

Original Research

Comparison of the Clinical Outcomes in Women with A or D PCOS Phenotypes versus Single Polycystic Ovary undergoing IVF-ET

Fangfang Dai¹, Yasong Geng¹, Meiyang Du¹, Shusong Wang^{2,3}, Guozhen Li¹, Linlin Tao¹, Bo Zheng^{1,*}¹Department of Obstetrics and Gynecology, Xingtai Infertility Specialist Hospital, 054000 Xingtai, Hebei, China²Department of Reproductive Medicine, Hebei Institute of Reproductive Health Science and Technology, 050051 Shijiazhuang, Hebei, China³Hebei Key Laboratory of Reproductive Medicine, 050051 Shijiazhuang, Hebei, China*Correspondence: zhengbo2025@126.com (Bo Zheng)

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Abstract

Background: The impact of polycystic ovary syndrome (PCOS) on endometrial receptivity and embryo quality is a subject of debate. Different PCOS patient types may exhibit different effects on these factors. This study aimed to identify causes for low live birth rate by comparing endometrial receptivity and embryo quality among different PCOS types. **Methods:** Overall, a total of 767 PCOS patients with first *in vitro* fertilization (IVF)/intracytoplasmic sperm injection (ICSI) treatment classified into phenotype A (n = 167 patients) and phenotype D (n = 600 patients) were eligible for analysis. Patients with single polycystic ovary (n = 406 patients) served as a control group to exclude the advantages of clinical outcome from higher number of oocytes retrieved in women with PCOS. **Results:** In phenotype A and D, Anti-Müllerian hormone (AMH), antral follicle count (AFC) and basic estradiol were significantly higher compared to single polycystic ovary. However, estradiol, progesterin and endometrial thickness on the human chorionic gonadotropin (hCG) day were significantly decreased. In fresh cycles, phenotype A had a significant statistical decrease in the live birth rate compared with single polycystic ovary (35/78 [44.87%] vs. 135/233 [57.94%], $p < 0.05$), although there was no significant difference in the number of embryo transplants and clinical pregnancy rate among the three groups. It might be associated with the significant reduction of total gonadotropin (Gn) dose, Gn duration, and follicular output rate (FORT) in all the typed PCOS groups. In the first frozen embryo transfer (ET) cycles, no significant difference was observed for estrogen, progesterin, or endometrial thickness on the day of ovulation and live birth rate. Women with live birth had a higher estradiol on the hCG day in the phenotype A (3763 [3121, 4752] vs. 2954 [2112, 4036] ng/mL) while a lower estradiol in the single polycystic ovary (3312 [2341, 4465] vs. 3417 [2350, 4638] ng/mL). In multivariate logistic regression analysis, estradiol on the hCG day was a significant independent factor predicting live birth for women with phenotype A (odds ratio (OR) >1.000, 95% confidence interval (95% CI): 1.000–1.001), $p = 0.034$ and single polycystic ovary (OR <1.000, 95% CI: 0.999–1.000, $p = 0.013$) in fresh ET. **Conclusions:** The various subtypes of PCOS have no significant adverse effect on embryonic outcome. It was not directly caused by PCOS; however, low levels of estradiol may be the reason for the low live birth rate owing to significant reduction of total Gn dose, Gn duration and FORT as a result to low incidence of ovarian hyperstimulation syndrome (OHSS) in phenotype A.

Keywords: polycystic ovary syndrome; live birth; endometrial receptivity; embryonic outcome; *in vitro* fertilization

1. Introduction

Polycystic Ovary Syndrome (PCOS), also known as a metabolic reproductive syndrome, is the most prevalent endocrine disorder among women of reproductive age [1]. The prevalence of PCOS in reproductive age women ranges widely from 4% to 21%; the syndrome is characterized by oligo or anovulation, clinical and/or biochemical signs of hyperandrogenism and polycystic ovaries [2,3].

Women with PCOS had a higher rate of spontaneous abortion compared with women without PCOS undergoing assisted reproductive treatment (ART) [4]. The hyper androgenic milieu affects the expression of insulin-signaling factors and glucose transporters in the endometrium of patients with PCOS [5]. Insulin resistance (IR) is prevalent in PCOS patients, particularly those with obesity and hyper-

insulinemia. Systemic IR, hyperinsulinemia, obesity, and inflammation can aggravate the IR degree of target tissues, destroy endometrial energy homeostasis, and affect the expression of gene expression profiles associated with decidualization and endometrial receptivity [6].

Moreover, embryos of patients with PCOS had a lower developmental potential and a higher rate of cell cycle arrest than patients without PCOS. Lu *et al.* [7] found that embryos took longer to reach the four-cell stage in PCOS patients when examined using a time-lapse system. It was observed that oocytes with PCOS had higher consumptions of nicotinamide adenine dinucleotide phosphate (NADPH) content, glucose and pyruvate, indicating increased reactive oxygen species production [8]. Lu *et al.* [7] observed significant down-regulation of genes related to oxidative phos-



Table 1. Baseline characteristics of the different subtypes of PCOS.

