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Original Article

Pregnancy outcomes and neonatal outcomes after pituitary down-regulation in patients with adenomyosis receiving IVF/ICSI and FET: results of a retrospective cohort study

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Abstract: The aim of this study was to analyze whether GnRH agonist treatment before frozen-thawed embryo transfer (FET) improved the pregnancy outcomes of adenomyosis patients and to study the effects of GnRH agonists to the health of offspring. This study was a retrospective analysis of 139 patients who underwent in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) between Jan 2011 and Dec 2014. For these patients, the total number of cycles was 212.The cycles were divided into groups A, B and C, according to different treatment methods before FET protocol. Group A consisted of non-adenomyosis patients who received pure hormone replacement therapy (HRT). Group B consisted of adenomyosis patients who received HRT. Group C consisted of adenomyosis patients who received GnRH agonist therapy and HRT. The patients' medical records were reviewed, including pregnancy outcomes and neonatal outcomes. Our study showed that among the adenomyosis patients, Group C had a significantly higher live birth rate than Group B (44.74% vs. 25%, P = 0.034). Neonatal outcomes, including birth weight, sex, birth defects, singleton vs. twins and mode of delivery, were compared. No differences were observed between the groups. GnRH agonist therapy before FET may offer a higher live birth rate in patients with adenomyosis. Our data appear to confirm other published findings that adenomyosis patients benefit from pre-FET pituitary down-regulation therapy. Additionally, the treatment itself appears not to increase birth defect risk.

Keywords: Adenomyosis, pituitary down-regulation, FET, pregnancy outcome, neonatal outcome

Introduction

Adenomyosis is a benign uterine disorder characterized by the direct infiltration of endometrial tissue into the myometrium [1]. Accumulated evidence suggests that adenomyosis can negatively impact pregnancy outcomes. It has been demonstrated that the clinical pregnancy rate and ongoing pregnancy rate are significantly lower in women with adenomyosis. Additionally, adenomyosis was associated with a higher incidence of miscarriage in women undergoing in vitro fertilization (IVF) [2, 3]. A similar conclusion was obtained by Lei Yan et al, who found that delivery rate for women undergoing IVF and intracytoplasmic sperm injection (ICSI) was significantly lower in the adenomyosis group compared with the control group [4].

Several measures have been used to improve pregnancy outcomes in adenomyosis patients. These include levonorgestrel-releasing intrauterine system (LNG-IUS) that is an effective treatment for adenomyosis. This system effectively down-regulates estrogen receptors (ER) in uterine endometrial tissues. Additionally, it may relieve pain by reducing prostaglandin production within the endometrium [5]. In addition, other studies have shown that a GnRH agonist administered before assisted reproductive technology (ART) can lead to a higher clinical pregnancy rate or higher ongoing pregnancy rate in patients with endometriosis [6, 7]. However, the role of GnRH agonists in the treatment of adenomyosis in frozen embryo transfer (FET) protocols has not been well studied. Zhihong Niu et al presented that pituitary down-

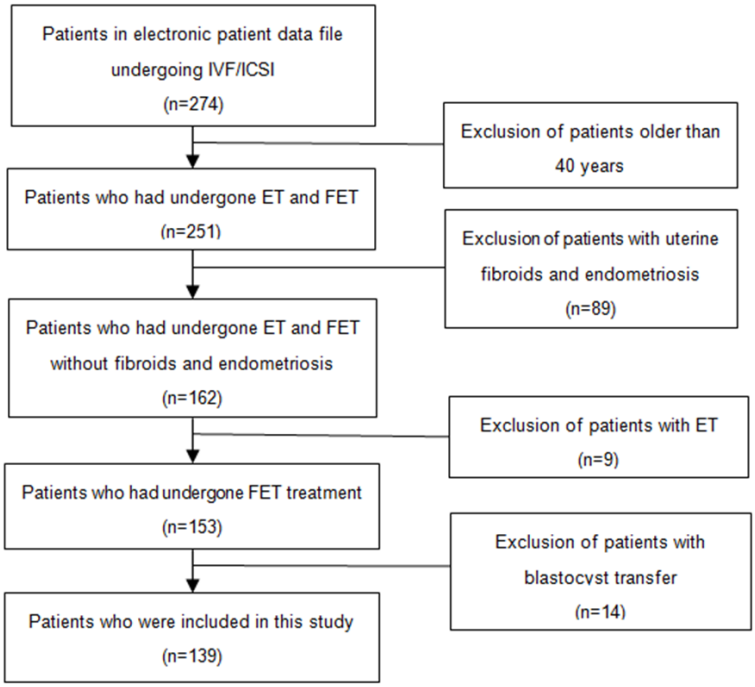

Figure 1. Flowchart of patient selection. IVF: In vitro fertilization, ICSI: Intracytoplasmic sperm injection, FET: Frozen-thawed embryo transfer, ET: Embryo transfer.

