Zha *et al. Reproductive Biology and Endocrinology* (2025) 23:72
https://doi.org/10.1186/s12958-025-01403-1

Reproductive Biology and Endocrinology

RESEARCH Open Access

GnRH-a use before programmed frozen embryo transfer cycles for women with PCOS: a retrospective cohort study

Luyang Zha[1,2], Jingzhi Yang[3], Fei Li[1,2], Bo Huang[1,2], Yaxin Guo[1,2*†] and Lei Jin[1,2*†]

Abstract

Background Programmed protocols are most commonly chosen as endometrial preparation for women with polycystic ovarian syndrome (PCOS) undergoing frozen-thawed embryo transfer (FET) cycles. However, the efficacy of gonadotropin-releasing hormone agonist (GnRH-a) pretreatment before programmed cycles is still up for debate. This study was to compare the pregnancy and perinatal outcomes of PCOS patients receiving programmed cycles with and without GnRH-a pretreatment as endometrial preparation in FET cycles.

Methods This is a retrospective cohort study conducted in the Reproductive Medicine Centre of Tongji Hospital. The primary analysis included 2733 FET cycles (223 were programmed cycles combined with GnRH-a pretreatment; 2510 were programmed cycles) during Jan. 2016 and Sept. 2022 from 1934 women with PCOS. Patients who had undergone both endometrial preparation protocols were further analyzed as a subgroup. The primary outcomes were pregnancy outcomes including live birth rate, clinical pregnancy rate, biochemical pregnancy loss rate, ectopic pregnancy rate, and multiple pregnancy rate. The secondary outcomes were perinatal outcomes. Propensity score matching (PSM) and generalized estimating equation were employed to eliminate essential confounders and account for patients with multiple cycles. The subgroup analysis included patients who underwent both endometrial preparation regimens and utilized the Wilcoxon's matched pairs test to compare the adjusted pregnancy outcomes rate, calculated by dividing the number of pregnancy outcomes by the number of cycles.

Results The essential baseline variables of the patients were balanced after conducting PSM. Pregnancy outcomes of the total PCOS population exhibited no variances ($P > 0.05$) between protocols after adjustments. When focusing on patients who had received both protocols, GnRH-a administration was associated with increased adjusted live birth rates ($P < 0.001$), singleton live birth rates ($P < 0.001$), multiple live birth rates ($P = 0.049$), clinical pregnancy rates ($P < 0.001$), and lower miscarriage rates ($P = 0.028$). Further analysis of these patients indicated that the pregnancy outcomes of therapy with GnRH-a were superior to those without only in the second transfer cycle. No significant

†Lei Jin and Yaxin Guo are joint senior authors.

*Correspondence:
Yaxin Guo
guoyaxin610@163.com
Lei Jin
leijintongjih@qq.com

Full list of author information is available at the end of the article

difference was exhibited in singleton perinatal outcomes in terms of gestational age, birth weight, delivery mode, gender, obstetric complications, and adverse birth outcomes between the two groups ($P > 0.05$).

Conclusions GnRH-a pretreatment before programmed cycles may not affect pregnancy or perinatal outcomes of general women with PCOS in FET cycles but may be beneficial for PCOS patients who did not achieve a live birth during the first cycle receiving a programmed protocol. The conclusion should be considered with caution. Further well-designed studies are required to validate our findings.

Keywords Polycystic ovary syndrome, Frozen-thawed embryo transfer, Endometrial Preparation, Programmed cycle, Gonadotropin-releasing hormone agonist

Introduction

Polycystic ovarian syndrome (PCOS) has an overall incidence rate of 8–13% according to Rotterdam diagnostic criteria, making it the most prevalent endocrinopathy in reproductive-aged women [1]. Numerous studies have demonstrated impaired fertility or reproductive complications among PCOS patients [2, 3]. In vitro fertilization and embryo transfer (IVF-ET) is recommended for women with PCOS who fail to induce ovulation or prefer not to receive surgical treatment to achieve pregnancy outcomes [4–6].

Frozen-thawed embryo transfer (FET) is widely applied among women with PCOS due to sufficient oocytes retrieved, significantly lower risks of ovarian hyperstimulation syndrome (OHSS), and better pregnancy outcomes in comparison to fresh embryo transfer [7, 8]. The establishment of a receptive endometrium constitutes a vital component of FET cycles, with various protocols being implemented in clinical practice [9]. Though the optimal endometrial preparation protocol for PCOS patients remains undetermined, programmed cycles are most commonly chosen for PCOS patients whose menstrual cycles are often not regular due to convenience and controllability [10–14]. However, the efficacy of gonadotropin-releasing hormone agonist (GnRH-a) pretreatment before programmed cycles as endometrial preparation is still up for debate [15]. PCOS patients frequently exhibit elevated estrogen levels and tonic hypersecretion of luteinizing hormone (LH), which are detrimental to embryonic development and endometrial function and ultimately result in unsuccessful pregnancy outcomes [16]. The administration of GnRH-a before estrogen administration may diminish the adverse factors above by suppressing the hypothalamic-pituitary-ovarian axis and therefore has potential benefits for PCOS patients [17]. Moreover, research has proved that GnRH-a pretreatment could regulate factors related to implantation and thereby enhance endometrial receptivity [18].

Indeed, some previous studies reported that the combination of GnRH-a administration and programmed protocols appears to yield enhanced reproductive outcomes in PCOS patients undergoing FET cycles [19–22]. Nevertheless, these findings were questioned in a randomized controlled trial (RCT) reporting that GnRH-a pretreatment failed to enhance live birth rates [11]. These conflicting findings make it questionable if GnRH-a pretreatment prior to the endometrial preparation could improve pregnancy outcomes among women with PCOS. Another problem is that limited research has focused on obstetric outcomes among women with PCOS, not to mention the fact that FET cycle itself may lead to an increased risk of maternal complications, which should be of particular concern [23]. Furthermore, a few studies have reported higher risks of low birthweight in GnRH-a pretreatment programmed cycles, which may have an impact on clinical decision-making and require further research to verify the conclusion [21, 24].

Consequently, the current study was designed to assess the difference in pregnancy and perinatal outcomes after programmed cycles combined or not combined with GnRH-a pretreatment among women with PCOS undergoing FET and to complement existing research findings.

Materials and methods

Patients

Patients with PCOS admitted to the Reproductive Medicine Center of Tongji Hospital who underwent programmed FET cycles from Jan. 2016 to Sept. 2022 were included in this historical cohort research. Based on the revised Rotterdam criteria introduced in 2004, the diagnosis of PCOS required the existence of at least two of the indications below: polycystic ovaries, oligo-anovulation, and clinical or biochemical signs of hyperandrogenism [25]. The exclusion criteria were as follows: (1) candidates with adrenal hyperplasia or hypogonadotropic hypogonadism; (2) cycles with preimplantation genetic testing (PGT); (3) fertilization by methods other than IVF, intracytoplasmic sperm injection (ICSI) or rescued ICSI; (4) non-autologous cycles or cycles using frozen oocytes; (5) canceled cycles; and (6) missing data regarding reproductive outcomes; (7) spouse with azoospermia. To observe and compare the efficacy of the two endometrial preparation protocols on the same patient, a subgroup analysis was conducted restricted to women with PCOS who had undergone both endometrial preparation

regimens. Additionally, we also analyzed another subgroup restricted to cycles with single blastocyst transfer. To comprehensively compare the two endometrial preparation protocols, we conducted further analysis of perinatal outcomes in patients with singleton liveborn infants (Fig. 1).

Data on perinatal outcomes were collected through a subsequent telephone interview by dedicated staff. Other data came from the electronic medical record system of the center. The study was granted ethical approval by the Institutional Review Board of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology (reference: TJ-IRB20230349).

