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Pregnancy outcomes of infertile women with ultrasound-diagnosed adenomyosis for in vitro fertilization and frozen–thawed embryo transfer

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Abstract

Objective This study aimed to investigate the effect of ultrasound-diagnosed adenomyosis on assisted pregnancy outcomes, i.e., in vitro fertilization–embryo transfer (IVF–ET).

Methods This was a retrospective cohort study of 18,568 women who had received their first frozen–thawed ET cycle in Center of Reproductive Medicine, Children's Hospital of Shanxi and Women Health Center of Shanxi and the Reproductive Medicine Center of Tianjin Central Obstetrics and Gynecology Hospital from January 2014 to May 2019. A total of 5,087 patients met the inclusion and exclusion criteria, and they were divided into two groups: adenomyosis with tubal factor infertility (study group, $n=193$) and only tubal factor infertility (control group, $n=4894$). After a 1:1 propensity score match (caliper value = 0.005), 360 cases were matched in the end.

Result There was no statistical difference in the embryo implantation rate, clinical pregnancy rate, or multiple pregnancy rate between the two groups (28.4% vs. 31.7%, 42.2% vs. 42.8%, and 11.7% vs. 12.8%, respectively; $P>0.05$). However, the early miscarriage rate in the adenomyosis group was significantly higher than that in the control group (13.3% vs. 5.6%, respectively; $P=0.012$). The live birth rate was 22.8% in the women with adenomyosis and was observed to be significantly lower than 33.3% in the control group ($P=0.026$). The patients with adenomyosis had a higher incidence of pregnancy complications than those without (4.4% vs. 0.6%, respectively; $P=0.018$), but the neonatal birth weight was not related to adenomyosis.

Conclusion Women with adenomyosis should be treated as being at high risk of early miscarriage. However, maternal adenomyosis has no effect on the birth weight of the newborn.

Keywords Adenomyosis · IVF · Frozen–thawed embryo transfer · Live birth · Miscarriage

Introduction

In 1925, Frankl first used the term "adenomyosis uteri". Adenomyosis is a benign uterine disease characterized by the invasion of endometrial glands and stroma in the myometrium with smooth muscle hyperplasia [1, 2]. The main clinical symptoms of adenomyosis include chronic pelvic pain, abnormal uterine bleeding (AUB), and infertility. However, about 30% of women with adenomyosis are asymptomatic [3]. And the average rate of infertility caused by adenomyosis is 24.4%, meaning that it is a relatively crucial condition that can affect fertility [3]. Uterine adenomyosis mostly occurs in women over the age of 40. Still, in recent years, it has been showing a gradually younger trend,

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which may be related to the increase in cesarean sections, induced abortions, and other intrauterine surgeries.

Postoperative histopathological examination is the gold standard for the diagnosis of adenomyosis. However, with the development of imaging technology, transvaginal sonography (TVS) and magnetic resonance imaging are becoming the first- and second-line diagnostic tools, respectively, for diagnosing adenomyosis. Of these, TVS is more accessible, cheaper, and less invasive than other imaging techniques and can perform dynamic examinations; thus, it is considered the primary imaging modality for adenomyosis diagnosis [3]. Moreover, the sensitivity of TVS diagnosis is about 82.5%, and the specificity is about 84.6% [4].

More and more unexplained infertile women are being diagnosed with adenomyosis. According to the literature, the overall adenomyosis incidence is 1% and the overall prevalence 0.8% based on a recent 10-year population cohort study among 16- to 60-year-old women [5]. However, the exact cause of adenomyosis is still unknown. Two main theories have been put forward to explain its origin and pathogenesis: invagination theory and metaplasia theory [6].

Several systematic reviews and meta-analyses have shown a significant reduction in the embryo implantation rate, clinical pregnancy rate, and live birth rate per cycle in women with adenomyosis compared with those without the condition. Furthermore, the miscarriage rate is higher for women with adenomyosis [7, 8]. Other studies, however, have not found an effect of adenomyosis on the outcome of assisted reproductive technology [9, 10]. Therefore, the impact of adenomyosis on the fertility of infertile women remains controversial. The purpose of this study was to investigate the pregnancy outcomes of infertile women with ultrasound-diagnosed adenomyosis on in vitro fertilization and frozen–thawed embryo transfer treatment.