regulation before FET could improve pregnancy outcomes in patients with adenomyosis [8]. However, some studies that evaluated children exposed to GnRH agonists around the time of conception found many congenital malformations. Studies in animal models reached similar conclusions. None of these authors reported whether GnRH agonists have negative impacts on perinatal outcomes in ART. Given the published literature, we anticipated finding that adenomyosis patients who received GnRH agonist treatment had better pregnancy rates than those who did not receive this treatment. On the basis of this hypothesis, the aim of the study was to analyze whether GnRH agonist treatment before FET improved the implantation rate, clinical pregnancy rate and live birth rate of patients with adenomyosis and to further to study the effects of GnRH agonist treatment on the health of offspring, by evaluating birth weight, sex and birth defects.

Materials and methods

Patient selection

Of all of the women who were admitted to the Reproductive Medical Center of Rui Jin Hospital Shanghai Jiao Tong University School of Medicine for IVF/ICSI treatment between January 2011 and December 2014, 274 were randomly selected by computer to be included in the study. We excluded 135 patients, leaving 139 women for inclusion in this study (**Figure 1**). Inclusion criteria consisted of: (1) aged 40 years or less at commencement of IVF/ICSI treatment, (2) frozen-thawed embryo transfer protocol, and (3) cleavage stage embryo transplantation. Exclusion criteria consisted of: (1) patients aged over 40, (2) presence of endometriosis and uterine fibroids, (3) fresh embryo transfer protocol, and (4) blastocyst transplantation. No patients had received endocrine therapy, including GnRH agonists, danazol, or hormone replacement therapy (HRT) for at least 6 months before this study. Diagnosis of adenomyosis was based on transvaginal sonographic (TVS) examination. Informed consent was obtained from all individual participants included in the study.

Because some patients have received multiple courses of FET cycles, so the number of patients and the number of FET cycles was inconsistent. For these 139 patients, they received a total of 212 FET cycles. Cycles were divided into groups A, B and C, according to treatment method before FET protocol. Group A consisted of non-adenomyosis patients who received pure HRT. Group B consisted of adenomyosis patients who received pure HRT. Group C consisted of adenomyosis patients who received pituitary down-regulation therapy and HRT. It should be noted that because many adenomyosis patients had more than one cycle, 30 women were in both the B and the C groups. Before frozen-thawed embryo transfer, all adenomyosis patients were informed of the probability of decreased pregnancy rate because of their adenomyosis and that GnRH agonist pretreatment may improve their pregnancy outcome but required more time and cost. Patients chose pituitary down-regulation therapy and HRT protocol or pure HRT protocol voluntarily. Ethical approval was

Table 1. Patient characteristics

	Group A (n = 92)	Group B (n = 44)	Group C (n = 76)	P
Age (years)	28.8 ± 4.8	31.0 ± 4.4*	31.9 ± 3.7*	< 0.001
BMI	21.4 ± 2.5	20.8 ± 2.0	21.0 ± 2.5	NS
Duration of infertility (years)	3.5 ± 3.2	3.0 ± 2.0	3.7 ± 3.2	NS
Cause of infertility				
Tubal factors				NS
No	31 (33.7)	15 (34.1)	24 (31.6)	
Yes	61 (66.3)	29 (65.9)	52 (68.4)	
PCOS				NS
No	78 (84.8)	40 (90.9)	70 (92.1)	
Yes	14 (15.2)	4 (9.1)	6 (7.9)	
Male factors				NS
No	42 (45.7)	24 (54.6)	42 (55.3)	
Yes	50 (54.4)	20 (45.5)	34 (44.7)	
Basal FSH (U/l)	6.7 ± 1.6	7.2 ± 1.5	7.1 ± 1.6	NS
Basal LH (U/l)	4.6 ± 2.1	4.3 ± 2.0	4.2 ± 2.3	NS
Basal E2 (pg/ml)	35.3 ± 14.1	38.2 ± 13.7	42.7 ± 31.3	NS
Basal P (ng/ml)	0.7 ± 0.4	0.7 ± 0.4	0.6 ± 0.4	NS
AEmAb				NS
No	52.0 (56.5)	19.0 (43.2)	35.0 (46.1)	
Yes	40.0 (43.5)	25.0 (56.8)	41.0 (54.0)	
CA125 (IU/l)	15.9 (11.5, 34.3)	21.8 (13.8, 40.4)*	34.5 (16.9, 55.8)*,#	0.013
Endometrium thickness on progesterone day (mm)	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.2	NS
E2 level on progesterone day (pg/ml)	224.5 (160.0, 275.0)	286.0 (172.5, 560.5)	251.0 (160.0, 322.0)	NS
No. of embryo transferred	1.9 ± 0.3	1.8 ± 0.4	1.9 ± 0.3	NS
Score of embryo transferred	7.3 ± 1.2	7.1 ± 1.3	7.2 ± 1.3	NS