Endometrial Preparation before FET

Detailed descriptions of endometrial preparation regimens can be found in our previously published works [26–29]. Briefly, in the programmed FET therapy, endometrial preparation began on day 2 of the menstrual cycle with oral estradiol (Progynova®; Bayer Schering Pharma AG, Germany) at a daily dose of 2 mg and was maintained for three consecutive days, followed by incremental increases of 2 mg/d every four days until day 12. The evaluation of ovulation and thickness of endometrium commenced by serial transvaginal ultrasound examination (USE) from day 13 and adjustment of estradiol dosage was made according to endometrial thickness. 40 mg intramuscular progesterone and 20 mg oral dydrogesterone were administered when the

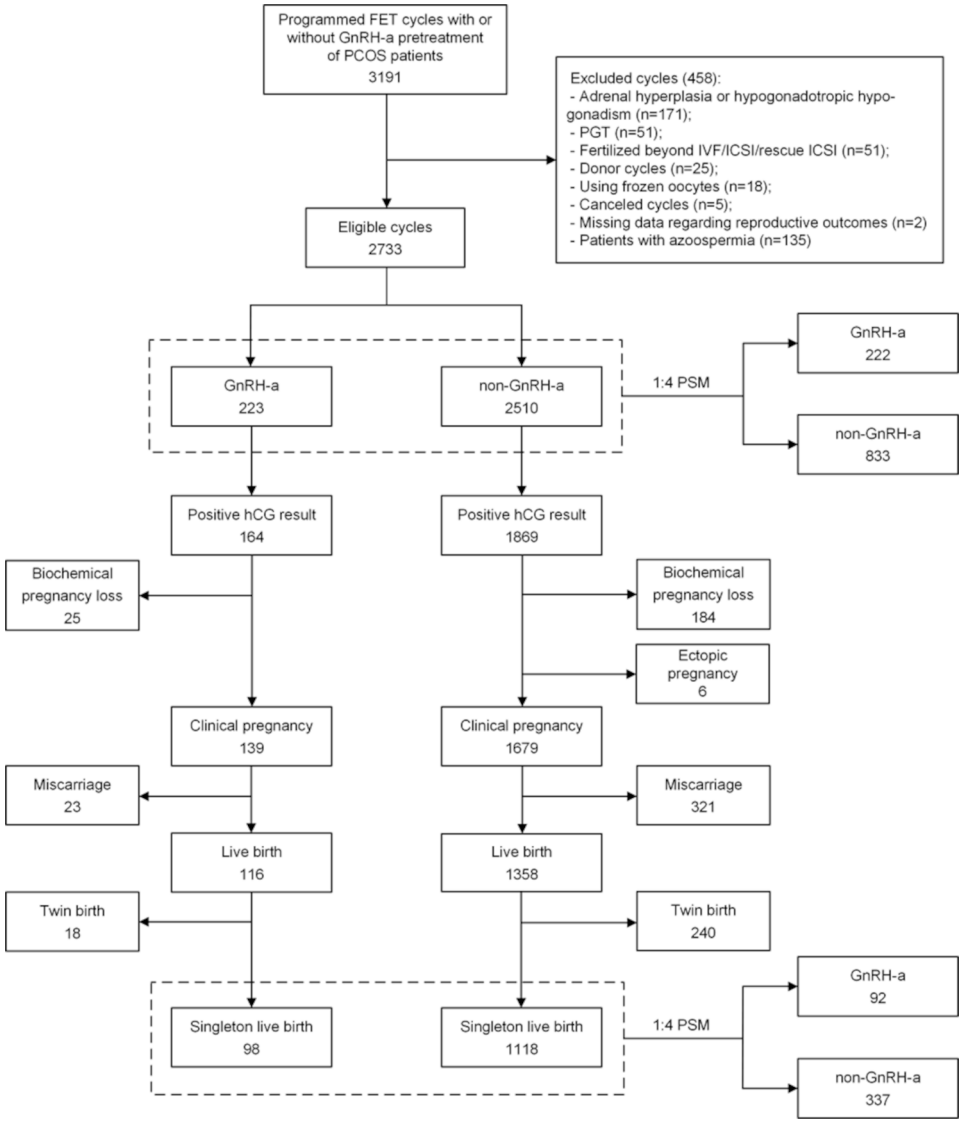

Fig. 1 The flowchart of patient recruitment. GnRH-a, gonadotropin-releasing hormone agonist / patients receiving programmed cycles with gonadotropin-releasing hormone agonist pretreatment; non-GnRH-a, patients receiving programmed cycles; PCOS, polycystic ovarian syndrome; FET, frozen-thawed embryo transfer; PGT, preimplantation genetic testing; ICSI, intracytoplasmic sperm injection; hCG, human Chorionic Gonadotrophin

endometrial thickness approached levels of the hCG day in fresh cycles or no less than 8 mm. If the endometrium was not thick enough, the decision to cancel the transfer would be made considering the patient's wishes alongside the physician's recommendations. In programmed protocols with GnRH-a pretreatment, 3.75 mg of GnRH-a (leuprorelin, Beijing Biote) was injected on day 2 of the menstrual cycle. Programmed cycles were then initiated as mentioned above after a follow-up visit 28 days later. 5 patients were excluded from the analysis due to cycle cancellation since their embryos did not survive post-thaw. All the patients included in the study completed transfers after around day 13 of estrogen administration.

The choice of endometrial preparation regimen was based on patients' conditions and preferences and the clinician's experience. The clinical protocols and success rates did not change between 2016 and 2022.

Embryo procedure

Thawing and transferring of embryos were performed on the third day (for D3 cleavage stage embryos) or on the fifth day (for D5 and D6 blastocysts) of progesterone administration. D3 good-quality cleavage embryos referred to normally fertilized embryos with 7 to 8 cells and < 20% fragmentation. Blastocysts of grades AA, AB, BA, and BB assessed by the Gardner scoring system, which grades blastocysts based on the expansion of the blastocoel cavity, inner cell mass, and trophoblast ectodermal cells, were identified as good quality [30]. Serum hCG was measured 2 weeks after FET for diagnosis of pregnancy.

Outcomes

Pregnancy outcomes and singleton perinatal outcomes of enrolled PCOS patients were measured.

Clinical pregnancy was defined by the identification of an intrauterine gestational sac via USE. No less than one live baby delivered was considered a live birth. Miscarriage referred to the loss of IUGS confirmed by USE. Biochemical pregnancy loss was classified as the situation when serum hCG was increased but no gestational sac existed. Ectopic pregnancy was classified as a confirmed pregnancy with an extrauterine gestational sac.

The main abnormal perinatal outcomes measured included obstetrical complications and adverse birth outcomes. Obstetrical complications were hypertensive disorder complicating pregnancy (HDP), gestational diabetes mellitus (GDM), placenta previa, premature rupture of membranes (PROM), and fetal malformation. Adverse birth outcomes were preterm birth (PTB, gestation < 37 weeks), very preterm birth (VPTB, gestation between 28 and 37 weeks), extremely preterm infant (EPTB, gestation < 28 weeks), macrosomia (> 4,000 g), low birth weight (LBW, < 2,500 g), small for gestational age (SGA, birthweight < 10th percentile of reference standard for gestational age) and large for gestational age (LGA, birthweight > 90th percentile of reference standard for gestational age). The references for the standard birthweight of each gestational age adjusted for sex were based on the Chinese population [31].

Statistical analysis

All continuous variables were non-normally distributed confirmed by the Shapiro-Wilk test. Baseline characteristics were described using median (with interquartile range) for continuous variables and count (with percentage) for categorical variables. Continuous variables among groups were compared using the Mann-Whitney U test. Categorical variables were analyzed by the Chi-squared test or Fisher's exact test.

To reduce confounding biases, propensity score matching (PSM) was employed to achieve a similar distribution of baseline covariates in the two cohorts. When analyzing pregnancy outcomes, PCOS patients receiving programmed cycles with or without GnRH-a pretreatment were matched 1:4 through nearest neighbor matching. In the PSM model incorporated with a caliper value set to 0.05, IVF age, body mass index (BMI), and endometrial thickness were included as continuous variables, while high-quality embryo, uterine factors, and rank of the transfer cycle (cycle rank) were treated as a categorical variable. A similar PSM analysis was also performed for prenatal outcomes incorporating variables of IVF age, BMI, endometrial thickness, high-quality embryo, and cycle rank. The standardized mean difference was less than 0.1 after matching, suggesting a negligible intergroup difference [32]. The propensity score distributions of the two matched groups were similar (Figure S1; Figure S2).

To show the strength of the relationship, univariate analysis was used to produce unadjusted odds ratios (ORs). Considering the presence of participants with multiple FET cycles, multivariate logistic regression models fitted with a generalized estimating equation (GEE) was employed to control confounders and compute adjusted odds ratios (aORs). GEE works well with correlations between repeated measurements, such as longitudinal data, with the advantage of providing consistent and unbiased estimates of parameters regardless of correlation structures [33].