	Phenotype A	Phenotype D	Control group
Cases, n	167	600	406
Female age, years	28 (25, 30)	28 (26, 31)	28 (26, 31)
BMI, kg/m ²	25.4 (22.8, 27.6) *	24.7 (22.4, 27.5) *	23.0 (20.8, 25.7)
HOMA-IR	2.48 (1.41, 3.55) *	2.29 (1.24, 3.55) *	1.51 (0.45, 2.61)
primary infertility rate, %	65.87 (110/167) *	54.83 (329/600) *	43.10 (175/406)
ICSI, %	18.56 (31/167)	25.17 (151/600)	22.66 (92/406)
AMH, ng/mL	8.54 (5.63, 11.90) *	7.20 (5.05, 9.95) *	4.81 (3.35, 6.46)
AFC, n	30 (26, 37) *	27 (24, 33) *	24 (22, 26)
Basic FSH, IU/L	5.55 (4.58, 6.61) *	5.74 (4.81, 6.93)	5.98 (5.05, 7.04)
Basic estradiol, ng/mL	50.3 (38.0, 66.2) *	41.0 (31.4, 54.6) *	37.0 (25.9, 49.1)
Basic progestin, ng/mL	0.36 (0.25, 0.51)	0.30 (0.20, 0.42)	0.33 (0.24, 0.46)
Basic luteinizing hormone, IU/L	10.10 (5.88, 13.60) *	7.58 (4.43, 11.2) *	4.54 (3.21, 5.89)
Basic testosterone, ng/dL	38.6 (26.0, 51.2) *	20.0 (20.0, 29.5) *	20.0 (20.0, 20.0)

PCOS, polycystic ovary syndrome; BMI, body mass index; HOMA-IR, insulin resistance by homeostatic model assessment; ICSI, intracytoplasmic sperm injection; AMH, anti-mullerian hormone; AFC, antral follicle count; FSH, follicle-stimulating hormone. Statistics presented as median (P25, P75) or percentage (number/total number). *Statistically significant compared with the control group.

phorylation, cellular biosynthesis and metabolic processes in PCOS arrested embryos. They also noted up-regulation of lipopolysaccharide (LPS) biosynthesis and glutamate catabolism compared to control embryos [7]. Those might associate with the early developmental arrest in embryos of PCOS patients.

In the PCOS group, the number of oocytes retrieved and the live birth rate remained unchanged. Additionally, older women with PCOS had a higher cumulative live birth rate (CLBR) over two years compared to age- and body mass index (BMI)-matched counterparts without PCOS [9]. In comparison to age- and BMI-matched women without PCOS, patients exhibited a better oocyte reserve and had more available embryos. This phenomenon helped overcome compromised oocyte quality, especially in older PCOS patients [9].

The risk of ovarian hyperstimulation syndrome could be reduced by frozen embryo transfer, while the live-birth rate among ovulatory women with infertility was not significantly different between fresh-embryo transfer and frozen-embryo transfer [10]. According to multivariate logistic regression analysis, the polycystic ovarian morphology did not affect CLBR [11]. In anovulatory women with PCOS, elective frozen-embryo transfer has been shown to lead to a higher live-birth rate than fresh-embryo transfer [12]. Yang *et al.* [13] evaluated the pregnancy outcome of patients with PCOS undergoing *in vitro* fertilization and embryo transfer (IVF-ET) predicted by the follicular output rate (FORT). FORT is a powerful tool for measuring ovarian reactivity. A high FORT can achieve better pregnancy outcome owing to high-quality embryos and frozen embryo transfer [13].

There has been debate on whether PCOS affects patients' endometrial receptivity or embryo quality. PCOS was classified into four types based on the 2003 Rotterdam consensus [14,15]; varying outcomes for IVF-ET may

be observed among these different types. The study result might be biased because patients with PCOS phenotype B had insufficient oocyte reserve, leading to a notable decrease in CLBR. Hence, PCOS patients classified into four phenotypes were analyzed to identify potential causes for the low live birth rate, by comparing endometrial receptivity and embryo quality. Additionally, we conducted a detailed comparison between live births and non-live births in fresh cycles, analyzing the potential factors influencing live births among women with PCOS.

2. Materials and Methods

2.1 Study Population

Patients ≤ 35 years of age who underwent undergoing their first IVF or intracytoplasmic sperm injection (ICSI) cycles between January 1, 2017 and December 31, 2020, at the Center for Reproductive Medicine in Xingtai Infertility Specialist Hospital (Xingtai, Hebei Province, China) were retrospectively analyzed. The study included 767 patients diagnosed with PCOS and 406 individuals diagnosed with single polycystic ovaries (defined as having a follicle count per ovary >20 or ovarian volume >10 mL). The diagnosis of PCOS was established if at least two of the following three conditions were met: oligo- or anovulation, clinical and/or biochemical signs of hyperandrogenism, and polycystic ovaries. PCOS cases were further classified into four phenotypes (A, B, C and D) based on the 2003 Rotterdam consensus [16]. Phenotype A has three symptoms, phenotype B has no polycystic ovaries, phenotype C has no oligo- or anovulation, and phenotype D has no hyperandrogenism. Individuals with an endometrial history or significant chromosomal abnormalities (including endometriosis, fibroids, intrauterine adhesion, endometritis and other chromosomal abnormalities) were excluded.

2.2 Stimulation Protocols for IVF

All patients used standard gonadotropin-releasing hormone (GnRH) agonist protocol or GnRH antagonist protocol. Patients following the GnRH agonist protocol received intramuscular injections of gonadotropin-releasing hormone analogue (H20030578, Ipsen Pharma Biotech, Signes, France) from the mid-luteal phase. Once downregulation was achieved, patients commenced treatment with recombinant follicle-stimulating hormone (FSH) (JS20160044, Merck Serono S.p.A., Modugno, Apulia, Italy) to promote ovulation. The GnRH antagonist protocol commenced with recombinant FSH (JS20160044, Merck Serono S.p.A., Modugno, Apulia, Italy) at 100–150 U, with the dose adjusted according to the follicle growth measured by vaginal B ultrasound. Human menopausal gonadotrophin (HMG) (H10940097, Lizhu Pharmaceutical Trading Co., Zhuhai, China) was used to promote ovulation in the middle and late stage of follicles. Patients were given GnRH antagonist (H20050128, Baxter Oncology GmbH, Halle, Saxony-Anhalt, Germany) at a dose of 0.25 mg daily when the dominant follicle reached 12 mm in diameter. At the clinician's discretion, the administration of 5000–10,000 IU human chorionic gonadotropin (hCG) (H44020672, Lizhu Pharmaceutical Trading Co., Zhuhai, China) was used to trigger the ovary as soon as one-third of all follicles reached a diameter of ≥ 18 mm. The retrieval of the oocyte was done using needle aspiration guided by transvaginal ultrasound, 36–37 hours after hCG injection.

