GnRH-a-free group (86/218, 39.4%) (P=0.098). The miscarriage rate in the GnRH-a treatment group (3/24, 12.5%) was significantly lower than that in the GnRH-a-free group (32/86, 37.2%) (P=0.044). The live birth rate in the GnRH-a treatment group (21/45, 46.7%) was significantly higher than that in the GnRH-a-free group (54/218, 24.8%) (P=0.009). However, the uterine volume did not change significantly before (82.0±13.4 cm^3) or after GnRH-a treatment (79.3±14.0 cm^3), with a P=0.123.

Conclusions: GnRH-a pretreatment before FET reduced the miscarriage rate and improved the live birth rate among infertile women with adenomyosis whose uterine volume was 56–100 cm^3.

Keywords: Gonadotrophin-releasing hormone agonist (GnRH-a); uterine volume; adenomyosis; infertility

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Introduction

Uterine adenomyosis is characterized by endometrial glands in the myometrium, which affects 20% of reproductive age women (1,2). Adenomyosis is clinically characterized by dysmenorrhea, dyspareunia, abnormal uterine bleeding, and subfertility. Primary treatments for adenomyosis-associated infertility include medical treatment, surgical treatment, and *in vitro* fertilization-embryo transfer (IVF-ET).

Existing studies support gonadotrophin-releasing hormone agonist (GnRH-a) treatment to improve pregnancy outcomes in adenomyosis-associated infertile patients. Younes G published a meta-analysis that showed that treatment with GnRH-a increases the spontaneous pregnancy rate in women with adenomyosis and concluded that pretreatment with long-term GnRH-a could be beneficial (3). One reason why GnRH-a treatment improves pregnancy outcomes in adenomyosis-associated infertile patients may be that it reduces the uterine volume. Matsushima T included women with adenomyosis diagnosed by magnetic resonance imaging and discovered that GnRH-a treatment could significantly reduce the uterine volume from 307.4±230.1 to 177.9±142.1 cm^3 ($P<0.001$) (4). Lethaby conducted a review that demonstrated that preoperative GnRH-a reduced the uterine and fibroid volume (5). However, we do not know whether GnRH-a is useful for adenomyosis-associated infertile patients with different uterine sizes.

An enlarged uterus is an important characteristic of adenomyosis and it is used as one of the diagnostic criteria of adenomyosis. The volume of the uterus is calculated according to the following formula: long diameter × width diameter × anteroposterior diameter × π/6 (6). The study of Sheth showed that the normal uterine volume range was 15–56 cm^3 (7). Previous studies by our research group have demonstrated an influence of uterine volume on pregnancy outcome in adenomyosis. We included a total of 158 patients with adenomyosis, and found that adenomyosis patients whose uterine volume exceeded 100 cm^3 before transferring frozen-thawed embryos (FETs) had an increased risk of miscarriage (8). Therefore, we recommend reducing the uterine volume to less than 100 cm^3 before FET. However, there is no clear conclusion about whether it is necessary to use GnRH-a treatment for patients whose uterine volume is less than 100 cm^3. Therefore, in this study, we included adenomyosis-associated infertile patients with a uterine volume less than 100 cm^3 to explore whether GnRH-a pretreatment could improve the clinical outcome of FET.

We present the following article in accordance with the STROBE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-21-6247/rc).

Methods

Study design and patients

This was a retrospective cohort study of adenomyosis patients with 56 $cm^3 \leq$ uterine volume $\leq$100 cm^3 who underwent IVF and FET at the Reproductive Center of Peking University Third Hospital from January 2009 to December 2019. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Review Committee of Peking University Third Hospital (No. LM2021243), and individual consent for this retrospective analysis was waived.

The inclusion criteria were: adenomyosis was diagnosed by transvaginal ultrasound scans (TVS) (9); 56 $cm^3 \leq$ uterine volume $\leq$100 cm^3; age $\leq$45 years old at the time of commencing FET; regular menstrual cycle; underwent FET; and cooperated with postoperative follow-up by telephone or clinic visit. The exclusion criteria were: patients with other endocrine severe diseases, immune diseases, and tumors; complicated with abnormal uterine cavities, such as intrauterine adhesion, submucosal leiomyoma, or ≥5.0 cm in diameter leiomyoma; with abnormal chromosomes in either partner; pregnancy outcome after FET was unknown.