In the subgroup analysis where patients underwent both endometrial preparation regimens, we used adjusted rates corresponding to the specified protocol for each patient determined by no. of pregnancy outcomes divided by no. of cycles. Adjusted rates were described as mean ± standard deviation and compared using paired samples Wilcoxon signed rank test to eliminate confounding factors between groups.

Data analysis was performed using SPSS 27. PSM was conducted using R (version 4.3.2) "MatchIt" packet. $P < 0.05$ was regarded as statistically significant.

Results

Baseline and cycle characteristics

The analysis comprised 2733 cycles from 1934 eligible PCOS patients in total, of which 223 were programmed cycles with GnRH-a pretreatment (GnRH-a group) and 2510 were programmed cycles alone (non-GnRH-a group), as seen in Fig. 1.

Demographics of the total patient cohort were significantly different ($P < 0.05$) in uterine factor, maternal age, the interval between embryo transfer and oocyte retrieval, cycle rank, endometrial thickness, ovarian stimulation protocols, and good-quality embryo. Women receiving GnRH-a pretreatment were older and experienced more FET cycles, whereas their endometrial thickness was slightly greater. After implementing PSM, statistically significant disparities only existed in the interval between embryo transfer and oocyte retrieval ($P = 0.001$), as shown in Table 1.

Pregnancy outcomes

The general PCOS population showed no differences ($P > 0.05$) in clinical pregnancy rate (CPR), live birth rate (LBR), singleton live birth rate (SLBR), multiple live births rate (MLBR), miscarriage rate (MR), ectopic pregnancy rate (EPR), and multiple pregnancy rate (MPR) between protocols. However, the GnRH-a group demonstrated a significantly higher biochemical pregnancy loss rate (BPR) in comparison to the non-GnRH-a group (11.2% vs. 7.3%; OR = 1.60; 95%CI, 1.01–2.53; $P = 0.047$) To further mitigate potential influences on clinical outcomes, GEE was conducted while adjusting for IVF age, BMI, endometrial thickness, the interval between embryo transfer and oocyte retrieval, duration of infertility, uterine factor, cycle rank, luteal-phase support, no. and stage of embryos transferred, and good-quality embryo, as shown in Table 2. The difference in BPR was still significant after adjustment (aOR = 1.60; 95%CI, 1.01–2.55; $P = 0.046$).

After PSM, the results remained non-significant in CPR, LBR, SLBR, MLBR, MR, and EPR. No evident difference was observed in BPR (OR = 1.55; 95%CI, 0.94–2.57; $P = 0.089$). Results were similar when adjusted by GEE.

Subgroup analysis

Interestingly, we found that 138 patients had undergone two protocols, resulting in a total of 356 transfer cycles (150 with GnRH-a administration and 206 without), as shown in Table S1. In the first cycle, 7 (5.07%) individuals achieved live births, while in the second cycle was 60 (43.48%). Some patients underwent further cycles, with a maximum of six transfer cycles (data not shown). The endometrium was thicker when using GnRH-a (9.40 vs. 9.00, $P = 0.008$). To comprehensively evaluate all cycles undertaken by the patients and ensure baseline comparability, we employed paired tests to compare the adjusted rates of pregnancy outcomes between two endometrial preparation protocols (Table 3). GnRH-a pretreatment was associated with higher LBR ($P < 0.001$), SLBR ($P < 0.001$), MLBR ($P = 0.049$), CPR ($P < 0.001$), MPR ($P = 0.008$) and lower MR ($P = 0.028$).

To further eliminate the influence of cycle order, we analyzed LBR, MR, CPR, and BPR for each cycle rank among the 138 patients (Table S2). Multivariate logistic regression models were employed to control key confounders, including IVF age, endometrial thickness, type of embryo transferred, and BMI. Due to the limited number of individuals undergoing cycles 4–6, adjustments were made only for cycles 1–3. The results indicated that LBR (aOR = 5.60; 95%CI, 2.38–13.19; $P < 0.001$) and CPR (aOR = 3.31; 95%CI, 1.57-7.00; $P = 0.002$) with GnRH-a protocol showed significant increases only in Cycle2. In contrast, no differences in pregnancy outcomes were observed between the two protocols for other cycle ranks. Additionally, the pregnancy outcomes in Cycle2 demonstrated a marked improvement compared to Cycle1. We further compared the baseline characteristics of patients in Cycle2 who added GnRH-a versus those who did not, following a programmed Cycle1 that failed to achieve a live birth. Patients who switched to downregulation had lower numbers of oocytes retrieved (18.5 vs. 24, $P = 0.015$) and fewer MII oocytes (16 vs. 22, $P = 0.012$) during IVF, with no significant differences in other characteristics (Table S3).

Since many patients in the subgroup attempted GnRH-a administration in Cycle2 after failing to receive a live birth in Cycle1 using a programmed protocol, we focused on the outcomes of their second cycle (Table S4). Consequently, we conducted a further analysis of this group of patients ($n = 86$). The results indicated a significant increase in CPR (OR = 7.83; 95%CI, 3.93–15.57; $P < 0.001$).

In another subgroup analysis focusing on PCOS patients who underwent single blastocyst transfer, endometrial preparation regimens were not associated with pregnancy outcomes (Table S5). Previous strategies for single blastocyst transfer often considered age factors. Therefore, we conducted a stratified analysis of patients aged 20–35 years and those over 35 years, and the results were consistent (Table S6).

Singleton perinatal outcomes

A total of 1216 singleton liveborn infants conceived through programmed cycles using GnRH-a ($n = 98$) and

Table 1 Demographics and pregnancy outcomes of the overall patient cohort pre- and post-PSM