2.3 In vitro Fertilization and Embryo Transfer

IVF/ICSI was carried out at 3–4 h after oocytes retrieval, and fertilization methods were performed depending on sperm parameters. IVF was performed by 30 to 50 μL micro droplets at 1 to 2 oocytes per drop with a concentration of 200,000 sperm per milliliter. The granule cells surrounding the oocytes were then removed from 4 to 6 h after fertilization. The evidence of fertilization was evaluated 16–18 hours after insemination, and zygotes with two pronuclei indicated that fertilization was normal. The cleavage-stage embryo morphology was observed on the third day after oocyte retrieval as follows: good, 7–10 cells, $< 10\%$ fragmentation, stage-specific cell size and no multinucleation; fair, 6 or > 10 cells, 10–25% fragmentation, stage-specific cell size for majority of cells and no evidence of multinucleation; poor, 2–5 cells, severe fragmentation ($> 25\%$), cell size not stage specific, or evidence of multinucleation [17]. One or two good embryos were selected for embryo transfer or freezing, with the other embryos cultured until day 6 post-fertilization to observe blastocyst formation. The blastocysts assessed as 3BC or better were transferred or frozen. In the event that patients showed or were at risk of ovarian hyperstimulation syndrome (OHSS) (number of oocytes retrieved > 20 , or estradiol > 7000 ng/mL on hCG day), ET was canceled and all

transferable embryos were cryopreserved. If patients exhibited evidence of OHSS or were at risk of OHSS, ET was canceled and all transferable embryos were cryopreserved. A Cryotop device was utilized to perform vitrification of human embryo freezing.

In fresh cycles, Flavestin (H20041902, Zhejiang Xianju Pharmaceutical Co., Ltd., Xianju, Zhejiang, China) patients received intramuscular injection for luteal support from the day of oocytes retrieval. According to the estradiol level on the hCG injection day, appropriate estradiol (H20160679, DELPHARM Lille S.A.S., Cedex, France) was supplemented on the transplant day. In frozen ET cycles, the endometria were prepared by natural or artificial cycles. Patients with regular menstruation underwent natural cycle monitoring. A dose of 10,000 IU hCG was administered intramuscularly on the day when follicles matured (≥ 18 mm diameter), as determined by vaginal B-ultrasound examination. The cleavage embryos were transferred on the third day and blastocysts on the fifth day after ovulation. For those with irregular menstruation using artificial cycle, estradiol was administered at a dosage of 3 mg twice daily from the second day of menstruation, with the dose adjusted according to the thickness and morphology of the endometrium. On the fourth day after the endometrial thickness reached 9 mm, the cleavage embryos were transferred, and the blastocysts were transferred two days later. From the day of ovulation, luteal support was supplemented in all embryo transfer cycles and maintained for at least 8 weeks. In all types of embryo transfer cycles, luteal support was supplemented from the day of ovulation and was continued for at least 8 weeks. The administration was ceased if the β -hCG test was negative.

2.4 Measurement

A pregnancy test was performed on day 14 after ET, and a positive result was indicated by a serum β -hCG level greater than 5 IU/L. Subsequently, a clinical pregnancy was defined as the detecting of the gestational sac on day 28 after ET. Cumulative live births were calculated, encompassing cycles without surplus embryos and those resulting in at least one live birth, combining fresh and all frozen ET cycles occurring over a two-year period. CLBR was calculated as cumulative live birth rate per ovarian stimulation cycle. The antral follicle count (AFC) was defined as a diameter of 3–10 mm at baseline. The pre-ovulatory follicle count (PFC) was defined as a diameter of 16–22 mm on the day of hCG injection. FORT was calculated as $\text{PFC}/\text{AFC} \times 100\%$.

2.5 Statistical Analysis

Statistical analyses were performed with SPSS version 23 (IBM Corporation, Armonk, NY, USA). The non-normally distributed continuous variables were expressed as median (25th quartile, 75th quartile), and comparisons were performed using the Wilcoxon rank sum test. Count

Table 2. Ovarian stimulation of the different subtypes of PCOS.

	Phenotype A	Phenotype D	Control group
Cases, n	167	600	406
Protocol			
Long GnRH agonist protocol, %	80.84 (135/167) *	83.50 (501/600) *	97.78 (397/406)
GnRH antagonist protocol, %	19.16 (32/167) *	16.50 (99/600) *	2.46 (10/406)
Total Gn dose, IU	1850 (1450, 2263) *	1925 (1550, 2475)	2013 (1650, 2419)
Duration of Gn stimulation, days	11 (9, 12) *	11 (10, 12)	11 (10, 12)
Estradiol, hCG day, ng/mL	3961 (2877, 5740) *	3947 (2676, 5728) *	4417 (3208, 5835)
Progesterin, hCG day, ng/mL	0.68 (0.50, 0.94) *	0.70 (0.51, 0.96) *	0.85 (0.63, 1.15)
Endometrial thickness, hCG day, mm	10.3 (9, 12) *	11 (9, 12) *	12 (10, 13)
FORT, %	61.3 (48.9, 75.0) *	60.6 (47.6, 77.8) *	72.0 (58.4, 88.2)
Oocytes retrieved rate, %	90.50 (74.00, 100.00)	89.50 (75.00, 100.00) *	93.90 (80.80, 100.00)
No. of oocytes retrieved, n	16 (12, 21)	15 (11, 20)	16 (13, 20)
No. of normal fertilization, n	9 (7, 13) *	9 (6, 13) *	10 (7, 14)
No. of transferable embryos, n	5 (3, 7) *	4 (3, 6)	4 (2, 6)
No. of high-quality embryos, n	2 (1, 5)	2 (1, 4)	2 (1, 4)
Blastocyst formation rate, %	42.42 (694/1636) *	41.19 (2358/5724) *	38.90 (1532/3938)
OHSS rate, %	5.39 (9/167)	8.50 (51/600)	6.65 (27/406)

GnRH, gonadotropin-releasing hormone; Gn, gonadotropin; hCG, human chorionic gonadotropin; FORT, follicular output rate; OHSS, ovarian hyperstimulation syndrome. Statistics presented as median (P25, P75) or percentage (number/total number). *Statistically significant compared with the control group.

data were indicated as a percentage (%), and comparisons were performed using the χ^2 test. Multivariate analysis and logistic regression were performed to evaluate independent risk factors for live birth. Statistical significance was accepted at $p < 0.05$.