NS: Not statistically significant, BMI: Body Mass Index, PCOS: Polycystic ovary syndrome, AEmAb: Anti-Endometrium Antibody Male factors included oligospermatism, asthenospermia, teratozoospermia and azoospermia. *P < 0.05 versus control group, #P < 0.05 versus pure HRT group.

obtained from the Institutional Ethics Committee of the Rui Jin Hospital Shanghai Jiao Tong University School of Medicine.

Transvaginal ultrasound for the detection of adenomyosis

The ultrasonographic diagnostic criteria for adenomyosis included: (1) enlargement of the uterus, (2) heterogeneity or hypoechoic linear striations of the myometrium, (3) endometrial-myometrial junction with poorly defined borders, (4) myometrial cysts, and (5) asymmetry of uterine walls. Criteria (1) and (2) were mandatory for a diagnosis of adenomyosis. The others were used to confirm the diagnosis [9]. All transvaginal ultrasound scans were conducted by a single doctor who was experienced in gynecological ultrasonography. A single operator was employed to reduce inter-observer variability.

FET protocol

Pituitary down-regulation therapy was implemented with 3.75 mg of triptorelin acetate (Diphereline®; Ipsen, France) administered during the early follicular phase of the menstrual cycle. Down-regulation was confirmed by ultrasound scan 28 days later. When reaching the criterion for down-regulation (no ovarian cysts > 8 mm; estradiol [E2] < 50 pg/L) [10], HRT was carried out by administering estradiol (Progynova®; Bayer Schering Pharma, Germany) and progesterone (Utrogestan®; Besins Healthcare, France) to prepare the endometrium for implantation. If the endometrium thickness was ≥ 8 mm, the embryo transfer was performed. All patients had luteal phase support with daily vaginal progesterone (Utrogestan®; Besins Healthcare, France) and oral progesterone (Dydrogesterone®; Abbott Biologicals B.V., Netherlands) until β-human chorionic gonadotropin (β-hCG) testing was conducted on day 11. For patients with a positive pregnancy test, progesterone was continued until the 12th week of pregnancy. All FET protocols were designed by a single doctor who was experienced in reproductive medicine. A single operator was employed to reduce inter-observer variability.

Table 2. Clinical outcomes of all groups

	Group A (n = 92)	Group B (n = 44)	Group C (n = 76)	χ^2	P
Implantation rate/cycle	29.4 (52/177)	25.0% (18/72)	33.8 (49/145)	1.9	NS
Clinical pregnancy rate/cycle	43.5% (40/92)	36.4 (16/44)	51.3% (39/76)	2.6	NS
Live birth rate/cycle	37.0% (34/92)	25.0% (11/44)	44.7% (34/76)	4.7	NS
First-trimester miscarriage rate/cycle	5.4% (5/92)	6.8% (3/44)	6.6% (5/76)	0.1	NS

No significant differences were found in any of the four outcome parameters (implantation rate, clinical pregnancy rate, live birth rate and first-trimester miscarriage rate) between the study groups.

Table 3. Clinical outcomes of the adenomyosis patients

	Group B (n = 44)	Group C (n = 76)	OR (95% CI)	P
Live birth rate/cycle	25.0% (11/44)	44.7% (34/76)	0.4 (0.2-1.0)	0.034
Implantation rate/cycle	25.0% (18/72)	33.8% (49/145)	0.7 (0.4-1.2)	NS
Clinical pregnancy rate/cycle	36.4% (16/44)	51.3% (39/76)	0.5 (0.3-1.2)	NS
First-trimester miscarriage rate/cycle	6.8% (3/44)	6.6% (5/76)	1.0 (0.2-4.6)	NS

Among the adenomyosis patients, pituitary down-regulation therapy and HRT group had a significantly higher live birth rate than the pure HRT group (44.74% vs. 25%, P = 0.034).