Variable	Pre-PSM			Post-PSM		
	non-GnRH-a (*n* = 2510)	GnRH-a (*n* = 223)	*P* value	non-GnRH-a (*n* = 833)	GnRH-a (*n* = 222)	*P* value
Baseline FSH, mIU/mL	6.33 (5.39–7.35)	6.35 (5.43–7.37)	0.872	6.32 (5.39–7.36)	6.35 (5.42–7.38)	0.979
AFC	24.00 (22.00–24.00)	24.00 (22.00–24.00)	0.819	24.00 (22.00–24.00)	24.00 (22.00–24.00)	0.924
AMH level, ng/ml	10.65 (7.24–15.20)	9.83 (7.12–15.26)	0.500	10.83 (7.26–15.22)	9.83 (7.12–15.26)	0.434
BMI, kg/m2	22.66 (20.61–25.12)	23.05 (21.09–25.59)	0.164	23.03 (20.81–25.53)	23.04 (21.08–25.60)	0.799
Duration of infertility, y	3.00 (2.00–5.00)	3.00 (2.00–4.00)	0.148	3.00 (2.00–5.00)	3.00 (2.00–4.00)	0.071
Infertility diagnosis			0.120			0.253
Primary infertility, n (%)	1811 (72.15%)	150 (67.26%)		592 (71.07%)	149 (67.12%)	
Secondary infertility, n (%)	699 (27.85%)	73 (32.74%)		241 (28.93%)	73 (32.88%)	
Infertility etiology, n (%)						
Male factor	520 (20.72%)	49 (21.97%)	0.658	173 (20.77%)	49 (22.07%)	0.672
Female factors						
Diminished ovarian reserve	10 (0.40%)	0 (0.00%)	> 0.999	6 (0.72%)	0 (0.00%)	0.353
Tubal factor	931 (37.09%)	90 (40.36%)	0.334	300 (36.01%)	90 (40.54%)	0.214
Endometriosis	79 (3.15%)	12 (5.38%)	0.075	26 (3.12%)	12 (5.41%)	0.105
Uterine factor	299 (11.91%)	45 (20.18%)	< 0.001*	125 (15.01%)	44 (19.82%)	0.082
Unexplained/Other	7 (0.28%)	1 (0.45%)	0.494	3 (0.36%)	1 (0.45%)	> 0.999
IVF age, y	29.00 (27.00–31.00)	29.00 (27.00–32.00)	0.031*	29.00 (27.00–32.00)	29.00 (27.00–32.00)	0.918
Ovarian stimulation protocols, n (%)			0.002*			0.084
Long GnRH-a	451 (17.97%)	23 (10.31%)		131 (15.73%)	23 (10.36%)	
GnRH antagonist	864 (34.42%)	82 (36.77%)		297 (35.65%)	82 (36.94%)	
GnRH-a ultra-long	1143 (45.54%)	107 (47.98%)		383 (45.98%)	106 (47.75%)	
Other protocols	52 (2.07%)	11 (4.93%)		22 (2.64%)	11 (4.95%)	
Duration of stimulation, d	10.00 (9.00–12.00)	10.00 (9.00–12.00)	0.821	10.00 (9.00–12.00)	10.00 (9.00–12.00)	0.967
Gonadotropin dose, IU	1597.50 (1245.00-2176.88)	1650.00 (1350.00-2197.50)	0.251	1650.00 (1275.00-2197.50)	1650.00 (1350.00-2197.50)	0.555
Fertilization, n (%)						
IVF	1774 (70.68%)	153 (68.61%)	0.810	575 (69.03%)	152 (68.47%)	0.983
ICSI	610 (24.30%)	58 (26.01%)		215 (25.81%)	58 (26.13%)	
Rescue ICSI	126 (5.02%)	12 (5.38%)		43 (5.16%)	12 (5.41%)	
Oocytes retrieved	19.00 (14.00–24.00)	18.00 (12.00–24.00)	0.132	19.00 (14.00–25.00)	18.00 (12.00–24.00)	0.119
MII oocytes	16.00 (12.00–21.00)	16.00 (11.00–20.00)	0.088	16.00 (12.00–22.00)	16.00 (11.00–20.00)	0.097
Oocyte maturation rate	0.92 (0.82-1.00)	0.89 (0.81-1.00)	0.356	0.92 (0.82-1.00)	0.89 (0.81-1.00)	0.246
2PN	11.00 (8.00–15.00)	11.00 (7.00–15.00)	0.156	11.00 (8.00–15.00)	11.00 (7.00–15.00)	0.156
Normal fertilization rate	0.67 (0.56–0.79)	0.68 (0.57–0.78)	0.763	0.68 (0.56–0.80)	0.68 (0.57–0.78)	0.535
Blastocyst formation rate	0.75 (0.58–0.87)	0.75 (0.57–0.86)	0.831	0.73 (0.57–0.86)	0.75 (0.57–0.86)	0.653
FET age, y	29.00 (27.00–32.00)	30.00 (28.00–33.00)	< 0.001*	30.00 (28.00–33.00)	30.00 (28.00–33.00)	0.536
Interval between embryo transfer and oocyte retrieval, d	93.00 (54.75–213.00)	173.00 (97.00-370.00)	< 0.001*	133.00 (68.00-322.00)	170.50 (96.75-370.25)	0.001*
Cycle rank						0.796
1	1839 (73.27%)	95 (42.60%)	< 0.001*	377 (45.26%)	95 (42.79%)	
2–3	620 (24.70%)	118 (52.91%)		422 (50.66%)	117 (52.70%)	
>3	51 (2.03%)	10 (4.48%)		34 (4.08%)	10 (4.50%)	
Endometrial thickness, mm	9.10 (8.40–10.00)	9.40 (8.50–10.40)	0.026*	9.20 (8.50–10.10)	9.40 (8.48–10.40)	0.430
No. of embryos thawed			0.764			0.911
1	1559 (62.11%)	144 (64.57%)		527 (63.27%)	144 (64.86%)	
2	938 (37.37%)	78 (34.98%)		300 (36.01%)	77 (34.68%)	
>=3	13 (0.52%)	1 (0.45%)		6 (0.72%)	1 (0.45%)	

Table 1 (continued)

Variable	Pre-PSM			Post-PSM		
	non-GnRH-a (*n* = 2510)	GnRH-a (*n* = 223)	*P* value	non-GnRH-a (*n* = 833)	GnRH-a (*n* = 222)	*P* value
No. of surviving embryos			0.407			0.718
1	1579 (62.91%)	144 (64.57%)		537 (64.47%)	144 (64.86%)	
2	926 (36.89%)	78 (34.98%)		294 (35.29%)	77 (34.68%)	
>=3	5 (0.20%)	1 (0.45%)	0.113	2 (0.24%)	1 (0.45%)	0.052
No. of surviving embryos/no. of embryos thawed	1.00 (1.00–1.00)	1.00 (1.00–1.00)		1.00 (1.00–1.00)	1.00 (1.00–1.00)	
No. of embryos transferred, n (%)			0.991			0.562
1	1678 (66.85%)	149 (66.82%)		576 (69.15%)	149 (67.12%)	
2	832 (33.15%)	74 (33.18%)		257 (30.85%)	73 (32.88%)	
Embryo stage, n (%)			0.413			
Blastocyst	2271 (90.48%)	198 (88.79%)		743 (89.20%)	197 (88.74%)	
Cleavage embryo	239 (9.52%)	25 (11.21%)		90 (10.80%)	25 (11.26%)	0.846
Good-quality embryo, n(%)	1986 (79.12%)	158 (70.85%)	0.004*	587 (70.47%)	158 (71.17%)	0.838
Luteal-phase support, n (%)			0.074			0.878
Intramuscular injection and oral administration	338 (13.47%)	18 (8.07%)		74 (8.88%)	18 (8.11%)	
Vaginal gel administration and oral administration	1150 (45.82%)	101 (45.29%)		390 (46.82%)	101 (45.50%)	
Vaginal suppository administration and oral administration	1019 (40.60%)	104 (46.64%)		368 (44.18%)	103 (46.40%)	
Others	3 (0.12%)	0 (0.00%)		1 (0.12%)	0 (0.00%)	

Note: Continuous data are described as median (Q1-Q3) and compared using Mann-Whitney U test. Categorical data are described as n (%) and compared using Chi-squared test or Fisher's exact test

Patients receiving programmed cycles with GnRH-a pretreatment were matched (1:4) to corresponding patients receiving programmed cycles alone using the nearest neighbour matching. The PSM model incorporated IVF age, BMI, endometrial thickness, embryo stage, high-quality embryo, uterine factor, and cycle rank with a caliper value of 0.05

non-GnRH-a = programmed cycles; GnRH-a = programmed cycles with gonadotropin-releasing hormone agonist pretreatment; FSH = follicle-stimulating hormone; AFC = antral follicle count; AMH = anti-Müllerian hormone; BMI = body mass index; MII = metaphase II; 2PN = zygotes with two pronuclei; IVF = in vitro fertilization; ICSI = intracytoplasmic sperm injection; FET = frozen-thawed embryo transfer

*$P < 0.05$

programmed cycles ($n = 1118$) were assessed for perinatal outcomes (Fig. 1, Table S7). The medium interval between embryo transfer and oocyte retrieval was 196.50 (108.25–361.00) days in the GnRH-a group and 89.00 (40.75–201.00) days in the non-GnRH-a group, which was statistically different ($P < 0.001$). The GnRH-a group revealed a relatively small percentage of first FET cycles compared to the non-GnRH-a group (44.90% vs. 75.80%; $P < 0.001$). The difference in cycle rank was not significant after PSM. Nevertheless, the two groups did not differ significantly regarding any of the perinatal outcomes.

As shown in Table 4, GEE was conducted while adjusting for IVF age, BMI, endometrial thickness, the interval between embryo transfer and oocyte retrieval, infertility diagnosis, duration of infertility, cycle rank, no. and stage of embryos transferred, and good-quality embryo. Pretreatment with GnRH-a did not exhibit any correlation with abnormal perinatal outcomes. The results were still retained even after eliminating confounding factors by PSM and GEE.

Discussion

Main findings

This large-scale study provided clinically relevant evidence suggesting that GnRH-a pretreatment before programmed cycles may not affect pregnancy and perinatal outcomes of general women with PCOS in FET. However, pregnancy outcomes were superior in the second cycles when GnRH-a was used, especially for those who were treated with programmed protocols in the first cycles and failed to achieve live births.