Materials and methods

Study design and participants

The clinical data of 18,568 patients who received their first frozen–thawed embryo transfer cycle in Center of Reproductive Medicine, Children's Hospital of Shanxi and Women Health Center of Shanxi and the Reproductive Medicine Center of Tianjin Central Obstetrics and Gynecology Hospital from January 2014 to May 2019 were retrospectively analyzed. The study was conducted in accordance with the Declaration of Helsinki (as was revised in 2013). The study was approved by Ethics Committee of Center of Reproductive Medicine, Children's Hospital of Shanxi and Women Health Center of Shanxi and informed consent was taken from all the patients.

The inclusion criteria were: women undergoing their first frozen–thawed embryo transfer cycle; adenomyosis diagnosed on TVS; and diagnosis of infertility due to simple tubal factors. The exclusion criteria were as follows: women aged over 40 years; women with congenital uterine malformation; women with chromosomal abnormalities; women with diabetes or hypertension; women with a uterine scar; women with endometriosis; women with polycystic ovary syndrome; women with menorrhea; and women with hydrosalpinx.

All patients underwent TVS at least twice during treatment, and a patient could be diagnosed with adenomyosis if ultrasound imaging showed three or more of the following criteria: uterine enlargement, asymmetrical myometrial thickening, presence of heterogeneous myometrial areas, findings of myometrial cysts, presence of echogenic striations in the sub-endometrium, sub-endometrial echogenic nodules, irregular endometrial–myometrial interface, and poor definition and thickening of the junction zone [3].

Once the inclusion and exclusion criteria were adopted, 5,087 women were selected from the original 18,568 and divided into two groups: adenomyosis with tubal factor infertility (study group, $n = 193$) and only tubal factor infertility (control group $n = 4894$) (Fig. 1).

Controlled ovarian stimulation and in vitro fertilization

Short gonadotropin-releasing hormone (GnRH) agonist protocol, GnRH antagonist protocol, or long GnRH agonist protocol was chosen to perform controlled ovarian stimulation (COH) according to each patient's medical history and basal hormone levels. During the process of COH, the growth of the follicles was monitored by vaginal ultrasound. When the diameter of two or more dominant follicles reached 18 mm, an appropriate dose of exogenous human chorionic gonadotropin (hCG) was used to trigger ovulation. Transvaginal ultrasound-guided oocyte retrieval was conducted 36 h after hCG administration, and the oocytes were fertilized using in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) based on sperm quality and history of infertility.

Frozen–thawed embryo transfer

According to each patient's menstruation and endometrium, a natural cycle, artificial cycle, or downregulation and artificial cycle was chosen to prepare the endometrium. Embryos in the cleavage stage were thawed and transferred on the third day after ovulation; blastocysts were thawed and transferred on the fifth day after ovulation. Up to three embryos were transferred in one cycle. All patients were given corpus luteum support from the day of transfer and

