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Enhancing understanding of endometrial function in patients with PCOS: clinical and immunological insights

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Abstract

Objective To evaluate the pregnancy and perinatal outcomes of different phenotypes of polycystic ovary syndrome (PCOS) patients during the frozen embryo transfer (FET) cycles. Additionally, to analyze the T cell balance in the endometrium of PCOS patients and explore its relationship with various PCOS phenotypes.

Design Retrospective cohort study.

Setting A single academically affiliated reproductive medicine center.

Patients 21,074 FET cycles were included and divided into two groups based on the diagnosis of PCOS. Patients with PCOS were further categorized into four phenotypic groups: PCOM + HA + OA, PCOM + HA, PCOM + OA, and HA + OA. Endometrial biopsies from 21 PCOS patients and 26 controls were obtained to analyze T cell subsets.

Methods Pregnancy and perinatal outcomes, as well as T cell subset abundance were compared between women with and without PCOS. Multiple logistic regression models were employed to adjust for confounding factors impacting pregnancy-related outcomes. Flow cytometry was utilized to analyze the abundance of T cell subsets.

Main outcome measures Pregnancy and perinatal outcomes were assessed. T cell subsets including $CD4^+CD8^-$T cells, $CD4^-CD8^+$T cells, Th1, Th2, Th17 and Treg cells in the endometrium were determined by flow cytometry.

Results There was a significantly increased incidence of miscarriage, hypertensive disorders of pregnancy (HDP), preterm birth (PTB), and even fetal malformations across different phenotypes of PCOS women, especially those with the hyperandrogenic phenotype. Th1 cells decreased while Th2 cells increased significantly in the PCOS endometrium.

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Conclusions The unfavorable pregnancy and perinatal outcomes in FET cycles and T cell imbalance both suggest the endometrial dysfunction of PCOS patients, especially those with the hyperandrogenic phenotype.

Keywords Polycystic ovary syndrome, Miscarriage, Hypertensive disorders of pregnancy, Preterm birth, T cells

Introduction

Polycystic ovary syndrome (PCOS) is a prevalent endocrine disorder encountered in individuals of reproductive age. This syndrome encompasses reproductive, metabolic, and psychological aspects that can impact the entire lifespan [1]. The diagnosis primarily relies on identifying at least two out of three key features: oligo- or anovulation (OA), hyperandrogenism (clinical or biochemical, HA), and polycystic ovarian morphology (PCOM) detected via ultrasound, after excluding alternative causes [2–4]. According to the newly published 2023 PCOS guidelines, anti-Müllerian hormone (AMH) can now be used as an alternative to ultrasound [4]. Consequently, based on their phenotypes, PCOS patients can be further categorized into four groups: PCOM + HA + OA, PCOM + HA, PCOM + OA, and HA + OA. The infertility linked to the syndrome predominantly stems from oligo- or anovulation in guidelines [5]. Consequently, treatment strategies are mainly directed towards enhancing ovulatory function [5, 6]. However, emerging clinical data highlight endometrial factors contributing to the suboptimal reproductive outcomes in PCOS patients with spontaneous ovulation such as increased risk of miscarriage and obstetric complications [7, 8].

Despite the widespread application of frozen embryo transfer (FET) among PCOS patients worldwide, the majority of adverse pregnancy outcomes associated with PCOS in assisted reproductive technology (ART) occurred in fresh cycles [9–11]. However, patients undergoing fresh embryo transfer may be influenced by ovarian stimulation factors, with a higher risk of ovarian hyperstimulation syndrome (OHSS) for PCOS patients [12]. Therefore, conducting a large sample clinical study to evaluate the association between pregnancy and perinatal outcomes and PCOS diagnosis during FET cycles is of vital importance, especially when comparing different PCOS phenotypes [13]. Although many studies extensively discuss the relationship between PCOS and adverse pregnancy outcomes, few studies take into account the heterogeneity of PCOS phenotypes, focusing on pathophysiological analysis specific to each phenotype [9, 11, 13].

Combining the elevated rates of adverse pregnancy outcomes observed in PCOS patients in this study with both indirect and direct evidence from previous research [7, 8, 14], it is suggested that endometrial receptivity in PCOS patients may be compromised. Endometrial immune balance is a key factor affecting receptivity [15]. Although the association of the syndrome with systemic and local low-grade inflammation is well known [16, 17], information on the immune characteristics of the endometrium in women affected by PCOS is relatively scarce. Some data indicate altered levels of macrophages and natural killer (NK) cells in the endometrium of PCOS patients [18, 19]. Despite the critical role of T lymphocytes in all adaptive immune responses, few studies have focused on T-cell subsets within the PCOS population. Hence a comprehensive analysis of T cells in PCOS endometrium was undertaken after finding poor pregnancy and perinatal outcomes in the PCOS population.

Here, we evaluate pregnancy and perinatal outcomes between different phenotypes of PCOS patients and non-PCOS patients during FET cycles. Specifically, T cells in the PCOS endometrium are analyzed to partially explain the unfavorable pregnancy outcomes observed in women with PCOS.

Materials and methods

Patients

In this retrospective cohort study, we analyzed 21,074 FET cycles undergoing oocyte aspiration from 2015 to 2020 and undergoing FET from 2016 to 2020 at the Reproductive Medical Center of Tongji Hospital. Patients were divided into two groups based on whether or not be diagnosed with PCOS [2–4]. PCOS patients were further categorized into four groups based on their phenotypes: PCOM + HA + OA, PCOM + HA, PCOM + OA, and HA + OA. None of the participants received a diagnosis of congenital adrenal hyperplasia, Cushing's syndrome, or tumors that secrete androgens. Patients with diagnoses of thyroid dysfunction or chromosomal abnormalities were ruled out. The FET cycles with embryos derived from donated oocytes were also excluded (Fig. 1). Individuals who were subjected to preimplantation genetic diagnosis (PGD) or preimplantation genetic screening (PGS) were also not included in the study (Fig. 1).

6732 singleton live births were selected to analyze perinatal outcomes. Only singleton live births with one initial gestational sac and one initial heart rate on ultrasound were screened for analysis. Patients with diagnoses of type 2 diabetes mellitus or hypertension were ruled out. Only infants with a gestational age ≥ 28 weeks were used for the final analysis (Fig. 1). The procedures for ovulation induction, in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI), embryo culture, cryopreservation, thawing, and embryo transfer adhered to standard protocols as outlined in previous literature [7–10].