3. Results

Overall, a total of 767 PCOS patients with first IVF/ICSI treatment classified into two types (A: $n = 167$, and D: $n = 600$) were eligible for analysis, together with 406 single polycystic ovary patients as control group (Fig. 1). Data reported in Table 1 show that female age and insemination method were comparable among the three groups. The basic progesterin, BMI, and primary infertility rate in phenotypes A and D of PCOS were significantly higher than those in single polycystic ovary. All types of PCOS had a higher basic testosterone than single polycystic ovary. Insulin resistance by homeostatic model assessment (HOMA-IR), AMH, AFC, basic estradiol, and basic luteinizing hormone (LH) were significantly increased in phenotype A and D relative to single polycystic ovary, but estradiol, progesterin and endometrial thickness on the hCG day were significantly decreased (Table 2).

This phenomenon could be related to a significant reduction of total Gn dose (1850 [1450, 2263] vs. 2013 [1650, 2419] IU), Gn duration (11 [9, 12] vs. 11 [10, 12] days) and FORT (61.3 [48.9, 75.0] vs. 72.0 [58.4, 88.2] %) in phenotype A relative to single polycystic ovary. No significant difference was observed in number of oocytes retrieved, high-quality embryo rate and moderate-severe OHSS rate among the three groups. Interestingly, although number

of normal fertilizations was lower, the blastocyst formation rates were higher in phenotype A and D relative to single polycystic ovary. Moreover, the number of transferable embryos was significantly higher in phenotype A (5 [3, 7] vs. 4 [2, 6]) than single polycystic ovary.

There was no significant difference in the ET cancel rate for OHSS risk and the cumulative live yield per oocyte retrieval among the three groups (Table 3). In fresh cycles, phenotype A had a significant statistical decrease in the live birth rate compared with single polycystic ovary (35/78 [44.87%] vs. 135/233 [57.94%], $p < 0.05$). Those might be associated with lower estrogen, progesterin and endometrial thickness on the hCG trigger day. In the initial frozen ET cycles, where fresh ET was withheld to mitigate the risk of OHSS, there were no significant differences observed in estrogen, progesterin and endometrial thickness on the ovulation day. There were no significant differences in biochemical pregnancy rates, clinical pregnancy rates, implant rates, and live birth rates among the three groups, although the biochemical pregnancy rate of phenotype A was significantly higher than that of the single polycystic ovary group.

Women with phenotype A, phenotype D and single polycystic ovary were divided into two subgroups according to whether they produced live births in fresh cycles; however, women with phenotype B, C were excluded due to the small number of cases. Women with live birth had a higher estradiol on the hCG day in the phenotype A (3763 [3121, 4752] vs. 2954 [2112, 4036] ng/mL) while a lower estradiol in the single polycystic ovary (3312 [2341, 4465] vs. 3417 [2350, 4638] ng/mL) (Table 4). There were no