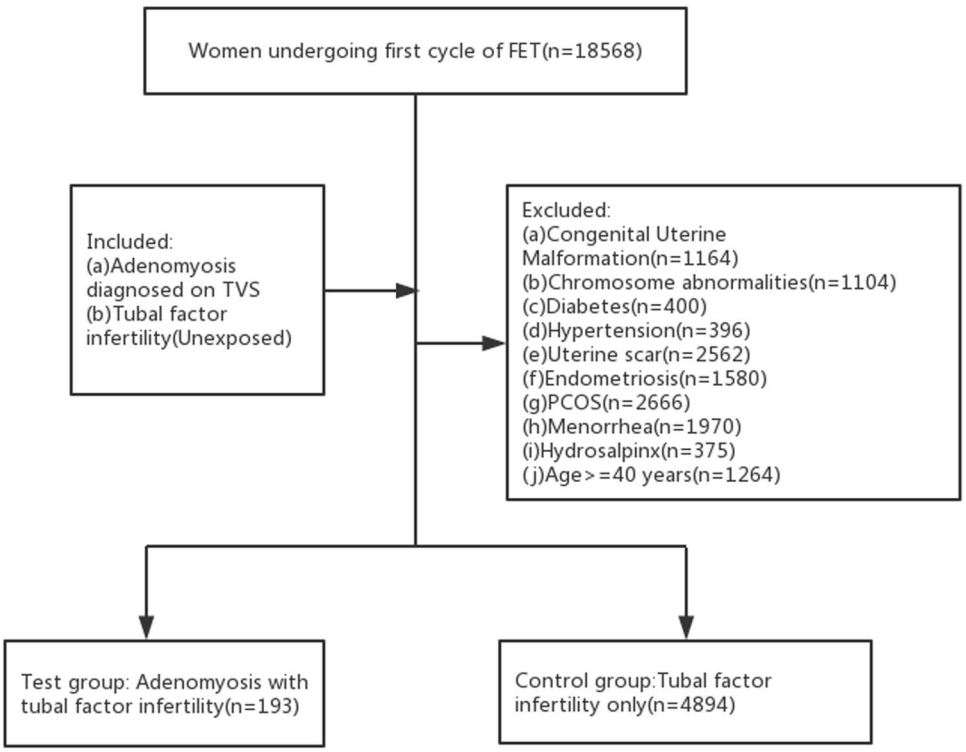

Fig. 1 Study flow chart

oral dydrogesterone (Duphaston, Abbott) 20 mg/time, bid × 14 days. After determination of pregnancy, the patients were given continuous progesterone supplementation until the tenth week of pregnancy.

Study outcomes

The primary outcomes of the study were the live birth rate, implantation rate, clinical pregnancy rate, ongoing pregnancy rate, and miscarriage rate. The secondary outcomes included the ectopic pregnancy rate, premature birth rate, multiple pregnancy rate, pregnancy complications (e.g., gestational diabetes, gestational hypertension, placenta previa, placental abruption), and neonatal birth weight.

Statistical analysis

The 1:1 propensity score (PS) based on age, body mass index (BMI), infertility duration, basal Follicle-Stimulating Hormone (FSH), and basal Luteinizing Hormone (LH) was used to match the study group and control group (caliper value = 0.005) to reduce the influence of selection bias. The measurement data results were expressed as $\overline{X} \pm s$, and the group t test was used to compare the normal distribution. The rank-sum test was used to compare the non-normal distribution; the count data were expressed as a percentage (%), and a chi-square test or Fisher's exact test was used for comparison of the categorical variables. Statistically significance was accepted at $P < 0.05$. The IBM Statistical Package for the Social Sciences (v. 26) was used to analyze the data.

Results

The demographics, baseline IVF characteristics, and perinatal outcomes of the entire study population ($n = 5087$) are displayed in Table 1. Briefly, the average age and BMI of the study population were 31.5 ± 3.9 years and 22.6 ± 3.1 kg/m^2, respectively. The average infertility duration was 4.2 ± 2.8 years. The average number of oocytes retrieved was 17.6 ± 8.2. The average high-quality embryo rate was 26.4 ± 38.7%. Of all newborns, 52.1% were males. The mean gestational age at delivery was 38.4 ± 2.2 weeks. The total proportion of preterm birth was 22.6%. The average birth weight of the newborns was 3,019.8 ± 639.6 g, and the low-birth weight rate and macrosomia rate were 19.8% and 6.4%, respectively.

After a 1:1 PS match (caliper value = 0.005), 360 cases were matched in the end. Before the PS matching, the baseline characteristics of the study group and the control group were significantly different. However, the PS matching process balanced these differences between the two groups (Table 2), indicating that the matched cohort had highly similar characteristics.