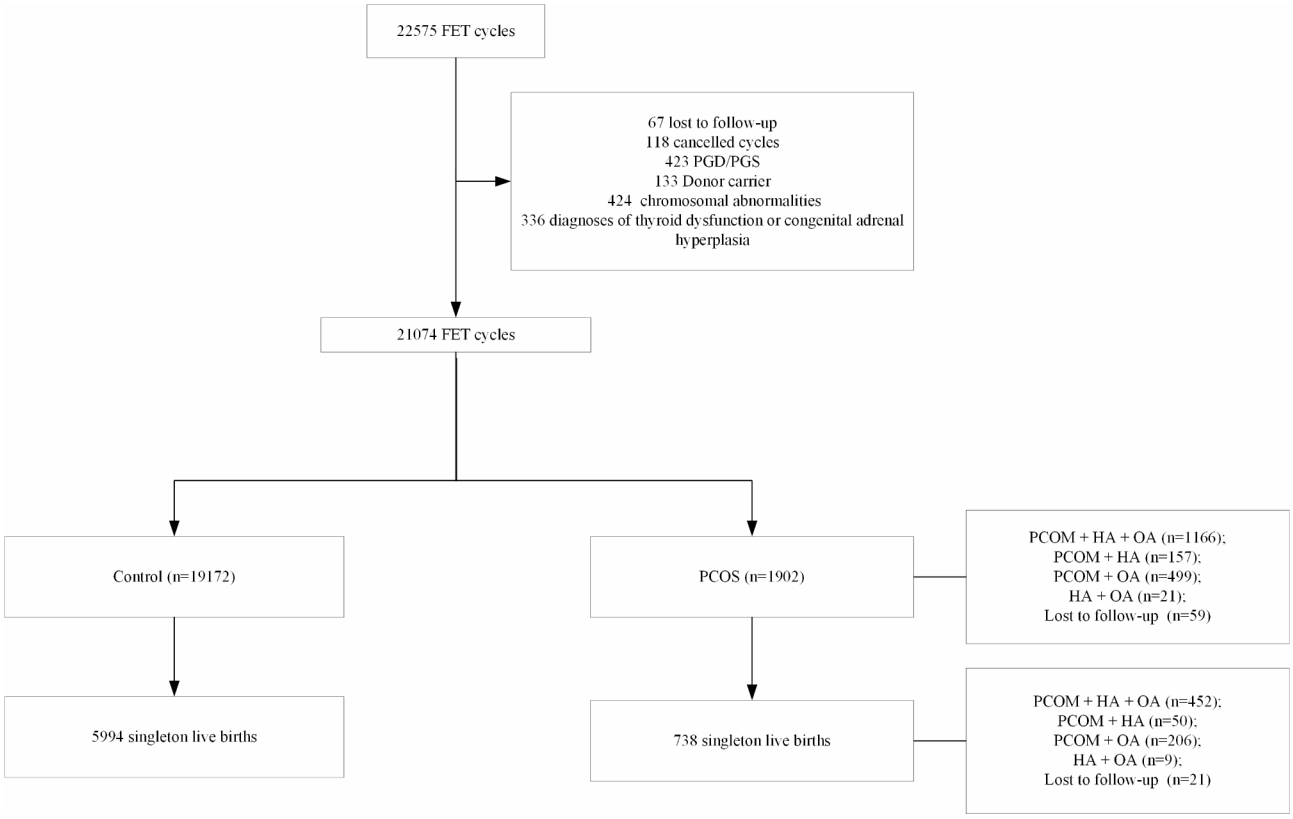

Fig. 1 Data selection process

This investigation received ethical approval from the Institutional Review Board of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology (No. TJ-IRB20210831). The retrospective data used in this study were anonymized, and therefore, the requirement for informed consent was waived by the Institutional Review Board of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology [20–22].

Outcome variables

The study encompassed both pregnancy and prenatal outcomes, with live birth defined as the successful delivery of at least one viable infant. A clinical pregnancy was confirmed by ultrasound evidence of one or more gestational sacs exhibiting fetal heart activity. A biochemical pregnancy loss was characterized by a positive pregnancy test that did not progress to a clinical pregnancy. Miscarriage was categorized as the spontaneous loss following the sonographic detection of an intrauterine gestational sac. An ectopic pregnancy was described as a gestation occurring outside the uterine cavity.

The gestational age was determined by adding 17 days for cleavage-stage embryo transfer and 19 days for blastocyst transfer from the frozen-thawed embryo transfer date. Preterm birth (PTB) is defined by the World Health Organization as delivery before 37 weeks of gestation, while a gestational age of less than 32 weeks is categorized as very preterm birth (VPTB). Low birth weight (LBW) was considered as a birth weight under 2500 g, while macrosomia was defined as exceeding 4000 g. Birth weight of fewer than 1500 g was recognized as very low birth weight (VLBW). Small for gestational age (SGA) was defined as a birthweight below the 10th percentile, whereas large for gestational age (LGA) was above the 90th percentile based on reference standards for Chinese populations, adjusted for sex and gestational age [23]. Birth weight < 3rd percentile of reference standard birth weight for gestational age was recognized as very small size for gestational age (VSGA). Information regarding all abnormal perinatal outcomes was collected via telephone follow-ups and subsequently entered into the electronic database. Furthermore, pregnancy complications in the analysis also included gestational diabetes mellitus (GDM), hypertensive disorders of pregnancy (HDP), and fetal malformation.

Human tissue collection and flow cytometry

All procedures involving human endometrium were conducted following the Institutional Review Board (IRB) guidelines for Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology.

Endometrial biopsies were obtained from women aged < 40 years with regular menstrual cycles, normal body mass index, normal karyotype, and negative serological tests for human immunodeficiency virus, hepatitis B virus, hepatitis C virus, and syphilis. Informed written consent was obtained from each donor before an endometrial biopsy was performed. The patient visited the reproductive center on the second day after her menstrual period ended to have her vaginal discharge tested. After receiving normal results on the same day, she will schedule a hysteroscopy and undergo the procedure as soon as possible. As a result, the hysteroscopy and endometrial biopsy were typically performed in the proliferative phase of the menstrual cycle. The endometrial phase was confirmed by histopathological examination results. Women with the following conditions were excluded from tissue collection: recent contraception (hormonal contraceptives in the past 3 months), uterine pathology (endometriosis, leiomyoma or adenomyosis; bacterial, fungal, or viral infection). For the endometrial biopsy, we used a small curette to carefully explore the uterine cavity's depth, gently scraping the anterior and posterior walls, as well as the lateral walls and the cavity's base. Endometrial biopsies from 21 PCOS patients and 25 controls were obtained and washed with cold phosphate-buffered saline (PBS) after being collected. After thoroughly rinsing the blood from the endometrial biopsy tissue, collagenase type IV was used to digest the tissue in a 37 °C water bath with gentle agitation. Following red blood cell lysis (Solarbio, China), we passed the resulting solution through a 30 μm filter to obtain a single-cell suspension for flow cytometric analysis. The cell surface of isolated immune cells was stained with appropriate fluorescently labeled conjugated monoclonal antibodies (mAb) for 20 min, away from light. T cell subsets including $CD4^+CD8^-$ T cells, $CD4^-CD8^+$ T cells, Th1, Th2, Th17, and Treg cells in the endometrium were determined by flow cytometry according to the manufacturer's protocol. The panel comprised monoclonal antibodies (mAbs) CD3-FITC, CD25-PE, CXCR3-PE-Cy7, CCR6-BV650, CD45-PerCP, CD4-APC, CCR4-BV421, CD127-BV510 for staining (Supplementary Table 5) and 8-color flow cytometric analysis. All antibodies used in this study were sourced from BD Biosciences, and results were obtained using the BD LSRFortessa. The data were analyzed with FlowJo software (TreeStar, USA).