Interpretation

Previous studies

Several previous studies have sought to identify the effect of GnRH-a use for endometrial preparation before programmed cycles but yielded different conclusions. In terms of pregnancy outcomes, whether GnRH-a improves LBR remains a subject of debate [11, 20–22, 34–36]. Only a few studies have focused on perinatal outcomes. Liu et al. observed an elevated risk of PTB in PCOS patients using the GnRH-a protocol [34]. However, Wang et al. disagreed and found that GnRH-a pretreatment was linked to a decreased risk of PTB and an

Table 2 Crude and adjusted odds ratios for pregnancy outcomes pre- and post-PSM

Pre-PSM						
Variable	non-GnRH-a ($n=2510$)	GnRH-a ($n=223$)	OR (95%CI)	P value	aOR (95%CI)	P value
Live Birth	1358 (54.10%)	116 (52.00%)	0.92 (0.70–1.22)	0.555	1.13 (0.85–1.51)	0.401
Singleton Live Birth	1118 (44.50%)	98 (43.90%)	0.98 (0.74–1.29)	0.865	1.14 (0.85–1.54)	0.378
Multiple Live Births	240 (9.60%)	18 (8.10%)	0.83 (0.50–1.37)	0.467	1.14 (0.63–2.06)	0.671
Miscarriage	321 (12.80%)	23 (10.30%)	0.78 (0.50–1.23)	0.288	0.75 (0.48–1.17)	0.199
Clinical Pregnancy	1679 (66.90%)	139 (62.30%)	0.82 (0.62–1.08)	0.160	0.98 (0.72–1.33)	0.891
Biochemical Pregnancy Loss	184 (7.30%)	25 (11.20%)	1.60 (1.01–2.53)	0.047*	1.60 (1.01–2.55)	0.046*
Ectopic pregnancy	6 (0.20%)	0 (0.00%)	-	>0.999	-	-
Multiple pregnancy	378 (15.10%)	32 (14.30%)	0.95 (0.64–1.39)	0.775	1.31 (0.80–2.15)	0.285
Post-PSM						
Variable	non-GnRH-a ($n=833$)	GnRH-a ($n=222$)	OR (95%CI)	P value	aOR (95%CI)	P value
Live Birth	408 (49.00%)	116 (52.30%)	1.14 (0.85–1.54)	0.390	1.21 (0.89–1.64)	0.218
Singleton Live Birth	344 (41.30%)	98 (44.10%)	1.12 (0.83–1.52)	0.445	1.20 (0.88–1.63)	0.258
Multiple Live Births	64 (7.70%)	18 (8.10%)	1.06 (0.61–1.83)	0.834	1.16 (0.62–2.17)	0.654
Miscarriage	110 (13.20%)	23 (10.40%)	0.76 (0.47–1.22)	0.257	0.75 (0.47–1.20)	0.227
Clinical Pregnancy	518 (62.20%)	139 (62.60%)	1.02 (0.75–1.38)	0.907	1.06 (0.77–1.46)	0.730
Biochemical Pregnancy Loss	63 (7.60%)	25 (11.30%)	1.55 (0.94–2.57)	0.089	1.57 (0.93–2.62)	0.089
Ectopic pregnancy	0 (0.00%)	0 (0.00%)	-	-	-	-
Multiple pregnancy	100 (12.00%)	32 (14.40%)	1.24 (0.80–1.90)	0.336	1.42 (0.83–2.43)	0.205

Note: OR (95%CI) were based on univariate analysis. aOR (95%CI) were based on generalized estimating equations adjusting for IVF age, BMI, endometrial thickness, the interval between embryo transfer and oocyte retrieval, duration of infertility, uterine factor, cycle rank, luteal-phase support regimen, embryo stage, no. of embryos transferred, and good-quality embryo

non-GnRH-a = programmed cycles; GnRH-a = programmed cycles with gonadotropin-releasing hormone agonist pretreatment; OR = odds ratios; aOR = adjusted odds ratios; CI = confidence interval

*$P<0.05$

Table 3 Clinical outcomes of patients who had undergone both endometrial Preparation protocols

Adjusted rate[a]	**non-GnRH-a ($n=138$)**	**GnRH-a ($n=138$)**	**Z statistics**	***P* value**
Live Birth	0.138 ± 0.302	0.446 ± 0.490	-5.471[b]	<0.001*
Singleton Live Birth	0.113 ± 0.280	0.377 ± 0.479	-5.099[b]	<0.001*
Multiple Live Births	0.024 ± 0.136	0.069 ± 0.250	-1.965[b]	0.049*
Miscarriage	0.192 ± 0.369	0.100 ± 0.289	-2.198[c]	0.028*
Clinical Pregnancy	0.329 ± 0.431	0.546 ± 0.487	-3.822[b]	<0.001*
Biochemical Pregnancy Loss	0.121 ± 0.296	0.132 ± 0.329	-0.458[b]	0.646
Ectopic pregnancy	0.002 ± 0.028	0.000 ± 0.000	-1.000[c]	0.317
Multiple pregnancy	0.052 ± 0.202	0.136 ± 0.340	-2.653[b]	0.008*

Note: Data are described as mean ± standard deviation and compared using paired samples Wilcoxon signed rank test

non-GnRH-a = programmed cycles; GnRH-a = programmed cycles with gonadotropin-releasing hormone agonist pretreatment

[a]Adjusted rate = No. of pregnancy outcomes/ No. of cycles per endometrial preperation protocol

[b] Based on negative rank

[c] Based on positive rank

*$P<0.05$

elevated SGA rate [21]. A similar finding was reported in an RCT suggesting that GnRH-a use may elevate the risk of delivering singleton infants with LBW [24].

Despite the contributions made by the above-mentioned studies to determining the optimum endometrial preparation regimen for women with PCOS in FET, their study designs presented certain shortages. Multiple pregnancy, as a common pregnancy outcome of IVF-ET among PCOS patients associated with increased abnormal obstetric and neonatal outcomes, was given little consideration [37, 38]. Additionally, all the studies enrolled patients who underwent multiple cycles without correcting for dependence between cycles within the same woman, and no studies specifically investigated potential differences in pregnancy outcomes when the same patient received the two therapies sequentially. Furthermore, obstetric outcomes should be emphasize given the rise in IVF [39]. Since only one RCT has examined this aspect, larger real-world observations are required for confirmation [24].

The current study, which attempted to address methodological issues in preceding studies while controlling

Table 4 Crude and adjusted odds ratios for Singleton perinatal outcomes pre- and post-PSM

Pre-PSM						
Variable	non-GnRH-a (*n* = 1118)	GnRH-a (*n* = 98)	OR (95%CI)	P value	aOR (95%CI)	P value
Birth weight, g	3400.00 (3100.00-3700.00)	3300.00 (3025.00-3500.00)	-	0.055	-	-
Gestational age, w	39.00 (38.00-39.57)	38.71 (37.50-39.36)	-	0.067	-	-
Delivery mode				0.562		0.669
Natural labor	149 (13.40%)	11 (11.30%)	1		1	
Cesarean delivery	961 (86.60%)	86 (88.70%)	1.21 (0.63–2.32)		1.16 (0.59–2.26)	
Gender				0.104		0.065
Male	644 (58.00%)	48 (49.50%)	1		1	
Female	466 (42.00%)	49 (50.50%)	1.41 (0.93–2.14)		1.50 (0.98–2.30)	
PTB	124 (11.20%)	12 (12.40%)	1.13 (0.60–2.12)	0.716	0.98 (0.50–1.93)	0.963
VTPB	16 (1.40%)	2 (2.10%)	1.44 (0.33–6.37)	0.629	1.17 (0.26–5.17)	0.838
EPTB	8 (0.70%)	0 (0.00%)	-	> 0.999	-	-
LBW	58 (5.20%)	6 (6.30%)	1.21 (0.51–2.87)	0.672	1.10 (0.45–2.70)	0.828
Macrosomia	91 (8.20%)	4 (4.20%)	0.49 (0.17–1.35)	0.167	0.45 (0.15–1.30)	0.138
SGA	46 (4.20%)	7 (7.30%)	1.80 (0.79–4.11)	0.161	1.63 (0.70–3.79)	0.258
LGA	231 (21.00%)	15 (15.60%)	0.70 (0.39–1.23)	0.214	0.77 (0.43–1.38)	0.379
HDP	69 (6.20%)	4 (4.10%)	0.65 (0.23–1.81)	0.408	0.65 (0.23–1.79)	0.399
GDM	70 (6.30%)	4 (4.10%)	0.64 (0.23–1.78)	0.391	0.60 (0.21–1.66)	0.322
Placenta previa	36 (3.20%)	2 (2.00%)	0.63 (0.15–2.64)	0.524	0.84 (0.20–3.58)	0.808
Premature rupture of membranes	39 (3.50%)	2 (2.00%)	0.58 (0.14–2.42)	0.452	0.79 (0.19–3.34)	0.749
Fetal malformation	22 (2.00%)	1 (1.00%)	0.51 (0.07–3.85)	0.517	0.59 (0.08–4.31)	0.599
Post-PSM						
Variable	non-GnRH-a (*n* = 337)	GnRH-a (*n* = 92)	OR (95%CI)	P value	aOR (95%CI)	P value
Birth weight, g	3350.00 (3100.00-3680.00)	3300.00 (3000.00-3500.00)	-	0.250	-	-
Gestational age, w	38.86 (38.00-39.43)	38.79 (37.46–39.43)	-	0.390	-	-
Delivery mode				0.926		0.887
Natural labor	39 (11.60%)	11 (12.00%)	1		1	
Cesarean delivery	297 (88.40%)	81 (88.00%)	0.97 (0.47–1.97)		0.95 (0.46–1.95)	
Gender				0.062		0.051
Male	201 (59.80%)	45 (48.90%)	1		1	
Female	135 (40.20%)	47 (51.10%)	1.56 (0.98–2.47)		1.61 (1.00-2.60)	
PTB	40 (11.90%)	12 (13.00%)	1.11 (0.56–2.22)	0.760	1.15 (0.56–2.33)	0.706
VTPB	6 (1.80%)	2 (2.20%)	1.23 (0.24–6.18)	0.805	1.30 (0.24–6.97)	0.756
EPTB	4 (1.20%)	0 (0.00%)	-	0.582	-	-
LBW	24 (7.20%)	6 (6.60%)	0.92 (0.36–2.31)	0.850	0.90 (0.34–2.40)	0.835
Macrosomia	35 (10.40%)	4 (4.40%)	0.39 (0.14–1.14)	0.086	0.35 (0.12–1.03)	0.056
SGA	16 (4.80%)	6 (6.60%)	1.39 (0.53–3.67)	0.501	1.43 (0.51–4.01)	0.493
LGA	68 (20.50%)	14 (15.40%)	0.71 (0.38–1.32)	0.278	0.68 (0.36–1.31)	0.249
HDP	21 (6.20%)	4 (4.30%)	0.68 (0.23–2.03)	0.491	0.71 (0.26–1.94)	0.498
GDM	20 (5.90%)	4 (4.30%)	0.72 (0.24–2.15)	0.553	0.69 (0.23–2.07)	0.510
Placenta previa	13 (3.80%)	2 (2.20%)	0.55 (0.12–2.49)	0.438	0.56 (0.11–2.86)	0.486
Premature rupture of membranes	14 (4.10%)	2 (2.20%)	0.51 (0.11–2.29)	0.379	0.53 (0.10–2.70)	0.442
Fetal malformation	9 (2.70%)	1 (1.10%)	0.40 (0.05–3.19)	0.386	0.36 (0.07–1.76)	0.208