A comparison of the clinical outcomes after PS matching is listed in Table 3. There were no significant differences in the endometrial thickness, number of oocytes retrieved,

Table 1 Demographics and perinatal outcomes of the study ($n=5087$)

Demographics	
Maternal age (year)	31.5 ± 3.9
BMI (kg/m^2)	22.6 ± 3.1
Type of infertility	
Primary	2639 (51.9%)
Secondary	2448 (48.1%)
Infertility duration (year)	4.2 ± 2.8
Basal FSH (mIU/L)	7.2 ± 43.2
Basal LH (mIU/L)	4.2 ± 2.6
No. oocytes retrieved	17.6 ± 8.2
High-quality embryo rate	26.4 ± 38.7
Pregnancy outcomes	
Neonatal gender	
Boy	1238 (52.1%)
Girl	1139 (47.9%)
Gestational age (week)	38.4 ± 2.2
Term birth	1840 (77.4%)
Preterm birth	537 (22.6%)
Neonatal birth weight (g)	3019.8 ± 639.6
Low birth weight	471 (19.8%)
Macrosomia	153 (6.4%)

Table 2 Baseline characteristics of the adenomyosis and tubal infertility only cohorts before and after PS matching

	Before matching ($n=5087$)		P	After matching ($n=360$)		P
	Adenomyosis ($n=193$)	Tubal infertility only ($n=4894$)		Adenomyosis ($n=180$)	Tubal infertility only ($n=180$)	
Maternal age (year)	34.6 ± 4.5	31.4 ± 3.8	< 0.001	34.0 ± 4.0	33.7 ± 3.6	0.482
Infertility duration (year)	5.0 ± 4.0	4.2 ± 2.8	0.006	4.6 ± 3.4	4.4 ± 3.2	0.542
BMI (kg/m^2)	23.8 ± 3.2	22.6 ± 3.1	< 0.001	23.8 ± 3.3	24.1 ± 3.6	0.43
Basal FSH (mIU/L)	6.6 ± 2.6	7.2 ± 4.0	0.849	6.5 ± 2.5	6.7 ± 2.2	0.501
Basal LH (mIU/L)	5.1 ± 2.3	4.2 ± 2.6	< 0.001	5.1 ± 2.3	5.2 ± 3.6	0.594

or number of embryos transferred between the two groups. However, the uterine size of the patients with adenomyosis was significantly larger than that of the patients without (355.0 ± 189.7 vs. 82.6 ± 5.9, respectively; $P<0.001$). The high-quality embryo rate in the adenomyosis group was significantly higher than that in the control group (54.0 ± 23.8% vs. 15.2 ± 32.0%, respectively; $P<0.001$). The embryo implantation rate, clinical pregnancy rate, and multiple pregnancy rate between the two groups were comparable (28.4% vs. 31.7%, 42.2% vs. 42.8%, and 11.7% vs. 12.8%, respectively; $P>0.05$). The early miscarriage rate in the study group was significantly higher than that in the control group (13.3% vs. 5.6%, respectively; $P=0.012$), but the late miscarriage rate was not statistically significant between the two groups (5.0% vs. 2.2%, respectively; $P>0.05$). The ongoing pregnancy rate in the control group was 36.7% and in the adenomyosis group 28.3%, but there was no statistical difference ($P=0.091$). The live birth rate was 33.3% in the control group and 22.8% in the study group. The preterm birth rate between the two groups was not statistically significant ($P>0.05$). The patients with adenomyosis had a significantly higher incidence of pregnancy complications than the patients in the control group (4.4% vs. 0. 6%, respectively; $P=0.018$).

The neonatal birth weight is presented in Table 4. Compared with the newborns of infertile women with tubal factors only, those of women with adenomyosis did not have a significantly different neonatal birth weight, incidence of low birth weight, or incidence of macrosomia ($P>0.05$).