Statistical analysis

SPSS 23.0 software (SPSS Inc., Chicago, IL, USA) was used for data analysis in this study. The normality of distribution for all continuous variables was evaluated using the Kolmogorov-Smirnov test and none of them were found normally distributed, therefore continuous variables were presented as the median and interquartile range. Categorical data were expressed as frequency and percentage. Continuous variables, including baseline data, pregnancy outcomes, and T cell subgroup proportions, were analyzed using the Mann-Whitney U test. Categorical variables were assessed using the chi-squared test or Fisher's exact test, as appropriate. To exclude the influence of confounding variables, multiple logistic regression was implemented. $P < 0.05$ was considered statistically significant.

Results

Pregnancy outcomes between controls and the four phenotypic groups of PCOS patients

Based on the diagnosis of PCOS, the 21,074 FET cycles were divided into 19,172 patients in the control group and 1,902 patients in the PCOS group. We first compared the clinical pregnancy outcomes of the overall PCOS group with those of the control group. General characteristics and clinical pregnancy outcomes of patients with and without PCOS were summarized in Supplementary Table 1. Significant differences were found in live birth rate (LBR), clinical pregnancy rate (CPR), and miscarriage rate (MR) between patients with and without PCOS. However, the biochemical pregnancy rate (BPR), and ectopic pregnancy rate (EPR) were similar in the two groups. To address potential confounders, binomial logistic regression analysis used maternal age at FET, No. and type of embryos transferred, duration and diagnosis of infertility as independent variables were performed. Supplementary Table 2 showed that LBR (aOR = 1.221; 95%CI, 1.104–1.349; $P < 0.001$), CPR (aOR = 1.349; 95%CI, 1.214–1.498; $P < 0.001$) and MR (aOR = 1.189; 95%CI, 1.020–1.385; $P = 0.027$) were associated with diagnosis of PCOS after adjustment.

Next, we compared the four PCOS subgroups with the control group. The general characteristics between controls and the four phenotypic groups of PCOS patients are detailed in Table 1. Imbalances in some factors were to be expected, including body mass index (BMI), FSH, AMH, AFC, ovarian stimulation protocols, duration of stimulation, No. of oocytes retrieved, No. of MII oocytes, and the number of 2PN. These are all reasonably predictable from the disease characteristics of PCOS. The normal fertilization rate was significantly lower in the PCOM + HA + OA and PCOM + OA groups, as compared to the control group (Table 1). Additionally, the total number of surviving embryos to the number of embryos thawed ratio showed significant declines across the four PCOS phenotype groups, reflecting impaired oocyte and embryo quality in patients with PCOS (Table 1).In addition, several factors contributing to the imbalance between the two groups need to be considered, including maternal age at oocyte retrieval and FET, duration of infertility, infertility diagnosis, type of fertilization, type

Table 1 General characteristics of control and four phenotypes of PCOS patients

Variable	Control (*n* = 19172)	PCOS (*n* = 1902)							
		PCOM + HA + OA (*n* = 1166)	*P* value	PCOM + HA(*n* = 157)	*P* value	PCOM + OA(*n* = 499)	*P* value	HA + OA (*n* = 21)	*P* value
Maternal age at oocyte retrieval, years	32.0 (29.0, 36.0)	28.0 (26.0, 31.0)	<.001[1*]	28.0 (27.0, 30.0)	<.001[1*]	29.0 (27.0, 31.0)	<.001[1*]	29.0 (26.0, 33.0)	0.015[1*]
Body mass index, kg/m^2	21.4 (19.7, 23.4)	22.9 (20.7, 25.4)	<.001[1*]	22.5 (20.0, 25.1)	<.001[1*]	22.1 (20.2, 24.3)	<.001[1*]	23.5 (21.1, 26.7)	0.003[1*]
Baseline FSH, mIU/mL	7.5 (6.4, 8.9)	6.4 (5.5, 7.4)	<.001[1*]	6.2 (5.4, 7.0)	<.001[1*]	6.3 (5.3, 7.5)	<.001[1*]	7.4 (6.3, 9.1)	0.917[1]
Antral follicle count (AFC)	11.0 (6.0, 16.0)	24.0 (23.0, 27.0)	0.000[1*]	24.0 (22.0, 25.5)	<.001[1*]	24.0 (22.0, 24.0)	<.001[1*]	13.0 (11.0, 17.0)	0.018[1*]
AMH level, ng/ml	3.5 (1.7, 6.0)	12.7 (9.0, 17.3)	0.000[1*]	10.7 (8.1, 15.0)	<.001[1*]	10.0 (6.6, 14.3)	<.001[1*]	7.3 (3.5, 10.3)	<.001[1*]
Duration of infertility, years	3.0 (2.0, 4.0)	3.0 (2.0, 5.0)	<.001[1*]	3.0 (2.0, 5.0)	0.084[1]	3.0 (2.0, 4.0)	0.015[1*]	3.0 (1.8, 5.0)	0.927[1]
Infertility diagnosis			<.001[2*]		0.042[2*]		<.001[2*]		0.511[2]
Primary infertility, *n* (%)	11,132 (58.2%)	831 (71.3%)		104 (66.2%)		369 (73.9%)		14 (66.7%)	
Secondary infertility, *n* (%)	8004 (41.8%)	335 (28.7%)		53 (33.8%)		130 (26.1%)		7 (33.3%)	
Ovarian stimulation protocols, *n* (%)			<.001[2*]		<.001[2*]		<.001[2*]		0.229[3]
Long GnRH-a	4088 (21.3%)	249 (21.4%)		54 (34.4%)		77 (15.4%)		4 (19.0%)	
GnRH-a ultra-long	5867 (30.6%)	613 (52.6%)		76 (48.4%)		264 (52.9%)		11 (52.4%)	
GnRH antagonist	4972 (25.9%)	277 (23.8%)		25 (15.9%)		148 (29.7%)		3 (14.3%)	
Other protocols	4245 (22.1%)	27 (2.3%)		2 (1.3%)		10 (2.0%)		3 (14.3%)	
Duration of stimulation, days	10.0 (9.0, 11.0)	10.0 (9.0, 12.0)	<.001[1*]	10.0 (9.0, 11.0)	0.003[1*]	10.0 (9.0, 12.0)	<.001[1*]	11.0 (10.0, 12.5)	0.010[1*]
No. of oocytes retrieved	12.0 (7.0, 18.0)	18.0 (13.0, 24.0)	<.001[1*]	21.0 (14.5, 26.0)	<.001[1*]	19.0 (14.0, 24.0)	<.001[1*]	13.0 (10.0, 18.5)	0.146[1]
No. of MII oocytes	10.0 (6.0, 15.0)	16.0 (12.0, 21.0)	<.001[1*]	18.0 (13.0, 23.0)	<.001[1*]	16.0 (12.0, 21.0)	<.001[1*]	12.0 (9.5, 16.0)	0.071[1]
Oocyte maturation rate	0.9 (0.8, 1.0)	0.9 (0.8, 1.0)	0.006[1*]	0.9 (0.8, 1.0)	0.126[1]	0.9 (0.8, 1.0)	0.112[1]	1.0 (0.8, 1.0)	0.281[1]
Fertilization, *n* (%)			0.007[2*]		0.028[2*]		0.147[2]		0.315[3]
IVF	12,765 (66.7%)	811 (69.6%)		120 (76.4%)		333 (66.7%)		12 (57.1%)	
ICSI	5511 (28.8%)	290 (24.9%)		30 (19.1%)		135 (27.1%)		7 (33.3%)	
Rescue ICSI	854 (4.5%)	64 (5.5%)		7 (4.5%)		31 (6.2%)		2 (9.5%)	
The number of 2PN	7.0 (4.0, 11.0)	11.0 (8.0, 15.0)	<.001[1*]	13.0 (8.0, 17.0)	<.001[1*]	11.0 (7.0, 15.0)	<.001[1*]	9.0 (6.0, 11.0)	0.176[1]
Normal fertilization rate	0.7 (0.5, 0.8)	0.6 (0.5, 0.8)	0.003[1*]	0.7 (0.5, 0.8)	0.831[1]	0.6 (0.5, 0.8)	0.016[1*]	0.7 (0.5, 0.8)	0.937[1]
Maternal age at FET, years	32.0 (29.0, 36.0)	29.0 (27.0, 32.0)	<.001[1*]	29.0 (27.0, 31.0)	<.001[1*]	29.0 (27.0, 32.0)	<.001[1*]	29.0 (26.5, 33.5)	0.016[1*]
Interval between FET and IVF/ICSI, days	94.0 (61.0, 191.0)	96.0 (64.0, 201.0)	0.098[1]	106.0 (68.0, 233.0)	0.022[1*]	96.0 (62.0, 194.0)	0.726[1]	120.0 (71.0, 307.0)	0.217[1]