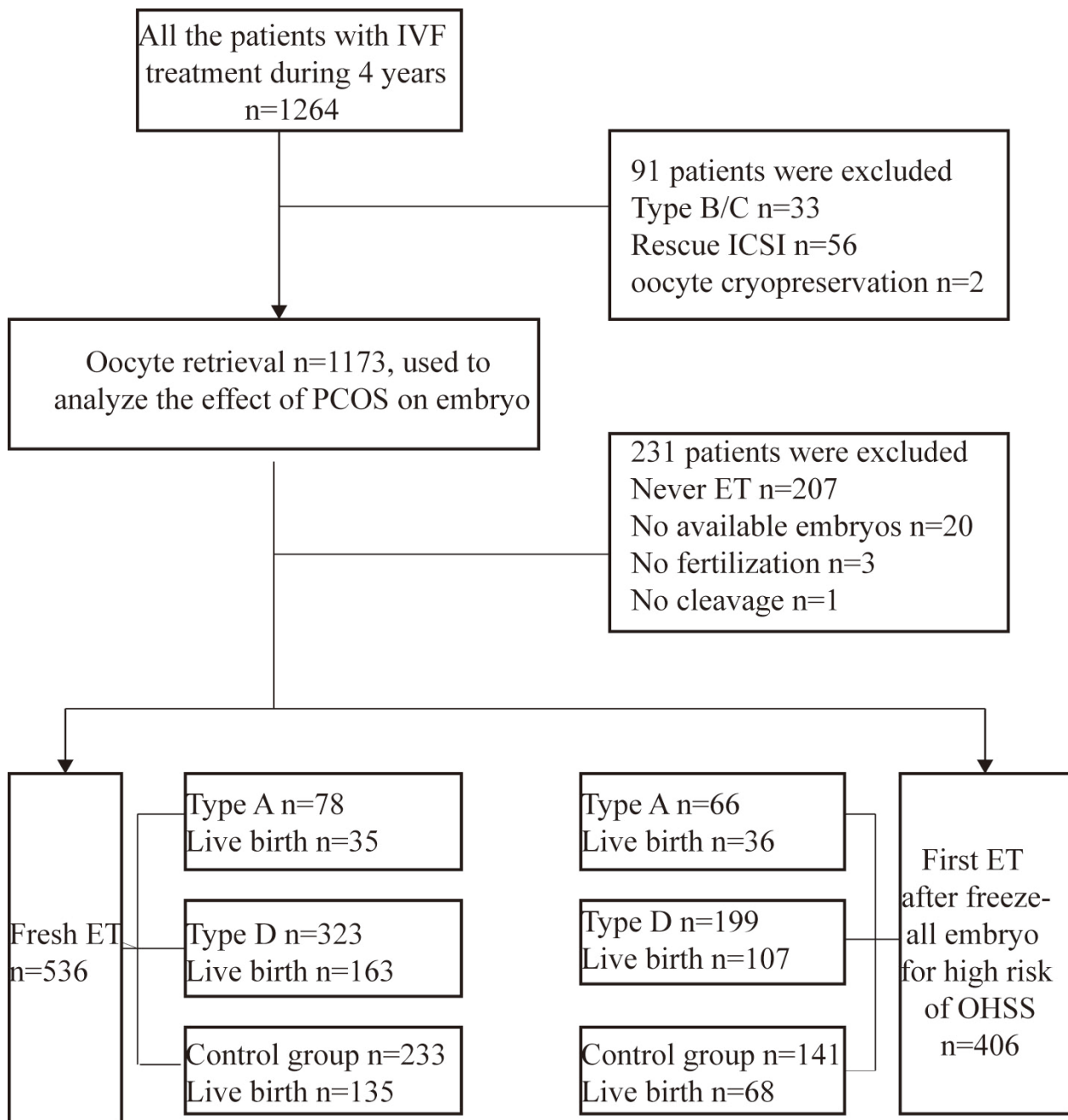


Fig. 1. Trial flow chart. An overview of the patient selection and the overall reproductive outcome of fresh embryo transfer (ET) and first frozen embryo transfer ET (FET). IVF, *in vitro* fertilization; OHSS, ovarian hyperstimulation syndrome.

significant differences of estradiol on the hCG day in the phenotype D. Furthermore, there was no significant difference in female age, BMI, HOMA-IR, AFC, number of oocytes retrieved, FORT, LH, FSH, progesterone (P) and endometrial thickness on the hCG between two subgroups (Table 4). In multivariate logistic regression analysis, after adjusting for female age, BMI, HOMA-IR, AFC, endometrial thickness, FSH, LH on the hCG days, and estradiol on the hCG day were significant independent factors predicting live birth in fresh ET for women with phenotype A (OR >1.000, 95% CI: 1.000–1.001), $p = 0.034$) and single poly-

cystic ovary (OR <1.000, 95% CI: 0.999–1.000, $p = 0.013$) (Table 5). The results presented in a violin plot indicate that women with live births had higher estradiol levels on the hCG day in the phenotype A, whereas lower estradiol levels were observed in the single polycystic ovary group (Fig. 2).

4. Discussion

Women with PCOS had a higher rate of spontaneous abortion compared with women without PCOS undergoing assisted reproductive treatment (ART) [4]. However, most

Table 3. Pregnancy outcomes of the different subtypes of PCOS.

Type	Phenotype A	Phenotype D	Control group
In fresh cycles			
Cases, n	78	323	233
ET cancel for OHSS risk, %	53.89 (90/167) *	46.17 (277/600)	42.36 (172/406)
Estradiol, hCG day, ng/mL	3327 (2417, 4435) *	3384 (2346, 4603)	3881 (2913, 5082)
Progesterin, hCG day, ng/mL	0.57 (0.42, 0.78) *	0.63 (0.45, 0.83)	0.79 (0.60, 1.06)
Endometrial thickness, mm	10.5 (10.0, 12.0) *	11.0 (9.5, 12.5) *	12.0 (10.5, 13.0)
No. of transferred embryos, n	1.85 ± 0.4	1.88 ± 0.41	1.87 ± 0.43
Biochemical pregnancy rate, %	76.92 (60/78)	73.38 (237/323)	75.97 (177/233)
Clinical pregnancy rate, %	60.26 (47/78)	60.06 (194/323)	64.81 (151/233)
Live birth rate, %	44.87 (35/78) *	50.46 (163/323)	57.94 (135/233)
Implantation rate, %	45.14 (65/144)	45.71 (277/606)	48.28 (210/435)
In the first frozen ET cycles withheld fresh ET due to the risk of OHSS			
Cases, n	66	199	141
Estradiol, ovulation day, ng/mL	263 (189, 390) *	290 (192, 455)	281 (196, 448)
Progesterin, ovulation day, ng/mL	0.62 (0.22, 12.9) *	10.40 (0.26, 16.50)	9.76 (0.28, 16.80)
Endometrial thickness, mm	9 (8.05, 9.6)	9 (8, 9.9)	8.8 (8, 10)
No. of transferred embryos, n	1.73 ± 0.48	1.8 ± 0.4	1.7 ± 0.46
Biochemical pregnancy rate, %	80.30 (53/66) *	74.37 (148/199)	68.09 (96/141)
Clinical pregnancy rate, %	66.67 (44/66)	63.82 (127/199)	55.32 (78/141)
Live birth rate, %	54.55 (36/66)	53.77 (107/199)	48.23 (68/141)
Implantation rate, %	49.12 (56/114)	45.25 (162/358)	43.33 (104/240)
Cumulative live birth rate, %	76.47 (104/136)	79.31 (391/493) *	72.83 (252/346)

ET, embryo transfer; FET, frozen embryo transfer ET. Statistics presented as median (P25, P75) or percentage (number/total number). *Statistically significant compared with the control group.

Table 4. Comparison of the clinical data between live births and non-live births in fresh cycles.