Outcome variables

The primary outcome measures were implantation rate (defined as the number of gestational sacs/number of embryos transferred), clinical pregnancy rate (defined as presence of an intrauterine gestational sac and a live fetus on TVS at 7 weeks gestation/total number of transferred cycles), live birth rate (defined as the number of live births/total number of transferred cycles) and first-trimester miscarriage rate (defined as loss of clinical pregnancy before 12 weeks gestation/clinical pregnancies). The secondary outcome measures were the neonatal outcomes. Neonatal outcomes, including birth weight, sex, birth defects (present at birth), number of babies born and mode of delivery, were compared.

Statistical analysis

All results are expressed as either mean ± SD or median and inter-quartile range (IQR). Continuous variables were tested for normal distribution using the t test and categorical variables were analyzed using χ^2 test where appropriate. For comparison among groups, the Kruskal-Wallis test was used. Statistical analysis was performed using SPSS version 21.0 (SPSS, Chicago, IL, USA). Significance was defined as $P < 0.05$. A database file was set up using Excel for Windows (Microsoft, Redmond, WA, USA) to facilitate data entry and retrieval. Follow-up on pregnancy outcomes was performed by phone and recorded in our electronic medical records.

Results

The 139 patients included 45 adenomyosis patients and 94 non-adenomyosis patients. Five cycles were canceled because of embryo recovery failure. Four cycles were canceled because of lack of sufficient data. Excluding these, 212 cycles remained. The demographic data are summarized in **Table 1**. No difference in body mass index (BMI), duration of infertility, cause of infertility, serum basic sexual hormone, Anti-Endometrium Antibody (AEmAb), endometrium thickness on progesterone day, E2 level on progesterone day, number of embryos transferred or score of embryos transferred were found between the groups. We noted a significant increase in serum CA-125 level in the adenomyosis group ($P = 0.013$). The number of embryos transferred varied between one and two. In a careful review of the patients, we found that the adenomyosis patients were older than the control group ($P < 0.001$).

The FET outcome parameters in study groups A, B and C are displayed in **Tables 2** and **3**. No significant differences were found in any of the four outcome parameters (implantation rate, clinical pregnancy rate, live birth rate and first-trimester miscarriage rate) between the study groups (**Table 3**). In the group of adenomyosis patients who received pituitary down-regula-

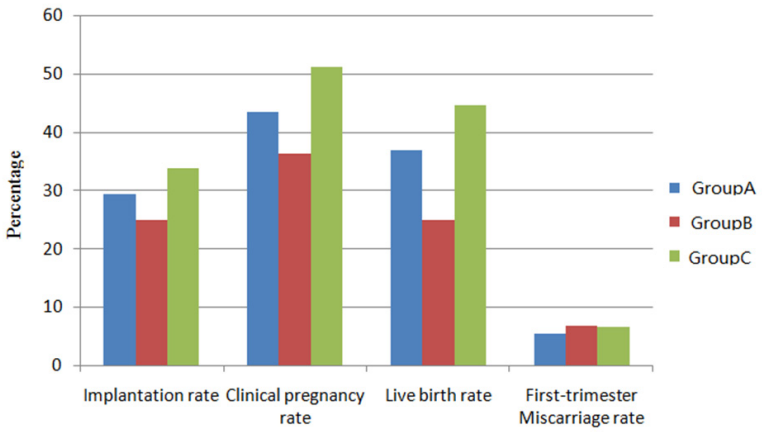

Figure 2. Clinical outcomes. In the group of adenomyosis patients who received pituitary down-regulation therapy and HRT (Group C), implantation rate, clinical pregnancy rate and live birth rate were higher but not significantly different from the other two groups. Additionally, the first-trimester miscarriage rate of the down-regulation group (Group C) was lower than the adenomyosis pure HRT group (Group B) but higher than the non-adenomyosis group (Group A). Among the adenomyosis patients, the pituitary down-regulation therapy and HRT group (Group C) had a significantly higher live birth rate than the pure HRT group (Group B).