Table 1 (continued)

Variable	Control (*n* = 19172)	PCOS (*n* = 1902)							
		PCOM + HA + OA (*n* = 1166)	*P* value	PCOM + HA(*n* = 157)	*P* value	PCOM + OA(*n* = 499)	*P* value	HA + OA (*n* = 21)	*P* value
No. of embryos thawed			0.002[2*]		<.001[3*]		0.142[2]		0.344[3]
1	11,153 (58.2%)	645 (55.3%)		64 (40.8%)		278 (55.7%)		12 (57.1%)	
2	7758 (40.5%)	516 (44.3%)		93 (59.2%)		2118 (43.7%)		8 (38.1%)	
≥ 3	261 (1.4%)	5 (0.4%)		0 (0.0%)		3 (0.6%)		1 (4.8%)	
No. of surviving embryos			0.025[3*]		<.001[3*]		0.177[3]		0.859[3]
1	11,257 (58.7%)	650 (55.7%)		65 (41.4%)		283 (56.7%)		12 (57.1%)	
2	7739 (40.4%)	514 (44.1%)		92 (58.6%)		216 (43.3%)		9 (42.9%)	
3	161 (0.8%)	2 (0.2%)		0 (0.0%)		0 (0.0%)		0 (0.0%)	
Total no. of surviving embryos/no. of embryos thawed	36.2 (32.0, 42.0)	32.1 (29.0, 36.6)	<.001[1*]	33.0 (29.9, 37.0)	<.001[1*]	32.5 (29.5, 37.1)	<.001[1*]	34.0 (27.5, 36.7)	0.023[1*]
No. of embryos transferred, *n* (%)			0.248[3]		0.002[3*]		0.751[3]		1.000[3]
1	11,836 (61.7%)	691 (59.3%)		74 (47.1%)		304 (60.9%)		13 (61.9%)	
2	7327 (38.2%)	475 (40.7%)		83 (52.9%)		195 (39.1%)		8 (38.1%)	
Type of embryos transferred, *n* (%)			<.001[2*]		<.001[2*]		<.001[2*]		0.470[2]
Cleavage embryo	5340 (27.9%)	109 (9.4%)		19 (12.1%)		46 (9.2%)		4 (19.0%)	
Blastocyst	13,827 (72.1%)	1055 (90.6%)		138 (87.9%)		452 (90.8%)		17 (81.0%)	
Endometrial thickness, mm	9.1 (8.4, 10.0)	9.2 (8.4, 10.2)	0.089[1]	9.2 (8.4, 10.2)	0.574[1]	9.1 (8.5, 9.9)	0.747[1]	8.6 (7.8, 9.9)	0.160[1]
Luteal phase support, *n* (%)			0.021[2*]		<.001[3*]		0.107[3]		0.311[3]
Intramuscular injection and oral administration	2668 (13.9%)	163 (14.0%)		43 (27.4%)		78 (15.6%)		6 (28.6%)	
Vaginal gel administration and oral administration	8220 (42.9%)	512 (43.9%)		65 (41.4%)		198 (39.7%)		7 (33.3%)	
Vaginal suppository administration and oral administration	8092 (42.2%)	490 (42.0%)		49 (31.2%)		222 (44.5%)		8 (38.1%)	
Others	189 (1.0%)	1 (0.1%)		0 (0.0%)		1 (0.2%)		0 (0.0%)	

[1]Mann-Whitney U tests; [2]Chi-Square p-value; [3]Fisher Exact p-value. Continuous data are reported as the median (quartiles). Categorical data are reported as *n* (%). PCOS = polycystic ovary syndrome. [*]$P < 0.05$

of embryo transferred, and luteal phase support. These factors were adjusted for as confounders in the subsequent multivariate logistic regression analysis. Due to the small sample sizes of the PCOM + HA and HA + OA groups, we only included the other two groups in the multiple logistic regression analysis.

As shown in Table 2, both LBR and CPR increased across all four PCOS subgroups. The increase in LBR in the HA + OA group, however, did not reach statistical significance, likely due to the small sample size. In contrast, significant increases in LBR and CPR were observed in the other PCOS subgroups ($P < 0.05$). After adjusting for confounding factors via multivariate logistic regression, the increases in LBR and CPR remained significant in the PCOM + HA + OA and PCOM + OA groups (Table 3). Regarding MR, only the PCOM + HA group showed rates similar to the control group, while the rates increased in the other groups. Notably, the PCOM + OA

Table 2 Clinical pregnancy outcomes of control and four phenotypes of PCOS patients

Variable	Control (*n* = 19172)	PCOS (*n* = 1902)							
		PCOM + HA + OA (*n* = 1166)	*P* value	PCOM + HA(*n* = 157)	*P* value	PCOM + OA(*n* = 499)	*P* value	HA + OA (*n* = 21)	*P* value
Live birth, *n* (%)	7686 (40.1%)	636 (54.5%)	<.001[1*]	83 (52.9%)	0.001[1*]	299 (59.9%)	<.001[1*]	11 (52.4%)	0.251[1]
Clinical pregnancy, *n* (%)	9530 (49.7%)	765 (65.6%)	<.001[1*]	97 (61.8%)	0.003[1*]	363 (72.7%)	<.001[1*]	15 (71.4%)	0.047[1*]
Miscarriage, *n* (%)	1844 (9.6%)	129 (11.1%)	0.105[1]	14 (8.9%)	0.767[1]	64 (12.8%)	0.017[1*]	4 (19.0%)	0.137[2]
Ectopic pregnancy, *n* (%)	107 (1.1%)	6 (1.5%)	0.472[1]	0 (0.0%)	1[2]	1 (0.7%)	1[2]	0 (0.0%)	1[2]
Biochemical pregnancy, *n* (%)	1235 (6.4%)	89 (7.6%)	0.109[1]	12 (7.6%)	0.542[1]	27 (5.4%)	0.354[1]	0 (0.0%)	0.643[2]