Table 3 Clinical outcomes of the adenomyosis and tubal infertility only cohorts before and after PS matching

	Before matching ($n=5087$)		P	After matching ($n=360$)		P
	Adenomyosis ($n=193$)	Tubal infertility only ($n=4894$)		Adenomyosis ($n=180$)	Tubal infertility only ($n=180$)	
Endometrial thickness	9.5 ± 1.7	9.4 ± 1.7	0.184	9.6 ± 1.7	9.3 ± 1.7	0.088
Uterine size	366.7 ± 188.1	82.2 ± 34.2	< 0.001	355.0 ± 189.7	82.6 ± 35.9	< 0.001
No. oocytes retrieved	19.9 ± 11.2	17.6 ± 8.1	0.082	20.1 ± 11.7	18.2 ± 8.2	0.217
High-quality embryo rate	50.3 ± 24.7	26.0 ± 38.8	< 0.001	54.0 ± 23.8	15.2 ± 32.0	< 0.001
No. embryos transferred			0.892			0.584
1	31 (16.1%)	823 (16.8%)		28 (15.6%)	22 (12.2%)	
2	144 (74.6%)	3657 (74.7%)		135 (75.0%)	143 (79.4%)	
3	18 (9.3%)	414 (8.5%)		17 (9.4%)	15 (8.3%)	
Embryo implantation rate	99 (26.5%)	3524 (37.6%)	< 0.001	99 (28.4%)	112 (31.7%)	0.331
Clinical pregnancy rate	76 (39.4%)	2597 (53.1%)	0.001	76 (42.2%)	77 (42.8%)	0.915
Multiple pregnancy rate	21 (10.9%)	773 (15.8%)	0.065	21 (11.7%)	23 (12.8%)	0.748
Miscarriage rate[a]	35 (18.1%)	785 (16.0%)	0.438	35 (19.4%)	17 (9.4%)	0.007
Early miscarriage rate	24 (12.4%)	279 (5.7%)	< 0.001	24 (13.3%)	10 (5.6%)	0.012
Late miscarriage rate	9 (4.7%)	53 (1.1%)	< 0.001	9 (5.0%)	4 (2.2%)	0.158
Pregnancy complications	–	–	–	8 (4.4%)	1 (0.6%)	0.018
Live birth rate	41 (21.2%)	1812 (37.0%)	< 0.001	41 (22.8%)	60 (33.3%)	0.026
Preterm birth rate	5 (2.6%)	532 (10.9%)	< 0.001	5 (2.8%)	10 (5.6%)	0.187

[a]Two cases of ectopic pregnancy in adenomyosis group before and after matching are included. Four hundreds and twenty-two cases of ectopic pregnancy in the control group before matching are included. Thirty-one cases of mid-term induction in the control group before matching are included. Three cases of ectopic pregnancy in the control group after matching are included

Table 4 Comparison of the incidence of low birth weight and macrosomia in the study patients

	Singleton pregnancy		P	Twins pregnancy		P
	Adenomyosis	Tubal infertility only		Adenomyosis	Tubal infertility only	
Neonatal birth weight	3208.1 ± 504.3	3183.4 ± 824.9	0.881	2777.8 ± 417.7	2637.2 ± 545.6	0.348
Low birth weight rate	2 (6.3%)	5 (11.4%)	0.284	3 (16.7%)	13 (40.6%)	0.081
Normal birth weight rate	29 (90.6%)	34 (77.3%)		15 (83.3%)	19 (59.4%)	
Macrosomia rate	1 (3.1%)	5 (11.4%)		–	–	–

Discussion

In recent years, due to the widespread use of high-resolution ultrasound and the increasing age of women seeking assisted reproductive treatment, the detection of adenomyosis has increased [7]. The prevalence of adenomyosis is 24.4% in infertile women. Moreover, in patients with endometriosis, recurrent miscarriage, and repeated implantation failure, the incidence of adenomyosis is higher [11]. Due to the lack of data and the controversies in the existing evidence, the impact of adenomyosis on IVF results is not yet fully understood. To minimize the influence of confounding factors and more clearly explore the effect of adenomyosis on the outcome of Frozen embryo transfer (FET), our study conducted a PS match between the study group and the control group. Our analysis suggested a negative effect of adenomyosis on IVF and frozen–thawed embryo transfer outcomes compared with only tubal factor infertility.