	Phenotype A		Phenotype D		Control group	
	No live birth	Live birth	No live birth	Live birth	No live birth	Live birth
Cases, n	43	35	160	163	98	135
Female age, years	29 (26, 30)	29 (26, 30)	29 (26, 31)	28 (27, 31)	29 (26, 31)	28 (27, 31)
BMI, kg/m ²	25.5 (22.9, 27.0)	26.0 (22.9, 28.4)	25.1 (22.7, 27.3)	24.7 (22.4, 27.1)	25.1 (22.7, 27.3)	24.7 (22.4, 27.1)
HOMA-IR	2.17 (1.55, 2.72)	2.98 (1.47, 4.01)	2.24 (1.17, 3.35)	2.28 (1.11, 3.28)	2.24 (1.17, 3.35)	2.28 (1.11, 3.28)
AFC, n	29 (26, 39)	29 (24, 37)	27 (23, 30)	26 (23, 30)	27 (23, 30)	26 (23, 30)
No. of oocytes retrieved, n	14 (10, 18)	16 (13, 19)	14 (11, 17)	14 (11, 17)	14 (11, 17)	14 (11, 17)
FORT, %	55.90 (43.90, 66.10)	59.70 (52.40, 073.30)	60.00 (47.80, 75.00)	59.10 (48.20, 70.80)	60.00 (47.80, 75.00)	59.10 (48.20, 70.80)
Estradiol, hCG day, ng/mL	2954 (2112, 4036)	3763 (3121, 4752) *	3417 (2350, 4638)	3312 (2341, 4465)	3417 (2350, 4638)	3312 (2341, 4465) *
LH, hCG day, IU/L	0.94 (0.66, 1.21)	0.89 (0.76, 1.23)	0.85 (0.67, 1.16)	0.87 (0.66, 1.17)	0.85 (0.67, 1.16)	0.87 (0.66, 1.17)
FSH, hCG day, IU/L	10.40 (8.38, 12.5)	11.20 (8.84, 14.20)	11.20 (8.99, 13.90)	11.40 (9.84, 14.20)	11.20 (8.99, 13.90)	11.40 (9.84, 14.20)
P, hCG day, ng/mL	0.57 (0.37, 0.73)	0.58 (0.45, 0.79)	0.63 (0.45, 0.83)	0.62 (0.45, 0.83)	0.63 (0.45, 0.83)	0.62 (0.45, 0.83)
Endometrial thickness, hCG day, mm	10.0 (9.0, 12.4)	11.0 (9.8, 12.6)	11.0 (9.5, 12.5)	11.0 (10.0, 12.5)	11.0 (9.5, 12.5)	11.0 (10.0, 12.5)

LH, luteinizing hormone; P, progesterone. *Statistically significant compared with the control group.

studies have shown that polycystic ovary does not affect embryo quality and CLBR, and may even improve pregnancy outcomes in older women [9–11]. Patients with single polycystic ovarian morphology (PCOM) were selected as control groups in this study to exclude the advantages

of better clinical outcome from a higher number of oocytes retrieved in patients with PCOS [18]. Similarly, patients were found to have lower live birth in phenotype A of PCOS compared with PCOM (35/78 [44.87%] vs. 135/233 [57.94%], $p < 0.05$). The low live birth rate in PCOS pa-

Table 5. Multivariate logistic regression analysis for the prediction of live birth in fresh cycles.

	Phenotype A			Control group				
	β	Standard error	p value	Exp (β) (95% confidence interval)	β	Standard error	p value	Exp (β) (95% confidence interval)
Female age	0.015	0.091	0.868	1.015 (0.849, 1.21)	0.021	0.043	0.632	1.021 (0.939, 1.110)
BMI	0.040	0.108	0.709	1.041 (0.843, 1.29)	0.013	0.052	0.807	1.013 (0.914, 1.122)
HOMA-IR	0.354	0.200	0.077	1.425 (0.962, 2.11)	0.158	0.092	0.083	1.172 (0.979, 1.402)
AFC	-0.047	0.039	0.233	0.954 (0.884, 1.03)	0.028	0.039	0.471	1.029 (0.952, 1.111)
Endometrial thickness, hCG day	0.156	0.138	0.259	1.168 (0.892, 1.53)	-0.050	0.069	0.464	0.951 (0.831, 1.088)
Estradiol, hCG day	0.001	0.001	0.034	>1.000 (1, 1.001)	-0.001	0.001	0.013	<1.000 (0.999, 1.000)
LH, hCG day	0.498	0.415	0.231	1.645 (0.729, 3.71)	-0.057	0.161	0.725	0.945 (0.690, 1.295)
FSH, hCG day	0.036	0.069	0.600	1.037 (0.906, 1.19)	-0.065	0.039	0.090	0.937 (0.869, 1.010)

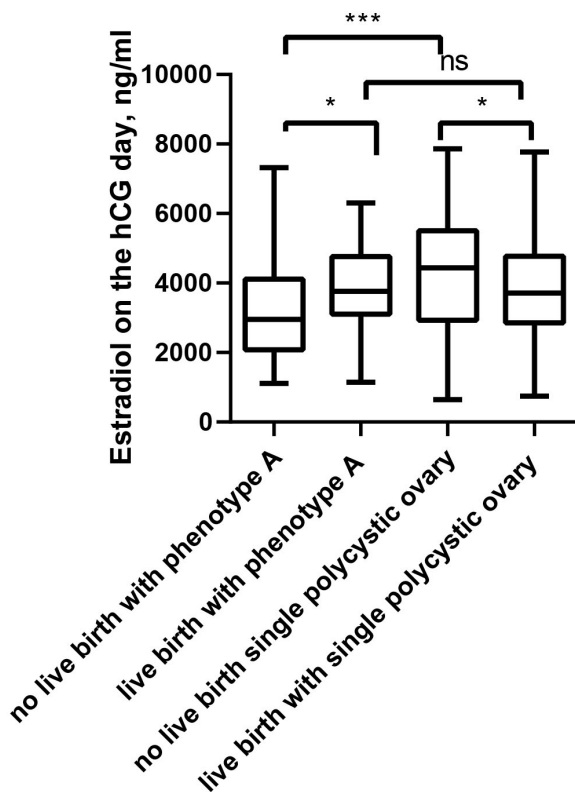


Fig. 2. Comparison of the estradiol on the hCG day between live births and non-live births in fresh cycles. * $p < 0.05$, * $p < 0.001$, ns, $p > 0.05$.**

tients undergoing ART has been attributed to endocrine alterations, obesity, insulin resistance, and embryonic chromosomal abnormalities. However, no definitive risk factors have been confirmed in association with this phenomenon [4,19,20]. Accordingly, we explored the possible reasons for the low live birth rate by comparing endometrial receptivity and embryo quality in PCOS patients undergoing IVF-ET.