[1]Chi-Square p-value; [2]Fisher Exact *p*-value. Categorical data are reported as *n* (%). PCOS = polycystic ovary syndrome. *$P < 0.05$

Table 3 Odds ratios and adjusted odds ratios of pregnancy outcomes

	Control vs. (PCOM + HA + OA)			Control vs. (PCOM + OA)		
	OR (95% CI)	aOR (95% CI)	*P*(a) value	OR (95% CI)	aOR (95% CI)	*P*(a) value
Live Birth	1.793 (1.592, 2.020)	1.157 (1.022, 1.309)	0.021*	2.234 (1.864, 2.678)	1.509 (1.251, 1.820)	< 0.001*
Clinical pregnancy	1.930 (1.705, 2.185)	1.246 (1.095, 1.418)	< 0.001*	2.700 (2.213, 3.295)	1.824 (1.486, 2.239)	< 0.001*
Miscarriage	1.169 (0.967, 1.412)	1.133 (0.934, 1.375)	0.205	1.383 (1.059, 1.805)	1.328 (1.013, 1.740)	0.040*
Ectopic pregnancy	1.354 (0.591, 3.100)	0.945 (0.405, 2.202)	0.896	0.660 (0.091, 4.764)	0.512 (0.070, 3.744)	0.510
Biochemical pregnancy	1.200 (0.960, 1.501)	1.094 (0.871, 1.374)	0.441	0.831 (0.561, 1.230)	0.740 (0.499, 1.099)	0.135

Odds ratios (ORs) and 95% confidence intervals (CIs) are based on the univariate analysis. Adjusted odds ratios (aORs), 95% CIs and adjusted *P* value are based on the multiple logistic regression model for each outcome in the two groups, adjusted for maternal age at FET, duration of infertility, type of embryos transferred, ovarian stimulation protocols, fertilization. *P*(a) = adjusted *P* value. *$P(a) < 0.05$

group exhibited a statistically significant difference ($P < 0.05$) (Table 2). After adjusting for confounding factors, this statistical difference persisted (aOR = 1.328; 95% CI: 1.013–1.740) (Table 3). However, BPR and EPR were similar between the control group and the four PCOS phenotype groups (Tables 2 and 3).

Singleton perinatal outcomes between controls and the four phenotypic groups of PCOS patients

A total of 6,732 FET cycles were screened for evaluation of obstetric complications and adverse birth outcomes, with 738 singleton live births from patients with PCOS and 5,994 singleton live births from patients without PCOS. Initially, the obstetric outcomes between the overall PCOS group and the control group were compared (Supplementary Table 3). The results revealed that gestational age, delivery mode, birth weight, and fetal gender were consistent between the two groups ($P > 0.05$). No statistically significant differences were observed in abnormal perinatal outcomes between the two groups, except for hypertensive disorders in pregnancy (HDP), where a significant difference was found ($P < 0.001$). To eliminate the influence of confounding factors, multivariate logistic regression was performed for each outcome, adjusting for maternal age at FET, duration of infertility, infertility diagnosis, type of fertilization, and number and type of embryos transferred. After adjusting for these factors, only preterm birth (PTB) (aOR = 1.358; 95% CI, 1.004–1.836) and HDP (aOR = 1.684; 95% CI, 1.175–2.413) were found to be significantly associated with PCOS (Supplementary Table 4).

Next, we further categorized PCOS patients into four subgroups based on phenotypic characteristics to analyze the relationship between phenotypic heterogeneity and obstetric as well as fetal outcomes. Interestingly, the incidence of PTB and GDM was similar between the control group and the PCOM + OA group ($P > 0.05$) (Table 4). However, in the other three subgroups, the incidence of PTB and GDM increased. Despite having only 50 cycles, the PCOM + HA group exhibited statistically significantly higher incidence rates of PTB ($P = 0.034$) and GDM ($P = 0.024$), along with significantly reduced gestational age ($P = 0.005$) (Table 4), prompting us to consider the potential impact of elevated androgen levels. Regarding HDP, the prevalence was elevated across all four PCOS subgroups, but statistical significance ($P < 0.05$) was only observed in three of the groups, excluding the PCOM + HA + OA group (Table 4). Additionally, the incidence of fetal malformations was significantly higher in the PCOM + HA + OA group ($P = 0.022$) (Table 4).

After adjusting for confounding factors through multivariate logistic regression, we found that the incidence of PTB (aOR = 1.680; 95% CI, 1.127–2.504), HDP (aOR = 1.961; 95% CI, 1.175–3.273), and GDM (aOR = 1.720; 95% CI, 1.094–2.705) was associated with the PCOM + HA + OA phenotype, whereas the PCOM + OA phenotype was only associated with HDP (aOR = 2.583; 95% CI, 1.390–4.802) (Table 5). This

Table 4 Perinatal outcomes of control and four phenotypes of PCOS patients giving birth to singletons after the frozen-thawed embryo transfers

Variable	Women without PCOS (*n* = 5994)	Women with PCOS (*n* = 717)							
		PCOM + HA + OA (*n* = 452)	*P* value	PCOM + HA(*n* = 50)	*P* value	PCOM + OA(*n* = 206)	*P* value	HA + OA (*n* = 9)	*P* value
Gestational age, weeks	39.0 (38.1, 39.6)	39.0 (38.0, 39.6)	0.451[1]	38.6 (37.4, 39.0)	0.005[1*]	39.0 (38.3, 39.7)	0.145[1]	38.7 (38.0, 39.5)	0.603[1]
Birth weight, g	3350.0 (3100.0, 3650.0)	3350.0 (3100.0, 3650.0)	0.988[1]	3300.0 (3000.0, 3663.0)	0.594[1]	3440.0 (3100.0, 3750.0)	0.063[1]	3600.0 (2950.0, 3950.0)	0.500[1]
Delivery mode			0.397[2]		0.488[2]		0.763[2]		1[3]
Natural labor	800 (13.3%)	54 (11.9%)		5 (10.0%)		29 (14.1%)		1 (11.1%)	
Cesarean delivery	5193 (86.7%)	398 (88.1%)		45 (90.0%)		177 (85.9%)		8 (88.9%)	
Gender			0.376[2]		0.485[2]		0.346[2]		0.527[3]
Male	3292 (54.9%)	258 (57.1%)		25 (50.0%)		120 (58.3%)		6 (66.7%)	
Female	2701 (45.1%)	194 (42.9%)		25 (50.0%)		86 (41.7%)		3 (33.3%)	
Abnormal perinatal outcomes									
VPTB	45 (0.8%)	4 (0.9%)	0.775[3]	0 (0.0%)	1[3]	1 (0.5%)	1[3]	0 (0.0%)	1[3]
PTB	497 (8.3%)	44 (9.7%)	0.288[2]	9 (18.0%)	0.034[3*]	14 (6.8%)	0.442[2]	1 (11.1%)	0.542[3]
VLBW	27 (0.5%)	2 (0.4%)	1[3]	0 (0.0%)	1[3]	1 (0.5%)	0.611[3]	0 (0.0%)	1[3]
LBW	260 (4.3%)	20 (4.4%)	0.916[2]	1 (2.0%)	0.724[3]	6 (2.9%)	0.326[2]	1 (11.1%)	0.330[3]
Macrosomia (≥ 4000 g)	375 (6.3%)	35 (7.7%)	0.203[2]	1 (2.0%)	0.371[3]	18 (8.7%)	0.145[2]	1 (11.1%)	0.442[3]
VSGA	115 (1.9%)	9 (2.0%)	0.906[2]	1 (2.0%)	0.622[3]	4 (1.9%)	0.799[3]	0 (0.0%)	1[3]
SGA	207 (3.5%)	19 (4.2%)	0.395[2]	1 (2.0%)	1[3]	8 (3.9%)	0.732[2]	0 (0.0%)	1[3]
LGA	951 (15.9%)	75 (16.6%)	0.662[2]	8 (16.0%)	0.982[2]	40 (19.4%)	0.164[2]	4 (44.4%)	0.041[3*]
HDP	234 (3.9%)	25 (5.5%)	0.089[2]	8 (16.0%)	<.001[3*]	14 (6.8%)	0.037[2*]	2 (22.2%)	0.046[3*]
GDM	343 (5.7%)	33 (7.3%)	0.167[2]	7 (14.0%)	0.024[3*]	8 (3.9%)	0.261[2]	1 (11.1%)	0.412[3]
Fetal malformation	62 (1.0%)	10 (2.2%)	0.022[2*]	1 (2.0%)	0.409[3]	1 (0.5%)	0.724[3]	1 (11.1%)	0.091[3]