A previous article on patients undergoing oocyte donation showed that adenomyosis does not affect the embryo implantation rate or clinical pregnancy rate [12]. This finding was in agreement with our study, in which patients received IVF and frozen–thawed embryo transfer. Another study observed that the implantation rate of asymptomatic women diagnosed with adenomyosis by transvaginal ultrasound is not compromised [13]. However, there have also been several studies showing different results. A previous study examining the effect of adenomyosis on IVF outcomes in patients who underwent GnRH antagonist protocol found that the existence of ultrasound-diagnosed adenomyosis was

associated with a noticeable reduction in successful implantation of good-quality embryos (clinical pregnancy rate 23.6% vs. 44.6%, respectively; $P=0.017$) [14]. The results of one study indicated that regardless of the quality of the oocytes and embryos, adenomyosis will reduce the chances of implantation and pregnancy [15]. Several scholars have studied women with different degrees of ultrasound features of adenomyosis and found that women with adenomyosis have a lower clinical pregnancy rate after IVF–embryo transfer (ET). The likelihood of a woman's clinical pregnancy decreases from 42.7% without adenomyosis features to 22.9% with four features and to 13.0% with all seven features. The severity of the adenomyosis as indicated by the morphological features of three-dimensional ultrasound examination increases the degree of this effect [16].

Our study found that patients with adenomyosis have a significantly higher early miscarriage rate (13.3% vs. 5.6%, respectively; $P=0.012$) and a significantly lower live birth rate (22.8% vs, 33.3%, $P=0.026$) than patients with infertility due to simple tubal factors. A systematic review and meta-analysis found that the risk of miscarriage in patients with adenomyosis with IVF pregnancy is increased more than threefold [odds ratio (OR) = 3.40, CI: 1.41–8.65] and that the risk of such miscarriage is not common in natural pregnancy studies [17]. Moreover, [18] found that compared with the control group and women with only endometriosis, the adenomyosis group had a higher miscarriage rate and lower live birth rate. Finally, [12] found that adenomyosis increases the miscarriage rate, which leads to a decrease in the term pregnancy rate.

The current study also found that patients with adenomyosis have a higher incidence of pregnancy complications and that the neonatal birth weight is not related to adenomyosis. According to a systematic review, women with adenomyosis have an increased incidence of premature birth and premature rupture of membranes [19]. A Japanese study indicated that women with adenomyosis are significantly more likely to have preeclampsia, placental malposition, and preterm delivery [20]. Scala et al.'s study [21] observed that in patients with endometriosis, diffuse adenomyosis (OR = 3.744; 95% CI 1.158–12.099) is the independent risk factor for small for gestational age.

Adenomyosis can be treated by medical intervention or surgical treatment but is difficult to cure, and the patient's symptoms can gradually ease after menopause. Therefore, the choice of clinical treatment needs to be personalized based on the patient's age, symptoms, and fertility requirements. The use of a levonorgestrel-releasing intrauterine system for pretreatment before FET could improve the intrauterine environment, creating better conditions for embryo implantation and clinical pregnancy [22]. One study showed that adenomyomectomy could be a conservative and effective option to treat severe uterine adenomyosis, especially among women seeking uterine and fertility preservation [23].

Themechanisms of embryo implantation are complex and the reasons for embryo transfer failure are not fully understood, at present it is speculated that embryo quality and maternal factors can affect it, such as poor maternal and the receptivity of endometrium, reproductive organs and anatomical structure, an abnormal blood clots before the state and the immune system, endometrial window period in advance or delay. Our study showed that delayed blastocyst transfer time of 1–2 days for RIF patients could improve the success rate of embryo transfer. The maternal pre-thrombotic state and immune factors are considered to be the important causes of RIF. If the mother is in a pathological state of abnormal hypercoagulability for a long time, it will cause changes in the blood flow state in the uterine placenta, easily forming micro-thrombosis, resulting in fetal ischemia and hypoxia, nutritional disorders, and embryo implantation failure or early abortion. Many studies also show that the application of anticoagulants and immunomodulation to RIF patients increases the implantation rate and clinical pregnancy rate. Below are potential mechanisms that impede embryo implantation and placenta formation in patients with adenomyosis:

1. Adenomyosis can cause abnormal blood flow in the endometrium and myometrium, leading to a decrease in endometrium receptivity.
2. Abnormal anatomical structure. JZ is the junction area between myometrium and endometrium with a normal thickness of 2–8 mm, also known as the functional uterine area. JZ structure and function in patients with uterine adenomyosis are changed, causing JZ cell hypertrophy of the nucleus, mitochondria, abnormal shape and contains abundant myelin [24], as well as the ultrastructure of abnormal cell calcium channel, which will result in abnormal rhythm of shrinkage and creep, followed by implantation dysfunction and uterine's inability to maintain a pregnancy. This may also be the root cause of IVF pregnancy failure and preterm delivery in patients withadenomyosis [25].
3. Inflammation factors also play an important role in embryo transfer failure. Severe uterine adenomyosis and ectopic endometrium women have more inflammatory immune cells, which can produce inflammation factor expression (IL-6, IL-8, IL-10) to affect the lining of the uterus affect fertility [26–28].
4. Both cellular immunity and humoral immunity are enhanced in adenomyosis patients, and multiple inflammatory immune signaling pathways, such as TGF-β/Smad [29], MAPK, RAS/RAF/P-C-RAF [30], are involved in the pathogenesis of adenomyosis. High expression of class II human leukocyte antigens in

patients with adenomyosis stimulates macrophages to produce T lymphocytes, secrete associated inflammatory molecules, and activate B lymphocytes, resulting in a variety of autoantibodies, affect endometrial glands function, cause the fertilized egg dysplasia, embryo implantation failure and abortion.

5. Endometrial structure and function are affected: studies have shown [31] that, compared with women with normal reproductive function, endometrial angiogenesis significantly increases in patients with adenomyosis during proliferative period.
6. Abnormal levels of free radicals in uterine patients with adenomyosis: a hypoxic environment in the uterus is a prerequisite for embryo implantation. Excess free radicals may inhibit embryonic development and pregnancy. The levels of superoxide dismutase (SOD) and nitric oxide synthase (NOS) in the endometrium of normal women in proliferative period were lower, and the levels of SOD and NOS were increased in early and middle period. However, the expression of NOS, XO and SOD in endometrium of adenomyosis and endometriosis did not fluctuate with menstrual cycle. These changes may affect the development of early embryos. In addition, after implantation, the embryo may be attacked by persistently high levels of NO and activated macrophages or T lymphocytes under the condition of abnormal free radical levels, leading to early abortion.

The following are our advantages: We had a relatively large sample size from two reproductive centers, and we used PS matching to balance the basic characteristics of the study and control groups. Therefore, the selection bias was reduced, and the results of the study are more reliable. In terms of the limitations of our study, the first is that it was a retrospective cohort study. Although we used PS matching, there were still other factors and selection biases that influenced the research. Moreover, we have not classified adenomyosis, and the severity of the disease may affect pregnancy outcomes. Lastly, the diagnosis of adenomyosis by TVS is not the gold standard, and there may have been missed diagnoses or misdiagnoses. Thus, a multi-center randomized controlled trial is needed to clarify the impact of adenomyosis on reproductive outcomes.

Conclusions

In infertile patients undergoing IVF and frozen–thawed ET, adenomyosis does not affect the embryo implantation rate or clinical pregnancy rate. Moreover, adenomyosis does not affect the birth weight of the newborn. However, the early miscarriage rate is significantly increased, and the live birth rate is significantly reduced.

Author contribution X-PZ and Y-FZ conceived the idea and conceptualized the study. RS and Y-JZ collected the data. X-LZ and X-MH analyzed the data. X-YH and Y-JH drafted the manuscript, then X-LZ and Y-JH reviewed the manuscript. All authors read and approved the final draft.

Declarations

Conflict of interest The authors declare that they have no competing interests.

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