tion therapy and HRT, implantation rate, clinical pregnancy rate and live birth rate were 33.79%, 51.32% and 44.74%, respectively. These values were significantly higher but not markedly different from the other two groups. Additionally, the first-trimester miscarriage rate of the down-regulation group was 6.58%, lower than the adenomyosis pure HRT group (6.82%) but higher than the non-adenomyosis group (5.43%) (**Table 2**; **Figure 2**). Among the adenomyosis patients, the pituitary down-regulation therapy and HRT group had a significantly higher live birth rate than the pure HRT group (44.74% vs. 25%, P = 0.034). Thus, a benefit was found in the down-regulation group (**Table 3**).

Table 4 presents the neonatal outcomes in the study groups. Data on singleton and multiple births was observed. No differences in birth weight, sex, birth defects at birth, singletons vs. twins and mode of delivery were observed between the groups. The rate of caesarean section was 85.7%. There was no infant mortality. There was only one child with ventricular septal defect in the non-adenomyosis group. No significant differences in the sex ratio were found between groups.

Discussion

Adenomyosis is one of the most common gynecological disorders in adult women, characterized by haphazard location of endometrial glands and stroma deep within the myometrium of the uterus. In women of reproductive age, adenomyosis is a major cause of infertility [11-13]. It also plays negative roles in the outcome of ART, owing to reduced likelihood of implantation and clinical pregnancy, and increased likelihood of early pregnancy loss [2, 3, 13].

The mechanisms for adenomyosis and infertility are unclear. Some studies showed that adenomyosis was associated with aggregation of macrophages, cytokines and immunological factors within the superficial endometrial glands that may have a negative impact on embryo implantation [2, 13]. In addition, the abnormal endometrial-myometrial interface disrupts the organization of myometrial muscle fibers and may disrupt normal uterine contraction activity, which may also negatively impact embryonic implantation [2]. It can also interfere with sperm transport [9, 14]. There are other possible biological interpretations for this effect, including alterations of adhesion molecules, cell proliferation, apoptosis and free radical metabolism [3].

Many measures have been used to improve pregnancy outcomes in adenomyosis patients. GnRH is a hypothalamic neuronal secretory decapeptide that plays a vital role in reproduction. There are three different forms of GnRH, hypothalamic GnRH (GnRH-I), mid brain GnRH (GnRH-II) and GnRH-III [15]. The actions of GnRH are mediated through binding to their receptors. GnRH agonists are commonly used for controlled ovarian stimulation (COH) in IVF/ICSI [11]. GnRH agonist therapy has been used extensively as an effective method of adenomyosis complex-therapy [5]. Available data suggest that GnRH agonist therapy is a good option for patients with endometriosis, owing to an increased pregnancy rate and reduced miscarriage rate [6, 7]. Our study reached similar clinical conclusions in patients with adenomyosis. It showed that among the adenomy-

Table 4. Summary of the neonatal outcomes

	Group A (n = 44)	Group B (n = 11)	Group C (n = 38)	χ^2	P
Birthweight (g)	3177.2 ± 556.0	3466.0 ± 271.9	3190.4 ± 683.6	0.9	NS
Children with any birth defects				1.2	NS
No	43 (95.6)	11 (100.0)	38 (100.0)		
Yes	1 (2.3)	0 (0)	0 (0)		
Baby sex (% female)	19 (43.2)	6 (54.6)	19 (50.0)	0.6	NS
Pregnancies				5.0	NS
Singleton	22 (66.7)	11 (100.0)	26 (76.5)		
Twin	11 (33.3)	0 (0)	8 (23.5)		
Mode of delivery				1.0	NS
Cesarean delivery (CD)	31 (93.9)	11 (100.0)	33 (97.1)		
Vaginal birth (VB)	2 (6.1)	0 (0)	1 (2.9)		

No differences in birth weight, sex, birth defects, singleton vs. twins or mode of delivery were observed between groups. There was only one child with ventricular septal defect in the non-adenomyosis group. N represented the number of offspring born in each group.