[1]Mann-Whitney U tests; [2]Chi-Square p-value; [3]Fisher Exact p-value. Continuous data are reported as the median (quartiles). Categorical data are reported as n (%). PCOS = polycystic ovary syndrome. [*]*P* < 0.05

Table 5 Odds ratios and adjusted odds ratios of abnormal perinatal outcomes

	Controls vs. (PCOM + HA + OA)			Controls vs. (PCOM + OA)		
	OR (95% CI)	aOR (95% CI)	*P*(a) value	OR (95% CI)	aOR (95% CI)	*P*(a) value
VPTB	1.180 (0.422–3.295)	1.060 (0.280–4.023)	0.931	0.645 (0.088–4.699)	0.858 (0.110–6.727)	0.884
PTB	1.192 (0.862–1.649)	1.680 (1.127–2.504)	0.011*	0.806 (0.465–1.397)	1.057 (0.573–1.951)	0.859
VLBW	0.986 (0.234–4.160)	2.143 (0.403–11.409)	0.371	1.083 (0.146–8.007)	1.994 (0.244–16.307)	0.520
LBW	1.025 (0.644–1.633)	1.145 (0.647–2.027)	0.641	0.665 (0.292–1.511)	0.914 (0.391–2.137)	0.836
Macrosomia (≥ 4000 g)	1.263 (0.881–1.811)	1.047 (0.675–1.622)	0.839	1.442 (0.879–2.365)	1.301 (0.742–2.283)	0.358
VSGA	1.042 (0.525–2.068)	0.878 (0.386–1.998)	0.757	1.016 (0.371–2.781)	1.117 (0.390–3.201)	0.837
SGA	1.231 (0.762–1.989)	1.512 (0.853–2.683)	0.157	1.134 (0.552–2.330)	1.060 (0.450–2.495)	0.894
LGA	1.059 (0.819–1.370)	0.915 (0.675–1.239)	0.564	1.284 (0.903–1.826)	1.223 (0.827–1.808)	0.314
HDP	1.441 (0.943–2.202)	1.961 (1.175–3.273)	0.010*	1.795 (1.027–3.136)	2.583 (1.390–4.802)	0.003*
GDM	1.298 (0.896–1.880)	1.720 (1.094–2.705)	0.019*	0.666 (0.326–1.361)	0.870 (0.396–1.910)	0.728
Fetal malformation	2.165 (1.102–4.251)	1.327 (0.550–3.203)	0.529	0.467 (0.064–3.382)	0.391 (0.052–2.949)	0.362

Odds ratios (ORs) and 95% confidence intervals (CIs) are based on the univariate analysis. Adjusted odds ratios (aORs), 95% CIs and adjusted *P* value are based on the multiple logistic regression model for each outcome in the two groups, adjusted for maternal age at FET, duration of infertility, infertility diagnosis, fertilization, type of embryos transferred, ovarian stimulation protocols, maternal age at oocyte retrieval, AMH level. *P*(a) = adjusted *P* value. **P*(a) < 0.05