Patients with PCOS were classified into phenotype A and D while phenotype B and C were excluded due to the small number of cases in this study. Clinical manifestations vary substantially among different subtypes of PCOS. There was no difference in the number of oocytes retrieved among the other groups, although AFC was higher in the groups of phenotype A and D. This finding is perhaps attributable to the deliberate reduction of FORT to reduce the OHSS rate. However, it is also possible that phenotype A and D are independent risk factors associated with low ovarian response, while rates of oocytes retrieved were significantly lower than those in the single polycystic ovary. This conclusion is supported by a previous retrospective observational study wherein oligo/amenorrhea is an independent risk factor associated with low ovarian response [21]. Interestingly, although number of normal fertilizations was lower, the blastocyst formation rates were higher in phenotype A and D relative to the single polycystic ovary. Moreover, the number of transferable embryos was significantly higher than in the cases of single polycystic ovary. This fact supports the supposition that PCOS has no adverse effect on the IVF embryo outcome. There was no significant difference in cumulative live birth rate among the three groups; as reported, the factors of cumulative live birth rates were primarily number of oocytes retrieved and embryo quality [9,22].

There was no significant difference in the clinical pregnancy rate of fresh embryo transfer among the three groups, but the live birth rate of PCOS phenotype A was significantly lower than that of single polycystic ovary. The biochemical pregnancy rate of phenotype A was significantly higher than that of the single polycystic ovary group. This also indicates that the low live birth rate of PCOS might not be due to embryo quality but to endometrial receptivity. It was found that estradiol, progesterin and endometrial thickness of PCOS phenotype A on trigger day were significantly lower than in the case of single polycys-

tic ovary. The endometrium is a dynamic tissue that undergoes cycles of growth, remodeling, and shrinkage steered by variations in the levels of estradiol and progesterin [23]. Although the ovary is known to produce numerous steroids throughout the menstrual cycle, only estradiol and progesterin have been shown to be necessary for the induction of endometrial receptivity [24,25]. The role of Rab-mediated intracellular transport modulated by estradiol and progesterin is important in endometrial receptivity [23].

This study also compared the clinical data between live births and non-live births in fresh cycles. Interestingly, women with live births had similar estradiol levels between the phenotype A and the single polycystic ovary. However, women with live birth had a higher estradiol on the hCG day in the phenotype A vs. a lower estradiol in the single polycystic ovary. In multivariate logistic regression analysis, after adjusting for female age, BMI, HOMA-IR, AFC, endometrial thickness, FSH, LH on the hCG days, and estradiol on the hCG day were significant independent factors predicting live birth in fresh ET for women with phenotype A (OR = 1.000, 95% CI: 1.000–1.001, $p = 0.034$) and single polycystic ovary (OR = 1.000, 95% CI: 0.999–1.000, $p = 0.013$). Low levels of estradiol may be the reason for the reduced live birth rates owing to significant reduction of total Gn dose, Gn duration and FORT as a result of low incidence of OHSS in phenotype A.

Estradiol, progesterin, and endometrial thickness on the day of ovulation did not differ significantly among the three groups in the first frozen ET cycles. Meanwhile, there were no statistically significant differences in clinical pregnancy rates and live birth rates among the three groups. The live birth rate in the first frozen ET cycles was greatly improved compared with fresh embryo transfer. These findings also support the hypothesis that PCOS may not have a direct effect on endometrial receptivity and embryo quality. Our results also confirm that women with live births had similar estradiol levels between the phenotype A and the single polycystic ovary. However, women with live births had a higher estradiol on the hCG day in the phenotype A, but a low estradiol in the single polycystic ovary.

Limitations of this study include the fact that patients with PCOS phenotype B and C could not be carefully analyzed due to the small number of cases. Whether FET or appropriate estrogen supplementation can improve live births is worthy of further exploration.

5. Conclusions

The various subtypes of PCOS have no significant adverse effect on IVF embryonic outcome. Low levels of estradiol may be the reason for the reduced live birth rate owing to significant reduction of total Gn dose, Gn duration and FORT as a result of low incidence of OHSS in phenotype A.

Availability of Data and Materials

The datasets generated and analyzed during the current study are not publicly available, since the dataset will be used for other retrospective analyses. The data are available from the corresponding author upon reasonable request.

Author Contributions

BZ, FD and SW contributed to conception and design of the study. FD and YG organized the database. MD, LT and GL performed the statistical analysis. FD wrote the first draft of the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

All procedures used in this study were conducted in accordance with the principles of conducting experiments with human participants as outlined in the Declaration of Helsinki. This study adopted the consent of the Ethics Committee of Xingtai Infertility Specialized Hospital (approval number: 2022-05). All process in IVF-ET were obtained by written informed consent.

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Conflict of Interest

The authors declare no conflict of interest.