osis patients, the pituitary down-regulation therapy group had a significantly higher live birth rate than the non-pituitary down-regulation therapy group (44.74% vs. 25%, P = 0.034). A benefit was found in the down-regulation group. Other research groups have detected similar conclusions for endometriosis. Surrey et al found that GnRH agonists administered before IVF-ET in patients with endometriosis resulted in significantly higher ongoing pregnancy rates than did standard COH regimens (80% vs. 53.85%, P < 0.05) [6]. van der Houwen et al also reached similar clinical conclusions in patients with severe endometriosis [16]. In addition, a positive impact on pregnancy outcome was also supported by Zhihong Niu et al, who compared adenomyosis patients with GnRH agonists (n = 194) and without GnRH agonists (n = 145) before FET. They observed higher clinical pregnancy, implantation and ongoing pregnancy rates in the former group (51.35% vs. 24.83%, P < 0.05; 32.56% vs. 16.07%, P < 0.01; 48.91% vs. 21.38%, P < 0.05) [8]. A period of down-regulation might be a favorable factor for adenomyosis patients and this effect might be due to increased endometrial receptivity. Results from previous studies have shown that GnRH agonist use in adenomyosis is associated with a decrease in myometrial width due to the hypoestrogenic environment [15, 17, 18]. Many previous reports have shown that GnRH has direct actions on extrapituitary tissues like endometrial tissue, suggesting that GnRH can also have regulating effects on the endometrial microenvironment [19]. Expression of GnRH mRNA has been demonstrated in human reproductive tissues [15]. These findings raise the possibility that GnRH could directly regulate the behavior of endometrial cells [19].

In our study, we found a better clinical outcome of adenomyosis patients treated with GnRH agonist compared with non-adenomyosis patients who didn't receive GnRH agonist. It has been hypothesized that GnRH agonists may play an autocrine or paracrine regulatory role in the growth of reproductive tissue. In addition, Edwards hypothesized that a period of uterine "rest" may restore full function to the steroid-sensitive systems. It is well known that endometrial growth and differentiation are sensitive to steroid hormones [11].

It should be noted that because many adenomyosis patients had more than one cycle, there were 30 women in both the B and the C groups in our study. This overlap of patients may affect the results. The adenomyosis patients who did not conceive in the pituitary down-regulation cycle conceived in the next non-pituitary down-regulation cycle. The former pituitary down-regulation cycle may be play a role, because the pituitary down-regulation effect can last for at least 9 weeks for the long-acting preparation [20].

We did not find any evidence that pituitary down-regulation before FET is associated with

an increased risk of birth defects. In a literature review, Elizur et al reported that when pregnant rabbits were exposed to GnRH agonists, their offspring had increased rates of birth defects [21]. Similarly, a negative impact on human pregnancies was also supported by Lahat et al. They evaluated the effects of GnRH agonists used around the time of conception. They found that one child had a cleft palate and four others had neurodevelopmental abnormalities [22]. Other studies reported abnormalities in the neonates including one case of trisomy [23] and one case of sacral agenesis and bladder extrophy [24]. In our study, there were no birth defects in the GnRH agonist therapeutic group. There was one ventricular septal defect in the non-adenomyosis group. This was consistent with the findings of previous research that there did not appear to be an increased risk of birth defects in human pregnancies exposed to GnRH agonist therapy [22, 23]. However, long term follow-up of these babies is still lacking and the number of reported cases is too small to adequately rule out the possibility of any detrimental effect of GnRH agonist administration in pregnancy. Long-term follow-up observation is needed.

There were a number of limitations to this study. First, our offspring number was low. We speculated that the lack of significance may be due to the small case numbers in our study. Larger, prospective cohorts of patients are needed to confirm these findings. Second, the follow-up time of the newborns was short. Some birth defects may not be apparent at the time of birth. In order to analyze the outcomes better, long-term follow-up observation is needed. Third, our research lasted 4 years, from January 2011 to December 2014. Procedures and techniques changed during the study period in a way that might have altered the results for women treated later compared with women treated earlier. These factors may have affected the results. Last but not least, we acknowledge that telephone follow-ups for pregnancy outcomes may be an imperfect and possibly inaccurate method of ascertaining negative birth outcomes. We are considering better ways of follow-up, such as outpatient follow-up.

In our retrospective study, we found that adenomyosis patients benefited from pre-FET pituitary down-regulation therapy. In this group, down-regulation before FET resulted in a higher live birth rate in patients with adenomyosis compared to HRT alone. Live birth rate is the most relevant outcome of interest in the treatment of infertility and human reproductive disorders. Additionally, no additional birth defect risk could be detected in this small sample size. Available data suggest that pre-FET pituitary down-regulation therapy is a good option for adenomyosis patients in ART.

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Disclosure of conflict of interest

None.

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