Ultrasound measurement and calculation of uterine volume

All TVSs were performed by two highly skilled radiologists. The main criteria for sonographic diagnosis of adenomyosis included a globular uterus or asymmetric myometrial thickening; heterogeneous myometrium, with thin "Venetian blind" shadows between areas of increased echogenicity; myometrial cysts; indistinctness of the margins of the endometrium and echogenic linear striations; and nodules extending from the endometrium into the myometrium (10). TVS was conducted before GnRH-a pretreatment and 28 days after the last GnRH-a injection (before commencing the FET cycle) for patients with GnRH-a pretreatment. For patients without GnRH-a pretreatment, TVS was conducted before commencing the FET cycle. The volume of the uterus was calculated by using a geometric formula for a prolate ellipsoid volume:

long diameter × width diameter × anteroposterior diameter × π/6 (6). Furthermore, the type of adenomyosis was divided into focal and diffuse according to the adenomyotic lesions. Focal adenomyosis (including adenomyoma) is classified when typical ultrasonographic adenomyotic signs are circumscribed in aggregates and surrounded by normal myometrium. Diffuse adenomyosis is classified when typical alterations at TVS spread throughout the myometrium (11).

Frozen-thawed embryo transfer and grouping method

In our reproductive center, clinicians always choose GnRH-a treatment for infertility patients with adenomyosis with a large uterine volume (generally those with a uterine volume greater than 8 weeks of gestation). For infertile patients with adenomyosis with a smaller uterine volume, the decision to pretreat with or without GnRH-a is a combination of different clinicians' experience as well as the patient's wishes and the patient's schedule. Some patients desire direct embryo transplantation and refuse GnRH-a pretreatment, while others desire GnRH-a pretreatment followed by transplantation. According to whether patients had GnRH-a pretreatment before the FET cycle, this study divided the FET cycles into two groups: (I) the GnRH-a treatment group and (II) the GnRH-a-free group. Patients in the GnRH-a treatment group were injected subcutaneously with long-acting GnRH-a (triptorelin acetate for injection, Ipsen, French, 3.75 mg) for 3 months, starting from the 1st day to the 5th day of menstruation, once per 28 days. However, some patients wanted to undergo embryo transfer as soon as possible, and they were pretreated with GnRH-a for less than 3 months. Endometrial preparation was started 28 days after the last GnRH-a injection with daily estradiol 4–6 mg, and progesterone was added when the thickness of the endometrium reached 8 mm. After 5–7 days of progesterone treatment, one or two embryos were transferred into the uterus. The quality of the embryos was evaluated by the number and regularity of the blastomeres and the degree of embryonic fragmentation and graded according to the Istanbul Consensus Workshop on Embryo Assessment criteria (12). A natural cycle was applied for GnRH-a-free patients.

Clinical data and definitions

The pregnancy outcomes collected included clinical pregnancy rate, miscarriage rate and live birth rate. Clinical pregnancy denoted the presence of at least one intrauterine gestational sac observed by ultrasonography 30 days after embryo transfer. Miscarriage was defined as a loss of clinical pregnancy before 24 weeks of gestation. Live birth was defined as delivery of any viable infant at 24 weeks or more of gestation during the FET cycles. In addition, the following information was also collected: maternal age, paternal age, primary infertility/secondary infertility, duration of infertility, gravidity times, parity times, adenomyotic lesions (diffuse/focal), uterine volume before GnRH-a pretreatment and FET, body mass index, anti-Müllerian hormone, follicle-stimulating hormone, endometrial thickness, number of embryos transferred, and transferred embryo type (cleavage embryo/blastocyst).

Statistical analysis

Patient characteristics are presented as the mean ± standard deviation (SD) for continuous variables and frequency and percentages for categorical variables. Comparisons between ratios were performed using the chi-square test or Fisher's exact test. Continuous variables were analyzed by *t*-tests or nonparametric tests. Logistic regression models were used to estimate the effect of GnRH-a pretreatment prior to FET on clinical outcomes. In the GnRH-a treatment group, uterine volume before and after GnRH-a pretreatment was also compared by *t*-tests. $P<0.05$ was considered statistically significant. Analysis was performed using the Statistical Package for Social Sciences (SPSS), version 25.0 (IBM, Armonk, New York, USA).

Results

According to the standards described above, a total of 186 patients undergoing 263 cryopreserved embryo transfer cycles were included in this analysis. The clinical pregnancy rate was 41.8% (110/263) among 263 frozen-thawed embryo transfer (FET) cycles. The miscarriage rate was 31.8% (35/110) among the 110 cycles obtaining a clinical pregnancy. The live birth rate was 28.5% (75/263).