References

- [1] Aversa A, La Vignera S, Rago R, Gambineri A, Nappi RE, Calogero AE, *et al.* Fundamental Concepts and Novel Aspects of Polycystic Ovarian Syndrome: Expert Consensus Resolutions. *Frontiers in Endocrinology.* 2020; 11: 516.
- [2] Rasquin Leon LI, Anastasopoulou C, Mayrin JV. Polycystic Ovarian Disease. *StatPearls: Treasure Island (FL).* 2022.
- [3] D'Alterio MN, Sigilli M, Succu AG, Ghisu V, Laganà AS, Sorrentino F, *et al.* Pregnancy outcomes in women with polycystic ovarian syndrome. *Minerva Obstetrics and Gynecology.* 2022; 74: 45–59.
- [4] Sun YF, Zhang J, Xu YM, Cao ZY, Wang YZ, Hao GM, *et al.* High BMI and Insulin Resistance Are Risk Factors for Spontaneous Abortion in Patients With Polycystic Ovary Syndrome Undergoing Assisted Reproductive Treatment: A Systematic Review and Meta-Analysis. *Frontiers in Endocrinology.* 2020; 11: 592495.
- [5] Zhao J, Chen Q, Xue X. An Update on the Progress of Endome-

- trial Receptivity in Women with Polycystic Ovary Syndrome. *Reproductive Sciences*. 2022; 29: 2136–2144.
- [6] Lee MH, Yoon JA, Kim HR, Kim YS, Lyu SW, Lee BS, *et al*. Hyperandrogenic Milieu Dysregulates the Expression of Insulin Signaling Factors and Glucose Transporters in the Endometrium of Patients with Polycystic Ovary Syndrome. *Reproductive Sciences*. 2020; 27: 1637–1647.
- [7] Lu C, Chi H, Wang Y, Feng X, Wang L, Huang S, *et al*. Transcriptome analysis of PCOS arrested 2-cell embryos. *Cell Cycle*. 2018; 17: 1007–1013.
- [8] Harris SE, Maruthini D, Tang T, Balen AH, Picton HM. Metabolism and karyotype analysis of oocytes from patients with polycystic ovary syndrome. *Human Reproduction*. 2010; 25: 2305–2315.
- [9] Mai Z, Liu M, Pan P, Li L, Huang J, Chen X, *et al*. Comparison of Cumulative Live Birth Rate Between Aged PCOS Women and Controls in IVF/ICSI Cycles. *Frontiers in Endocrinology*. 2021; 12: 724333.
- [10] Shi Y, Sun Y, Hao C, Zhang H, Wei D, Zhang Y, *et al*. Transfer of Fresh versus Frozen Embryos in Ovulatory Women. *The New England Journal of Medicine*. 2018; 378: 126–136.
- [11] Mackens S, Drakopoulos P, Moeykens MF, Mostinckx L, Boudry L, Segers I, *et al*. Cumulative live birth rate after ovarian stimulation with freeze-all in women with polycystic ovaries: does the polycystic ovary syndrome phenotype have an impact? *Reproductive BioMedicine Online*. 2022; 44: 565–571.
- [12] Chen Z, Shi Y, Sun Y, Zhang B, Liang X, Cao Y, *et al*. Fresh versus Frozen Embryos for Infertility in the Polycystic Ovary Syndrome. *The New England Journal of Medicine*. 2016; 375: 523–533.
- [13] Yang H, Lin J, Jin C, Meng L, Wu S, Chen Y. The Predictive Value of the Follicular Output Rate on Pregnancy Outcome of Patients with Polycystic Ovary Syndrome Undergoing In Vitro Fertilization and Embryo Transfer. *Medical Science Monitor*. 2020; 26: e916175.
- [14] Teede HJ, Misso ML, Costello MF, Dokras A, Laven J, Moran L, *et al*. Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. *Human reproduction*. 2018; 33: 1602–1618.
- [15] 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). *Human Reproduction*. 2004; 19: 41–47.
- [16] Hoeger KM, Dokras A, Piltonen T. Update on PCOS: Consequences, Challenges, and Guiding Treatment. *the Journal of Clinical Endocrinology and Metabolism*. 2021; 106: e1071–e1083.
- [17] Alpha Scientists in Reproductive Medicine, ESHRE Special Interest Group Embryology. Istanbul consensus workshop on embryo assessment: proceedings of an expert meeting. *Human Reproduction*. 2011; 26: 1270–1283.
- [18] Chen YH, Wang Q, Zhang YN, Han X, Li DH, Zhang CL. Cumulative live birth and surplus embryo incidence after frozen-thaw cycles in PCOS: how many oocytes do we need? *Journal of Assisted Reproduction and Genetics*. 2017; 34: 1153–1159.
- [19] Agarwal A, Aponte-Mellado A, Premkumar BJ, Shaman A, Gupta S. The effects of oxidative stress on female reproduction: a review. *Reproductive Biology and Endocrinology*. 2012; 10: 49.
- [20] Yang X, Quan X, Lan Y, Wei Q, Ye J, Yin X, *et al*. Serum chemerin level in women with PCOS and its relation with the risk of spontaneous abortion. *Gynecological Endocrinology*. 2018; 34: 864–867.
- [21] Hu KL, Gan K, Ying Y, Zheng J, Chen R, Xue J, *et al*. Oligo/Amenorrhea Is an Independent Risk Factor Associated With Low Ovarian Response. *Frontiers in Endocrinology*. 2021; 12: 612042.
- [22] De Vos M, Pareyn S, Drakopoulos P, Raimundo JM, Anckaert E, Santos-Ribeiro S, *et al*. Cumulative live birth rates after IVF in patients with polycystic ovaries: phenotype matters. *Reproductive BioMedicine Online*. 2018; 37: 163–171.
- [23] Leiva NL, Nolly MB, Ávila Maniero M, Losinno AD, Damiani MT. Rab Proteins: Insights into Intracellular Trafficking in Endometrium. *Reproductive Sciences*. 2021; 28: 12–22.
- [24] Paulson RJ. Introduction: Endometrial receptivity: evaluation, induction and inhibition. *Fertility and Sterility*. 2019; 111: 609–610.
- [25] Smith MB, Paulson RJ. Endometrial preparation for third-party parenting and cryopreserved embryo transfer. *Fertility and Sterility*. 2019; 111: 641–649.