Note: OR (95%CI) were based on univariate analysis. aOR (95%CI) were based on generalized estimating equations adjusting for IVF age, BMI, endometrial thickness, the interval between embryo transfer and oocyte retrieval, infertility diagnosis, duration of infertility, cycle rank, embryo stage, no. of embryos transferred, and good-quality embryo

non-GnRH-a = programmed cycles; GnRH-a = programmed cycles with gonadotropin-releasing hormone agonist pretreatment; PTB = preterm birth; VPTB = very preterm birth; EPTB = extremely preterm birth; LBW = low birth weight; SGA = small for gestational age; LGA = large for gestational age; HDP = hypertensive disorders of pregnancy; GDM = gestational diabetes mellitus. OR = odds ratios; aOR = adjusted odds ratios; CI = confidence interval

for multiple notable confounders including cycle rank, retrospectively observed the reproductive outcomes of PCOS patients undergoing different endometrial preparation regimens in the real world.

Pregnancy outcomes of the total PCOS cohort

In our study, the advantageous effect of GnRH-a was not observed in the overall PCOS cohort as pregnancy outcomes including LBR and MPR showed no difference

between the two therapies, which was consistent with a recent meta-analysis [40]. The cohort before PSM exhibited a rise in BPR in patients receiving GnRH-a pretreatment, while the difference was rendered non-significant upon balancing the distribution of essential confounders with PSM. This result was expected since factors including maternal age, obesity, endometrial receptivity, and embryo quality may be correlated with biochemical pregnancy loss [41]. Considering the prevalence of single embryo transfer for the benefit of reducing multiple pregnancy rates [42], we also focused specifically on women with PCOS undergoing transfer of single vitrified-warmed blastocyst which showed similar results.

Pregnancy outcomes of subgroup

We discovered that some patients had undergone both endometrial protocols, and we examined this subgroup. To our surprise, GnRH-a pretreatment before programmed cycles significantly improved LBR, SLBR, MLBR, CPR, and MPR while reducing MR in this subgroup, which was discordant with the results of the entire PCOS cohort. Through controlling for cycle rank, we found that the primary contribution to improved pregnancy outcomes originated from Cycle2, evidenced by a significant increase in both LBR and CPR. In clinical practice, patients may switch and add GnRH-a following a failed programmed cycle; therefore, we focused on the first two cycles of this subset of patients. Our analysis revealed that switching to a GnRH-a downregulated cycle enhanced CPR, subsequently leading to an increase in LBR.

The improvement in pregnancy outcomes following the switch of endometrial preparation protocol may be attributed to the potential benefits of GnRH-a. GnRH-a suppression may mitigate the adverse effects of elevated LH on the "implantation window" [43]. Androgen deprivation following GnRH-a administration could improve endometrial function [19]. Additionally, GnRH expression may inhibit inflammatory factors within the endometrium and enhance the expression of endometrial adhesion molecules [11]. In this study, we also found that the endometrium was thicker when GnRH-a was used.

We attempted to identify the characteristics of patients suitable for adding GnRH-a and found that those who benefited from switching to a downregulation protocol exhibited relatively fewer oocytes retrieved and MII oocytes in IVF. Currently, there is a lack of research on the relationship between oocyte retrieval, ovarian response, and endometrial preparation protocols in frozen cycles, and it remains unclear whether this characteristic is incidental. A higher oocyte retrieval number in PCOS women undergoing controlled ovarian hyperstimulation (COH) suggests a high ovarian response, which increases the risk of OHSS and elevated supraphysiological steroid levels in fresh IVF treatment [44]; however, these factors do not seem to influence frozen cycles. PCOS patients tend to retrieve more oocytes in COH, while these oocytes are often of lower quality [16]. An excessively high number of oocytes may also indicate poorer oocyte quality [45, 46]; however, the oocyte maturation rate, normal fertilization rate, blastocyst formation rate, and embryo quality were comparable, suggesting no difference in oocyte quality. Moreover, the LBR and CPR in Cycle2 for patients who underwent downregulation remained significantly higher compared to those who did not after adjusting for the number of oocytes and MII (data not shown). Furthermore, it was reported that patients with recurrent implantation failure may achieve better reproductive outcomes when using protocols with GnRH-a [46]. However, we found that in women with PCOS, GnRH-a downregulation may only benefit those with a history of a single failed transfer cycle. We could not determine whether this benefit arises from PCOS, the history of failed transfers, or the combined effect of both factors on endometrial receptivity. Existing evidence does not provide a definitive conclusion regarding the potential benefits of GnRH-a application in patients with a history of implantation failure, indicating a need for more well-designed studies [47–50]. It is difficult to provide a unified or comprehensive explanation for why this group of patients is suitable for downregulation protocols based on the available data and literature. There may be factors not addressed in our study that are related to endometrial preparation protocols or pregnancy outcomes, which could help explain the observed results.

Undeniably, Our results may partly stem from regression to the mean, as the majority of patients who failed in Cycle1 exhibited improved pregnancy outcomes in Cycle2, regardless of the endometrial preparation protocol utilized; however, the effects of adding GnRH-a in Cycle2 were still superior to those without GnRH-a, particularly for patients who failed to receive livebirth in Cycle1 using programmed protocols, as switching to downregulation yielded satisfactory pregnancy outcomes. The failure of the first cycle may indicate that these patients are unsuitable for programmed cycles and might be better suited for downregulation therapy. Our study reflected real clinical practice, indicating that switching to GnRH-a downregulation after a failed programmed cycle may be beneficial, representing a viable transfer strategy for clinicians to consider.

Singleton perinatal outcomes

We retrospectively observed the impacts of both regimens on singleton perinatal outcomes. No superiority was demonstrated of one protocol over the other. Although the GnRH-a group exhibited higher SGA rates

(7.30% vs. 4.20%) and slightly greater PTB rate (12.40% vs. 11.20%) compared to the non-GnRH-a group, the difference did not achieve statistical significance, which contrasts with previous studies [21, 24]. Given the inconsistency of these findings with previous studies, further research is necessary to confirm the validity of our findings.