Of the 263 FET cycles, 218 (82.9%) cycles were not treated with GnRH-a, and 45 (17.1%) cycles were treated with GnRH-a. In the GnRH-a treatment group, patients with adenomyosis were pretreated with 1-3 GnRH-a injections before FET (every 28 days): the percentages of cycles with one, two and three GnRH-a injections before FET were 4/45 (8.9%), 15/45 (33.3%) and 26/45 (57.8%), respectively. Comparison results between the GnRH-a treatment group and the GnRH-a-free group are shown

Table 1 Baseline characteristics were balanced between GnRH-a treatment group and GnRH-a-free group

Characteristics	GnRH-a treatment, n=45 cycles	GnRH-a-free, n=218 cycles	P value
Maternal age (years), mean ± SD	33.5±3.7	34.8±4.7	0.087
Paternal age (years), mean ± SD	35.2±5.2	36.7±6.0	0.121
Infertility type (%)			0.098
Primary infertility	23/45 (51.1%)	82/218 (37.6%)	
Secondary infertility	22/45 (48.9%)	136/218 (62.4%)	
Duration of infertility (years), median (IQR)	3 (2, 6)	4 (2, 8)	0.289
Gravidity times, median (IQR)	0 (0, 2)	1 (0, 2)	0.265
Parity times, median (IQR)	0 (0, 0)	0 (0, 0)	0.093
Uterine volume (cm^3), mean ± SD	81.3±13.1	78.9±11.7	0.220
Adenomyotic lesions (%)			0.145
Diffuse	31/45 (68.9%)	172/218 (78.9%)	
Focal	14/45 (31.1%)	46/218 (21.1%)	
BMI (kg/m^2), mean ± SD	23.9±3.9	23.0±4.1	0.184
AMH (ng/mL), mean ± SD	3.36±2.6	3.50±2.9	0.873
FSH (mIU/mL), mean ± SD	6.52±1.5	6.53±2.2	0.985
Endometrial thickness (mm), mean ± SD	10.0±2.2	10.0±1.7	0.964
No. of embryos transferred, mean ± SD	1.48±0.6	1.49±0.6	0.852
Transferred embryo (%)			0.475
Cleavage embryo	11/45 (24.4%)	68/218 (31.2%)	
Blastocyst	34/45 (75.6%)	150/218 (68.8%)	
Clinical pregnancy rate (%)	24/45 (53.3%)	86/218 (39.4%)	0.098*
Miscarriage rate (%)	3/24 (12.5%)	32/86 (37.2%)	0.025*
Live birth rate (%)	21/45 (46.7%)	54/218 (24.8%)	0.006*

*, P value of univariate analysis. GnRH-a, gonadotrophin-releasing hormone agonist; SD, standard deviation; IQR, interquartile range; BMI, body mass index; AMH, anti-Müllerian hormone; FSH, follicle-stimulating hormone.

in *Table 1*, indicating that the baseline characteristics were balanced between the two groups. No significant difference was observed in maternal age, paternal age, primary infertility/secondary infertility, duration of infertility, gravidity times, parity times, adenomyotic lesions (diffuse/focal), uterine volume, body mass index, anti-Müllerian hormone, follicle-stimulating hormone, endometrial thickness, number of embryos transferred, or transferred embryo (cleavage embryo/blastocyst) between the two groups (see *Table 1*).

In terms of clinical pregnancy, GnRH-a pretreatment did not improve the clinical pregnancy rate of adenomyosis-associated infertile women with 56 $cm^3 \leq$ uterine volume $\leq$100 cm^3 (P>0.05), as shown in *Table 1*. There was no significant difference in terms of the clinical pregnancy rate between patients in the GnRH-a treatment group (24/45, 53.3%) and the GnRH-a-free group (86/218, 39.4%) (P=0.098).

In terms of miscarriage, univariate analysis and logistic regression analysis demonstrated that GnRH-a treatment was closely related to the miscarriage outcome. The miscarriage rate in the GnRH-a treatment group (3/24, 12.5%) was significantly lower than that in the GnRH-a-free group (32/86, 37.2%) (P=0.044), as shown in *Table 2*.

Table 2 Comparison of miscarriage rate and live birth rate between GnRH-a treatment and GnRH-a-free groups with logistics regression

	OR	95% CI	P value
Miscarriage rate	0.261	0.071–0.964	0.044[#]
Live birth rate	2.453	1.252–4.808	0.009[#]

[#], adjusted by maternal age, infertility type. GnRH-a, gonadotrophin-releasing hormone agonist; OR, odds ratio; CI, confidence interval.

Table 3 Changes of uterine volume before and after GnRH-a treatment in the GnRH-a treatment group

	Before	After	P value
Uterine volume (cm^3), mean ± SD	82.0±13.4	79.3±14.0	0.123

GnRH-a, gonadotrophin-releasing hormone agonist; SD, standard deviation.

In terms of live births, univariate and multivariate analysis showed that GnRH-a treatment was closely related to the live birth rate. The live birth rate in the GnRH-a treatment group (21/45, 46.7%) was significantly higher than that in the GnRH-a-free group (54/218, 24.8%) (P=0.009), as shown in *Table 2*.