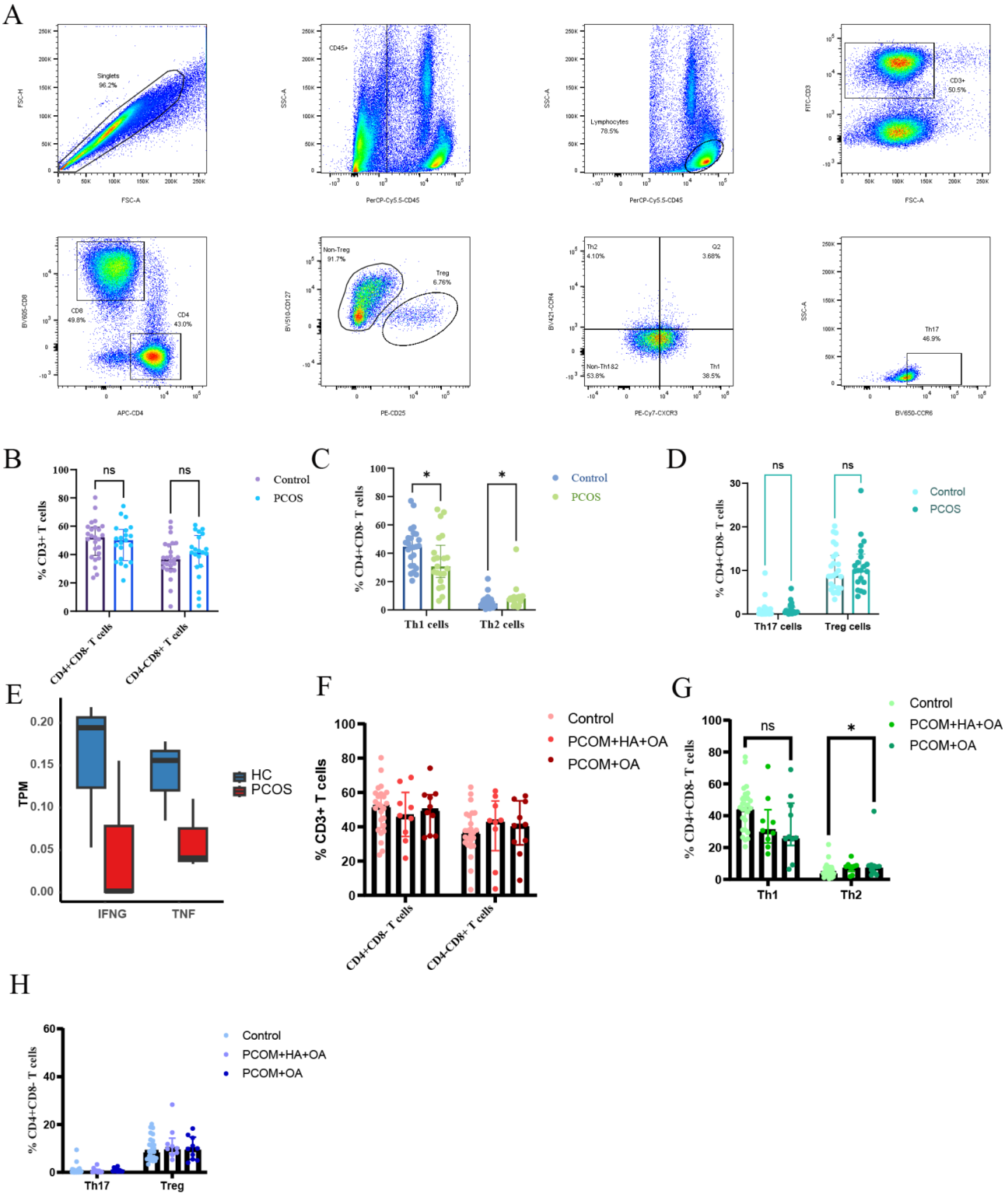

Fig. 2 (See legend on next page.)

discrepancy may be due to differences in sample size or androgen levels.

Endometrial T cell profiles of PCOS patients and controls

Considering that the diagnosis of PCOS was independently associated with an increased risk of pregnancy complications, the study went further to explore the

(See figure on previous page.)

Fig. 2 Comparison of T cell subsets in PCOS endometrium and normal endometrium by flow cytometry. **(A)** Pseudocolor plots showing the gating strategy for $CD4^+CD8^-$ T cells, $CD4^-CD8^+$ T cells, Th1, Th2, Th17, and Treg cells. Single cells were gated to eliminate debris and clumped cells. The exclusion of CD45-negative cells was followed by the identification of lymphocytes. After $CD3^+$T cells were identified, $CD4^+CD8^-$ T cells and $CD4^-CD8^+$ T cells were examined. $CD4^+$ $CD8^-$ T cells were selected, and Treg, Th1, Th2, and Th17 cells were identified successively. Values inside the plots represent the percentages from the parent gate. SSC-A: side scatter area, FSC-A: forward scatter area, FSC-H: forward scatter height. (**B**) Comparison of $CD4^+CD8^-$ T cells and $CD4^-CD8^+$ T cells in PCOS endometrium and normal endometrium. (**C**) Comparison of Th1 and Th2 cells in PCOS endometrium and normal endometrium. (**D**) Comparison of Th17 and Treg cells in PCOS endometrium and normal endometrium. (**E**) Comparison of IFNG and TNF in PCOS endometrium and normal endometrium (F) Comparison of CD4 + CD8- T cells and CD4-CD8 + T cells in the endometrium of controls and the four phenotypic subgroups of PCOS patients. (**G**) Comparison of Th1 and Th2 cells in the endometrium of controls and the four phenotypic subgroups of PCOS patients. (**H**) Comparison of Th17 and Treg cells in the endometrium of controls and the four phenotypic subgroups of PCOS patients. (*) $P < 0.05$ by Mann-Whitney U test

endometrial T-cell profiles of patients with and without PCOS (Fig. 2A). Th1 cells in PCOS endometrium were significantly lower and Th2 cells were significantly higher compared with controls by flow cytometry ($P < 0.05$) (Fig. 2C). However, $CD4^+CD8^-$ T cells, $CD4^-CD8^+$ T cells, Th17, and Treg cells were not statistically different between the two groups ($P > 0.05$) (Fig. 2B, D). To further validate the changes in T cell subsets, we downloaded RNA sequencing data from databases to analyze the expression of TNF and IFNG [24]. Both of these Th1 cytokines were found to be decreased in the pre-receptive phase of PCOS endometrium (Fig. 2E).

To further investigate the relationship between PCOS phenotypes and T-cell subsets, we categorized 21 PCOS patients based on phenotypic heterogeneity into three groups: PCOM + HA + OA (9 patients), PCOM + OA (10 patients), and PCOM + HA (2 patients). Due to the small sample size of the PCOM + HA group, we compared the T-cell subsets between the other two phenotypic groups and controls, as shown in Fig. 2F, G, H. Both the PCOM + HA + OA and PCOM + OA groups exhibited a trend of reduced Th1 cells and elevated Th2 cells, consistent with the overall PCOS population. However, only the PCOM + OA group showed a statistically significant increase in Th2 cells ($P < 0.05$) (Fig. 2G).

Discussion

This study highlights a significant increase in the incidence of miscarriage, HDP, PTB, GDM, and even fetal malformations across different phenotypes of PCOS women, especially those with the hyperandrogenic phenotype. Moreover, we observed a trend toward dysregulated T-cell profiles in the endometrium of PCOS patients, which may contribute to these unfavorable pregnancy outcomes. Notably, this is the first study to investigate differences in T-cell subsets between PCOS patients and controls, offering new insights into the potential immunological mechanisms underlying these complications.

Some studies have reported an increased MR in women with PCOS undergoing FET cycles A previous retrospective study showed that the PCOS group had an increased risk of miscarriage ($P < 0.001$) during the FET cycles but only the women who conceived singleton were selected [25]. A recent study believed that PCOS is an independent risk factor for late miscarriage in patients who conceived following a single-thawed blastocyst transfer [26]. Our results align with these findings and further explore the association between different PCOS phenotypes and MR. Except for the PCOM + HA group, where rates were similar to the control group due to the small sample size, MR increased in the other PCOS subgroups. This increased miscarriage risk in PCOS patients may be attributed to factors such as insulin resistance, hyperandrogenism, obesity, impaired oocyte quality, and endometrial abnormalities [26].

As reported in prior studies, miscarriage serves as an early risk indicator for obstetric complications [27]. In line with this, our study found poor perinatal outcomes in PCOS patients. A recent study showed an elevated risk of PTB among PCOS women [28]. However, another study declared that PCOS women had a higher risk of some pregnancy complications, such as gestational diabetes mellitus (GDM) and pregnancy-induced hypertension (PIH), but not included VPTB after FET cycles [29]. In the current study, we observed the elevated odds of miscarriage, HDP, PTB, GDM, and even fetal malformations in different subgroups of PCOS patients. Although PCOS people can produce more eggs and thus more embryos [30], it is vital to note that there is still an increased MR and severe pregnancy complications after the transfer of the best embryos from such a large number of embryos.