Strengths and limitations

This real-world study utilized a substantial population size and employed multiple statistical methods, with the conclusions being repeatedly verified. Through the combination of PSM and GEE and Wilcoxon's matched pairs test, we minimized the impact of known confounding factors. We focused on real clinical practice where some patients may consider changing endometrial preparation therapies after failing the first cycles and provided recommendations to support clinical decision-making. Moreover, our study further contributed to assessing the safety of GnRH-a pretreatment in PCOS patients by conducting a comprehensive analysis of perinatal outcomes.

We acknowledge that the study has its limitations. Due to the retrospective design, it was not possible to control for all confounders and selection bias may exist. This may help explain why the addition of GnRH-a showed no benefit in the overall cohort but proved beneficial only for Cycle2 of those who underwent both protocols. Baseline characteristics on hormones including E2 and LH were not collected, nor did we assess subsequent hormone levels. In perinatal outcomes and subgroup analyses, some results need to be considered with caution due to sample size limitations, such as VPTB and EPTB. Moreover, alternative protocols for endometrial preparation exist, including ovarian stimulation protocols using letrozole, and it remains controversial which protocol is medically preferable [12, 13, 51]. This topic was not explored in this study due to the small patient population utilizing ovarian stimulation protocols at our center, indicating a need for further investigation in future studies.

Conclusions

The study is instructive for choosing appropriate endometrial preparation therapies for PCOS patients undergoing FET in the clinical setting, suggesting that GnRH-a administration before programmed cycles may not improve reproductive outcomes or affect perinatal outcomes in general PCOS patients. However, for PCOS patients who did not achieve a live birth during the first cycle receiving a programmed protocol, switching to a GnRH-a downregulation protocol in the subsequent cycle may be beneficial. Further large-scale RCTs are required to verify our conclusions, alongside fundamental research to elucidate the underlying mechanisms.

Abbreviations

PCOS	Polycystic ovary syndrome
GnRH-a	Gonadotropin-releasing hormone agonist
IVF	In vitro fertilization
ICSI	Intracytoplasmic sperm injection
FET	Frozen-thawed embryo transfer
BMI	Body mass index
PSM	Propensity score matching
GEE	Generalized estimating equation
OR	Odds ratio
aOR	Adjusted odds ratio
CI	Confidence interval

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12958-025-01403-1.

Supplementary Material 1

Acknowledgements

We are grateful for the contributions of all the staff of the Reproductive Medicine Center and the obstetric ward in Tongji Hospital.

Author contributions

Lei Jin and Yaxin Guo conceived and designed the study. Yaxin Guo, Jingzhi Yang, Fei Li acquired the data. Luyang Zha performed the statistical analyses and wrote the original manuscript. Luyang Zha, Yaxin Guo, and Bo Huang interpreted the data. Other authors provided comments and revised the paper. All authors contributed to the article and approved the final version.

Funding

The work was funded by the National Key Research and Development Program of China (2022YFC2702503).

Data availability

The primary datasets generated and analyzed in the current study are not publicly available but are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

The study was granted ethical approval by the Institutional Review Board of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology (reference: TJ-IRB20230349) and conducted in accordance with the declaration of Helsinki. Given that all analyses were retrospectively and non-interventional, the requirement for informed consent was waived.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

[1]Reproductive Medicine Center, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, 1095 JieFang Avenue, Wuhan 430030, China
[2]National Clinical Research Center for Obstetrics and Gynecology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, 1095 JieFang Avenue, Wuhan 430030, China
[3]Department of Orthopedics, Qilu Hospital of Shandong University, Jinan 250063, Shandong, China