In addition, for the GnRH-a treatment group, changes in uterine volume before and after GnRH-a treatment were analyzed by *t*-tests. In the GnRH-a treatment group, the uterine volume did not change significantly before (82.0±13.4 cm^3) or after GnRH-a treatment (79.3±14.0 cm^3), with a P=0.123, as shown in *Table 3*.

Discussion

In our previous study, adenomyosis patients with a larger uterine volume (>100 cm^3) before FET had an increased risk of miscarriage and a decreased live birth rate. This study focused on the value of GnRH-a in women with adenomyosis whose uterine volume were 56–100 cm^3 before FET. The results showed that GnRH-a pretreatment is beneficial to reduce the miscarriage rate and increase the live birth rate of FET even for adenomyosis patients with uterine volume below 100 cm^3.

A meta-analysis found that implantation, clinical pregnancy per cycle, clinical pregnancy per embryo transfer, ongoing pregnancy, and live birth were significantly lower and that the miscarriage rate was higher in women with adenomyosis than in those without adenomyosis (3). The abnormal uterine conditions in adenomyosis account for this effect, including an enlarged uterine cavity, dysperistalsis of the uterus resulting in impaired sperm transport (13), the chronic inflammatory condition caused by infiltration of ectopic endometrial glands (14), the increased estrogen in endometrium caused by the overexpression of aromatase P450 (15), and changes of endometrial receptivity related molecules, such as osteopontin, integrin β3, leukemia-inhibiting factor, and the HOXA-10 gene during the implantation window (16).

Some research has shown focal adenomyosis excision leads to increased pregnancy rates (17,18). A few authors have also reported that surgery for diffuse adenomyosis effectively reduces the uterine volume, but some studies have reported uterine ruptures during pregnancy after surgery (19,20). Compared with surgery, GnRH-a is certainly less invasive and more practical.

A recent retrospective study reported that the use of long-acting GnRH-a could significantly reduce the miscarriage rate of FET cycles for patients with adenomyosis (21). A systematic review showed that a significantly higher proportion of women with adenomyosis with GnRH-a pretreatment plus hormone preparation had live births compared to those treated with hormone preparation alone (22). Our results showed that the use of GnRH-a reduced the miscarriage rate and increased the live birth rate of FET among women with adenomyosis, which is consistent with previous studies. GnRH-a treatment can suppress the hypothalamus-pituitary-ovarian axis, induce a hypoestrogenic effect and indirectly reduce the uterine size as well as relieve symptoms (16). Interestingly, our study found that GnRH-a treatment did not improve pregnancy outcomes by reducing the uterine volume, suggesting that GnRH-a treatment may improve pregnancy outcomes in other ways. First, GnRH receptors are present in adenomyotic tissue (3), and GnRH-a induces apoptosis of endometrial cells and suppresses the development of ectopic lesions. Second, GnRH-a reduces the inflammatory reaction and angiogenesis (23). Third, the downregulation effect of GnRH-a may play a direct immunomodulatory role in disrupting the Th17/Treg imbalance and then improving endometrial receptivity (24).

Niu and colleagues found that the use of long-term GnRH-a before FET significantly improved the clinical pregnancy rate among patients with adenomyosis (21). Another retrospective study showed that FET following GnRH-a pretreatment increased the pregnancy rate

in patients with adenomyosis (16). Other studies have also reported increased pregnancies in the IVF/intracytoplasmic sperm injection (ICSI) cycle following GnRH-a treatment in infertile women with adenomyosis. We found that GnRH-a did not affect the clinical pregnancy rate of FET. The reason may be that our study only included patients with mild to moderate adenomyosis and excluded women with severe adenomyosis, resulting in a non-obvious benefit of GnRH-a in increasing clinical pregnancy rates.

Our study is the first to demonstrate the influence of GnRH-a pretreatment before FET on the clinical outcome of adenomyosis patients whose uterine volume is 56 cm^3-100 cm^3, and we have identified that GnRH-a is beneficial for these women to reduce the risk of miscarriage and enhance the live birth rate. More importantly, our study suggests that GnRH-a treatment may improve pregnancy outcomes in infertility patients with adenomyosis by means other than reducing the uterine volume. Nevertheless, this was a retrospective study, and selection and recall bias may affect its findings. A prospective randomized controlled study is required to validate these findings.

In conclusion, our results showed that the application of GnRH-a before FET reduced the miscarriage rate and improved the live birth rate among infertile women with adenomyosis whose uterine volume was 56–100 cm^3.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-21-6247/rc

Data Sharing Statement: Available at https://atm.amegroups.com/article/view/10.21037/atm-21-6247/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-21-6247/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Review Committee of Peking University Third Hospital (No. LM2021243), and individual consent for this retrospective analysis was waived.

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