HDP is one of the leading causes of pregnancy-related maternal and fetal morbidity and mortality worldwide [31]. In addition to traditional cardiovascular disease risks, affected women also experience increased cardiovascular disease risk later in life [32]. Preterm birth remains the leading cause of infant mortality and morbidity [33]. Women with GDM are at higher risk for other obstetric complications and may face long-term effects on both maternal and infant health [34]. Fetal malformations are another serious complication, which can bring lasting pain and challenges to both the child and the entire family. Our study, through subgroup analysis of PCOS phenotypes, suggests that the increased incidence of these adverse obstetric outcomes in PCOS patients may be related to hyperandrogenism, which remains a topic of debate in the existing literature. While some

studies suggest that obstetric complications are similar across different phenotypes [35], the majority of the literature aligns with our findings [36, 37]. Additionally, basic research also suggests that hyperandrogenism and the associated metabolic disorders may influence various aspects related to obstetric complications. The hyperandrogenic PCOS phenotype is associated with increased insulin resistance and metabolic complications [38, 39]. Therefore, it is not difficult to explain its strong correlation with the incidence of GDM, which is consistent with previous studies [40].Additionally, hyperandrogenism may affect endometrial receptivity [41, 42] and is intricately linked to the onset and extent of early trophoblast infiltration and microstructural changes in the placenta [11, 43]. These factors could contribute to the increased risk of PTB and adversely affect fetal development. Therefore, we recommend increased clinical attention to PCOS patients with high androgen levels, even after successful conception, to monitor for adverse obstetric outcomes.

The great obstetrical syndromes, which encompass preeclampsia, PTB, and late spontaneous abortion, are increasingly understood to be rooted in disorders of placentation [44, 45]. Therefore, we reasonably suspect abnormalities in placental development among women with PCOS [13], with immune cells playing a significant role [46, 47]. Both adverse obstetric outcomes and increased abortion rates are closely linked to endometrial immune imbalance [48].Although numerous studies suggest that impaired endometrial receptivity may play a key role in the reduced fertility observed in women with PCOS, currently, there is no proven evidence for any intervention to improve uterine factors in PCOS to enhance endometrial receptivity [14].Therefore, investigating the endometrial immune status in PCOS is crucial, as it may aid in the development of targeted therapeutic strategies. Previous studies have indicated that the PCOS endometrium exhibits altered cytokine expression and a distinctive immune cell chemo-attractant profile [49]. In the overall population, the role of T cells in the endometrium is also ambiguous. Very few studies of Tregs in the pre-implantation endometrium showed controversial results, reporting both increased and decreased numbers of Treg, respectively, in women suffering from infertility [50]. There are some studies stating that $CD8^+$ cytotoxic T lymphocytes are consistently present throughout the menstrual cycle although their ability to induce cytotoxicity diminishes during the secretory phase to prevent fetal rejection [51]. Th1 immunity, known for its immune-inflammatory responses, contrasts with Th2 cells, which foster an anti-inflammatory environment. Considerable studies reported Th1 is dominant during the peri-implantation period, and shifted to the Th2 anti-inflammatory immune responses after the placental implantation [52–54]. Nevertheless, the latest high-quality review put forward that it is controversial whether there is a bias towards Th2 cells away from Th1 cells throughout pregnancy [55].

Concurrent with the previous study [19], we found the level of Treg was comparable in patients with versus without PCOS. Whereas, no difference was observed in $CD8^+$ T cells. Most importantly, there was a decrease in Th1 and an increase in Th2 in the endometrium of PCOS in the current study. Additionally, RNA sequencing data from databases revealed a reduction in Th1 cytokine expression in the PCOS endometrium [24], which are consistent with our data. Furthermore, when we subcategorized the PCOS samples based on patient phenotypes, similar trends were observed. Both the PCOM + HA + OA and PCOM + OA subgroups showed a tendency towards a decrease in Th1 cells and an increase in Th2 cells. Achieving a successful pregnancy requires a delicate and stringent equilibrium between immune activation and embryonic antigen tolerance, which if disrupted, may lead to adverse pregnancy outcomes [48]. A delicate equilibrium of pro-inflammatory and anti-inflammatory factors is necessary for intrauterine tissue remodeling, feto-placental development, and parturition throughout pregnancy [56]. It is worth noting that the appropriate Th1 immunity benefits the pregnancy process rather than harm [52]. However, the results of our study reported Th1/Th2 imbalance in PCOS endometrium, which will have a series of adverse effects on pregnancy process and may be the cause of obstetric complications in PCOS population. Moreover, emerging experimental findings have given rise to the notion that the decidualized endometrium functions as a biosensor of embryo quality. If the decidua function is abnormal, it may result in the implantation of embryos destined to miscarry [57]. Therefore, we speculate that an aberrant immune environment in PCOS endometrium may bring about the implantation of poor-quality embryos, which could explain both the increase in CPR and MR. However, the precise role of Th1 and Th2 balance in pregnancy is disputable [55], and the exact mechanism by which T cell imbalance promotes miscarriage and obstetric complications still needs to be further explored.

The study benefits from its substantial cohort size and generally comprehensive baseline and cycle data. And we classified PCOS patients into four subtypes and analyzed their pregnancy and obstetric outcomes. This type of detailed analysis is rarely seen in previous studies. Additionally, we tried to analyze the endometrial immune environment of PCOS patients through some basic experimental evidence. Nevertheless, given the retrospective nature of our study design, we cannot rule out the possibility of selection bias. And we overlooked the possible influence of endometrial preparation protocols

on outcomes [58]. Endometrial biopsy was performed a few days after the end of menstruation, and histopathological examination confirmed that the tissue was in the proliferative phase, which ensured as much consistency as possible among the patients within the group. However, we cannot guarantee that endometrial biopsies were performed on the same day of the proliferative phase for all patients due to the heterogeneity of menstrual cycles among different patients and the variability across different menstrual cycles for the same patient. Although flow cytometry has advantages in immunological and cell subset analysis, we must acknowledge that this experimental method has limitations. For instance, there is a possibility that blood immune cells may have been inadvertently included, even though we made every effort to wash the samples thoroughly. What's more, the impact on infertility and pregnancy complications might also be related to the quality of oocytes and embryos, rather than solely to endometrial function. Although we made every effort to transfer high-quality embryos, this confounding factor remains unavoidable. Further randomized control trials, basic experiments, and bioinformatics analysis are required to determine the impact of the PCOS diagnosis on the pregnancy process and explore possible mechanisms.

Taken together, our findings indicate an elevated incidence of miscarriage, HDP, PTB, GDM, and even fetal malformations in different phenotypes of PCOS patients, with hyperandrogenism further increasing these risks. We also presented evidence of abnormal uterine endometrial immune microenvironments in PCOS, particularly the imbalance between Th1 and Th2 cells. Given the high prevalence of PCOS and the adverse pregnancy and perinatal outcomes, we propose that the PCOS population should be classified as a high-risk group during the FET cycles in clinical practice, especially for those with the hyperandrogenic phenotype. Additionally, greater attention should be paid to the endometrial health of individuals with PCOS. Developing new strategies to enhance endometrial immune function in PCOS patients may prove beneficial.

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

Supplementary Material 5

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Author contributions
YG, FL and LJ conceived of and designed the study. YG and JY collected and analyzed the data. YG wrote the paper. HC, YZ, LZ, DB, WL and XT assisted in collecting tissue samples and clinical data. YY, BW, and ZF have provided assistance in study design, data analysis and interpretation of the results. All authors contributed to the article and approved the submitted version.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Competing interests
The authors declare no competing interests.

Ethical statement and consent to participate
Approval for this study was obtained from the Institutional Review Board of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology(No. TJ-IRB20210831). All endometrial biopsies were performed after ethical approval, and written informed consent to participate in the study was obtained from each endometrial donor.

Clinical trial number
Not applicable

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