Received: 15 April 2024 / Accepted: 25 April 2025
Published online: 15 May 2025

References

1. Bozdag G, Mumusoglu S, Zengin D, Karabulut E, Yildiz BO. The prevalence and phenotypic features of polycystic ovary syndrome: a systematic review and meta-analysis. Hum Reprod. 2016;31:2841–55.
2. Palomba S, de Wilde MA, Falbo A, Koster MPH, La Sala GB, Fauser BCJM. Pregnancy complications in women with polycystic ovary syndrome. Hum Reprod Update. 2015;21:575–92.
3. Guedikian AA, Lee AY, Grogan TR, Abbott DH, Largaespada K, Chazenbalk GD, et al. Reproductive and metabolic determinants of granulosa cell dysfunction in normal-weight women with polycystic ovary syndrome. Fertil Steril. 2018;109:508–15.
4. Carson SA, Kallen AN. Diagnosis and management of infertility: A review. JAMA. 2021;326:65–76.
5. Azziz R. Polycystic ovary syndrome. Obstet Gynecol. 2018;132:321–36.
6. Thessaloniki ESHRE, ASRM-Sponsored PCOS Consensus Workshop Group. Consensus on infertility treatment related to polycystic ovary syndrome. Fertil Steril. 2008;89:505–22.
7. Wei D, Ma J, Chen Z-J. Fresh versus frozen embryo transfer in PCOS: arguments for and against. Semin Reprod Med. 2017;35:359–63.
8. Chen Z-J, Shi Y, Sun Y, Zhang B, Liang X, Cao Y, et al. Fresh versus frozen embryos for infertility in the polycystic ovary syndrome. N Engl J Med. 2016;375:523–33.
9. Jc L, Ml B, Jf K. The impact of endometrial Preparation for frozen embryo transfer on maternal and neonatal outcomes: a review. Reprod Biol Endocrinol RBE. 2022;20:40.
10. Kotlyar AM, Seifer DB. Women with PCOS who undergo IVF: a comprehensive review of therapeutic strategies for successful outcomes. Reprod Biol Endocrinol RBE. 2023;21:70.
11. Luo L, Chen M, Wen Y, Zhang L, Zhou C, Wang Q. Pregnancy outcome and cost-effectiveness comparisons of artificial cycle-prepared frozen embryo transfer with or without GnRH agonist pretreatment for polycystic ovary syndrome: a randomised controlled trial. BJOG Int J Obstet Gynaecol. 2021;128:667–74.
12. Ka V, Ym C, Da C, Ws V, S A-G. Ovulation-induced frozen embryo transfer regimens in women with polycystic ovary syndrome: a systematic review and meta-analysis. J Assist Reprod Genet. 2024;41:2237–2251.
13. Yuan Y, Chang Q, Wen Y, Gao J, Huang S, Xu Y, et al. Letrozole during frozen embryo transfer in women with polycystic ovarian syndrome: A randomized controlled trial. Obstet Gynecol. 2023;142:1087–95.
14. Pan Y, Li F, Yang C-X, Sun Y, Zhang C-W, Zhang S-M, et al. Correlation between different endometrial Preparation protocols and pregnancy outcome of frozen embryo transfer in patients with polycystic ovary syndrome: a retrospective study. Gynecol Endocrinol. 2023;39:2217260.
15. Bosdou JK, Anagnostis P, Kolibianakis EM. Is pretreatment with GnRH agonist necessary for endometrial Preparation for frozen embryo transfer cycles in women with polycystic ovary syndrome? BJOG Int J Obstet Gynaecol. 2021;128:675.
16. Qiao J, Feng HL. Extra- and intra-ovarian factors in polycystic ovary syndrome: impact on oocyte maturation and embryo developmental competence. Hum Reprod Update. 2011;17:17–33.
17. Li M, Xu L, Zhao H, Du Y, Yan L. Effects of artificial cycles with and without gonadotropin-releasing hormone agonist pretreatment on frozen embryo transfer outcomes in patients with adenomyosis. Sci Rep. 2021;11:19326.
18. Xu B, Geerts D, Hu S, Yue J, Li Z, Zhu G, et al. The depot GnRH agonist protocol improves the live birth rate per fresh embryo transfer cycle, but not the cumulative live birth rate in normal responders: a randomized controlled trial and molecular mechanism study. Hum Reprod Oxf Engl. 2020;35:1306–18.
19. Tsai H-W, Wang P-H, Lin L-T, Chen S-N, Tsui K-H. Using gonadotropin-releasing hormone agonist before frozen embryo transfer May improve ongoing pregnancy rates in hyperandrogenic polycystic ovary syndrome women. Gynecol Endocrinol Off J Int Soc Gynecol Endocrinol. 2017;33:686–9.
20. Xie D, Chen F, Xie S-Z, Chen Z-L, Tuo P, Zhou R, et al. Artificial cycle with or without a depot Gonadotropin-releasing hormone agonist for Frozen-thawed embryo transfer: an assessment of infertility type that is most suitable. Curr Med Sci. 2018;38:626–31.
21. Wang Y, Hu W-H, Wan Q, Li T, Qian Y, Chen M-X, et al. Effect of artificial cycle with or without GnRH-a pretreatment on pregnancy and neonatal outcomes in women with PCOS after frozen embryo transfer: a propensity score matching study. Reprod Biol Endocrinol RBE. 2022;20:56.
22. Xu B, Hou Z, Liu N, Zhao J, Li Y. Pretreatment with a long-acting GnRH agonist for frozen-thawed embryo transfer cycles: how to improve live birth? J Ovarian Res. 2023;16:197.
23. Zhang B, Wei D, Legro RS, Shi Y, Li J, Zhang L, et al. Obstetric complications after frozen versus fresh embryo transfer in women with polycystic ovary syndrome: results from a randomized trial. Fertil Steril. 2018;109:324–9.
24. Jie H-Y, Hu R, Zhang L, Dong K, Wu C, Wang Q, et al. Obstetric and neonatal outcomes after programmed frozen embryo transfer with or without GnRH agonist for polycystic ovary syndrome: secondary analysis results from a randomized controlled trial. AJOG Glob Rep. 2023;3:100201.
25. Rotterdam ESHRE, ASRM-Sponsored PCOS consensus workshop group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Hum Reprod Oxf Engl. 2004;19:41–7.
26. Huang B, Hu D, Qian K, Ai J, Li Y, Jin L, et al. Is frozen embryo transfer cycle associated with a significantly lower incidence of ectopic pregnancy? An analysis of more than 30,000 cycles. Fertil Steril. 2014;102:1345–9.
27. Hu S, Xu B, Long R, Jin L. Pregnancy and perinatal outcomes in pregnancies resulting from time interval between a freeze-all cycle and a subsequent frozen-thawed single blastocyst transfer. BMC Pregnancy Childbirth. 2020;20:161.
28. Guo Y, Fang Z, Yu L, Sun X, Li F, Jin L. Which endometrial Preparation protocol provides better pregnancy and perinatal outcomes for endometriosis patients in frozen-thawed embryo transfer cycles? A retrospective study on 1413 patients. J Ovarian Res. 2023;16:7.
29. Zheng Y, Dong X, Chen B, Dai J, Yang W, Ai J, et al. Body mass index is associated with miscarriage rate and perinatal outcomes in cycles with frozen-thawed single blastocyst transfer: a retrospective cohort study. BMC Pregnancy Childbirth. 2022;22:118.
30. Gardner DK, Lane M, Stevens J, Schlenker T, Schoolcraft WB. Blastocyst score affects implantation and pregnancy outcome: towards a single blastocyst transfer. Fertil Steril. 2000;73:1155–8.
31. Dai L, Deng C, Li Y, Zhu J, Mu Y, Deng Y, et al. Birth weight reference percentiles for Chinese. PLoS ONE. 2014;9:e104779.
32. Wang M, Cao H-Y, Tan K-W, Qiu Q-C, Huang Y-H, Ge S-S, et al. Venetoclax plus hypomethylating agents in newly diagnosed acute myeloid leukemia patients with RUNX1::RUNX1T1: a retrospective propensity score matching study. Blood Cancer J. 2023;13:173.
33. Eberg M, Platt RW, Filion KB. The Estimation of gestational age at birth in database studies. Epidemiol Camb Mass. 2017;28:854–62.
34. Liu X, Shi J, Bai H, Wen W. Pretreatment with a GnRH agonist and hormone replacement treatment protocol could not improve live birth rate for PCOS women undergoing frozen-thawed embryo transfer cycles. BMC Pregnancy Childbirth. 2021;21:835.
35. Pan Y, Li F, Yang C-X, Sun Y, Zhang C-W, Zhang S-M, et al. Correlation between different endometrial Preparation protocols and pregnancy outcome of frozen embryo transfer in patients with polycystic ovary syndrome: a retrospective study. Gynecol Endocrinol Off J Int Soc Gynecol Endocrinol. 2023;39:2217260.
36. Li X, Lin J, Zhang L, Liu Y. Effects of gonadotropin-releasing hormone agonist pretreatment on frozen embryo transfer outcomes in artificial cycles: a meta-analysis. Arch Gynecol Obstet. 2023;308:675–83.
37. Chien P. Multiple pregnancy and assisted conception treatment. BJOG Int J Obstet Gynaecol. 2020;127:525–6.
38. Balen AH, Morley LC, Misso M, Franks S, Legro RS, Wijeyaratne CN, et al. The management of anovulatory infertility in women with polycystic ovary syndrome: an analysis of the evidence to support the development of global WHO guidance. Hum Reprod Update. 2016;22:687–708.
39. Kushnir VA, Smith GD, Adashi EY. The future of IVF: the new normal in human reproduction. Reprod Sci Thousand Oaks Calif. 2022;29:849–56.
40. Wu Y, Tu M, Liu Y, Zhang D. GnRH agonist pretreatment for frozen embryo transfer among women with polycystic ovary syndrome: a narrow systematic review and meta-analysis of randomized controlled trials. Reprod Biol Endocrinol RBE. 2024;22:121.
41. Vaiarelli A, Cimadomo D, Patrizio P, Venturella R, Orlando G, Soscia D, et al. Biochemical pregnancy loss after frozen embryo transfer seems independent of embryo developmental stage and chromosomal status. Reprod Biomed Online. 2018;37:349–57.
42. Practice Committee of the American Society for Reproductive Medicine and the Practice Committee for the Society for Assisted Reproductive Technologies. Electronic address: ASRM@asrm.org. Guidance on the limits to the number of embryos to transfer: a committee opinion. Fertil Steril. 2021;116:651–4.
43. Ghobara T, Gelbaya TA, Ayeleke RO. Cycle regimens for frozen-thawed embryo transfer. Cochrane Database Syst Rev. 2017;7:CD003414.

44. Magnusson Å, Källen K, Thurin-Kjellberg A, Bergh C. The number of oocytes retrieved during IVF: a balance between efficacy and safety. Hum Reprod Oxf Engl. 2018;33:58–64.
45. Sunkara SK, La Marca A, Seed PT, Khalaf Y. Increased risk of preterm birth and low birthweight with very high number of oocytes following IVF: an analysis of 65 868 Singleton live birth outcomes. Hum Reprod Oxf Engl. 2015;30:1473–80.
46. Bahadur G, Homburg R, Jayaprakasan K, Raperport CJ, Huirne JAF, Acharya S, et al. Correlation of IVF outcomes and number of oocytes retrieved: a UK retrospective longitudinal observational study of 172 341 non-donor cycles. BMJ Open. 2023;13:e064711.
47. Pan D, Yang J, Zhang N, Wang L, Li N, Shi J, et al. Gonadotropin-releasing hormone agonist downregulation combined with hormone replacement therapy improves the reproductive outcome in frozen-thawed embryo transfer cycles for patients of advanced reproductive age with idiopathic recurrent implantation failure. Reprod Biol Endocrinol RBE. 2022;20:26.
48. Khayat S, Elliott B, Dahan MH. Management of recurrent implantation failure by gonadotropin-releasing hormone agonist and aromatase inhibitor suppression, in women without evidence of endometriosis. Gynecol Endocrinol Off J Int Soc Gynecol Endocrinol. 2019;35:267–70.
49. Steiner N, Shrem G, Tannus S, Dahan SY, Balayla J, Volodarsky-Perel A, et al. Effect of GnRH agonist and letrozole treatment in women with recurrent implantation failure. Fertil Steril. 2019;112:98–104.
50. Xia L, Tian L, Zhang S, Huang J, Wu Q. Hormonal replacement treatment for Frozen-Thawed embryo transfer with or without GnRH agonist pretreatment: A retrospective cohort study stratified by times of embryo implantation failures. Front Endocrinol. 2022;13:803471.
51. Zhang Y, Fu X, Gao S, Gao S, Gao S, Ma J, et al. Letrozole use in vitrified single-blastocyst transfer cycles is associated with lower risk of large for gestational age infants in patients with polycystic ovary syndrome. J Assist Reprod Genet. 2023;40:2885–94.

Publisher's note