

Individualized ART Treatment Strategies for Polycystic Ovary Syndrome Patients Based on Different Phenotypes: A Study on Ovarian Response Prediction and Optimization of Pregnancy Outcomes

Yanyi Li

chengde central hospital

Fan Si

1024780226@qq.com

chengde central hospital

Zhuo Wang

chengde central hospital

Research Article

Keywords: Polycystic Ovary Syndrome, Phenotype, Assisted Reproductive Technology, Individualized Treatment, Inflammatory Cytokines, Pregnancy Outcomes

Posted Date: October 8th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-11068074/v1>

License:  This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

Additional Declarations: No competing interests reported.

Abstract

Objective: To explore the clinical heterogeneity among patients with polycystic ovary syndrome (PCOS) classified according to the Rotterdam criteria, and to evaluate the impact of personalized ovarian stimulation protocols tailored to each phenotype on ovarian response, the inflammatory microenvironment, and pregnancy outcomes in assisted reproductive technology (ART).

Method: This study is a retrospective cohort study that included 181 PCOS patients and 60 control patients who underwent ART treatment at our hospital from January 1, 2024, to January 1, 2026. The PCOS patients were classified into four phenotypes according to the Rotterdam criteria: Phenotype A (hyperandrogenism + ovulatory dysfunction + polycystic ovaries), Phenotype B (hyperandrogenism + ovulatory dysfunction), Phenotype C (hyperandrogenism + polycystic ovaries), and Phenotype D (ovulatory dysfunction + polycystic ovaries). Each phenotype group received an individualized ovarian stimulation protocol (such as the antagonist protocol, pre-treatment followed by controlled ovarian hyperstimulation, metformin combined with ovarian stimulation, mild stimulation protocol, etc.), while the control group received the standard antagonist protocol. We compared baseline characteristics, ovarian stimulation parameters, embryo quality, pregnancy outcomes, and serum levels of inflammatory cytokines (IL-6, TNF- α , CRP) among the groups, and analyzed independent risk factors influencing pregnancy rates.

Baseline characteristic differences: Significant differences were observed among the groups in terms of BMI, AMH, AFC, and testosterone levels ($P < 0.05$). Among these, phenotype B exhibited a unique profile characterized by "high metabolic risk and low ovarian reserve." It had the highest BMI ($27.9 \pm 2.0 \text{ kg/m}^2$) and testosterone level ($3.3 \pm 1.2 \text{ nmol/L}$), yet its AMH level ($6.2 \pm 2.0 \text{ ng/mL}$) and AFC (4.4 ± 0.9) were significantly lower than those in other PCOS phenotypes ($P < 0.001$). **Ovarian stimulation response:** Phenotype D showed the lowest gonadotropin dosage ($1729.9 \pm 557.3 \text{ IU}$); phenotype B had significantly fewer oocytes retrieved (10.1 ± 2.5) and fewer mature oocytes (MII oocytes) (7.5 ± 2.1) compared to other groups ($P < 0.001$). **Pregnancy outcomes:** Phenotype D had the highest clinical pregnancy rate (63.2%) and live birth rate (54.4%), as well as the lowest incidence of OHSS (2.9%); phenotype B had the lowest live birth rate (29.4%). Phenotype A had the highest risk of OHSS (16.4%). **Inflammatory markers and regression analysis:** Serum levels of IL-6, TNF- α , and CRP in phenotypes A and B were significantly higher than those in other groups ($P < 0.001$). Multivariate logistic regression analysis revealed that elevated CRP levels were an independent risk factor for clinical pregnancy rate ($\text{OR} = 0.672$, $P = 0.002$). After adjusting for confounding factors, the live birth rate in phenotype A was significantly lower than that in the control group ($\text{OR} = 0.401$). $P = 0.011$.

Conclusion: Different phenotypes of PCOS exhibit significant heterogeneity in metabolic characteristics, ovarian reserve, and the inflammatory microenvironment. Phenotype B displays high-risk features—"hyperandrogenism, high BMI, and low ovarian reserve"—and has the worst prognosis. Implementing phenotype-based, individualized ovulation-induction protocols can effectively balance the number of oocytes retrieved with the risk of OHSS, thereby optimizing clinical pregnancy outcomes. Elevated levels of CRP are associated with adverse pregnancy outcomes, highlighting the importance of inflammation management in PCOS-assisted reproductive treatments.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is an endocrine disorder affecting 8% to 13% of women of reproductive age [1]. Ovulatory dysfunction significantly impacts fertility in affected women, making PCOS a major contributor to infertility—accounting for as much as 70% of cases of anovulatory infertility [2]. The Rotterdam criteria established in 2003 provided clear guidelines for the clinical diagnosis of PCOS [3] and acknowledged the heterogeneous nature of different PCOS phenotypes [4]. Based on varying combinations of three core diagnostic criteria—ovulatory dysfunction, hyperandrogenism, and polycystic ovarian morphology—the Rotterdam criteria classify PCOS into four

distinct clinical phenotypes: Phenotype A: Hyperandrogenism + ovulatory dysfunction + polycystic ovarian morphology; Phenotype B: Hyperandrogenism + ovulatory dysfunction; Phenotype C: Hyperandrogenism + polycystic ovarian morphology; Phenotype D: Ovulatory dysfunction + polycystic ovarian morphology. Studies conducted both domestically and internationally have demonstrated significant differences among PCOS patients with different phenotypes in terms of ovarian responsiveness, metabolic characteristics, and pregnancy outcomes [5][6][7]. Patients with phenotype A typically exhibit a hyperresponse of the ovaries, with a higher risk of OHSS, yet their embryo quality and pregnancy outcomes tend to be relatively poorer. In contrast, patients with phenotype D, although having lower ovarian responsiveness, demonstrate a relatively higher clinical pregnancy rate. Additionally, well-established studies conducted within the framework of the Rotterdam classification system-based on metabolic characteristics and incorporating BMI and insulin resistance indices have further subdivided PCOS patients into “obese-metabolically high-risk type” and “lean-metabolically abnormal type.” The latter group, despite having a completely normal body weight, still exhibits abnormal body fat distribution and chronic low-grade inflammation, posing a significantly higher long-term risk of diabetes. Currently, many PCOS patients remain undiagnosed and untreated, leaving substantial gaps in care [8]. The current one-size-fits-all clinical approach clashes with the heterogeneity of the disease itself; the widely adopted uniform treatment strategy fails to address the unique physiological characteristics and therapeutic needs of different patient subgroups, resulting in suboptimal treatment outcomes-including poor clinical responses and unfavorable pregnancy outcomes-and low rates of spontaneous conception [8]. Moreover, ovulation induction, often used as a second-line treatment, also proves ineffective for these patients. Although third-line treatment-IVF-can improve pregnancy rates, it dramatically increases the incidence of OHSS and the risk of complications in offspring [5,6], thereby driving up medical costs and eroding patient confidence. Furthermore, the lack of comprehensive studies investigating the relationship between phenotype-specific characteristics and ART success rates leaves significant gaps in both clinical practice and guideline development. This study aims to explore the clinical heterogeneity among PCOS patients with different phenotypes and their impact on assisted reproductive technologies. By achieving early identification and precise prediction, we seek to implement targeted, individualized treatments, evaluate patients’ ovarian stimulation parameters and clinical outcomes, and ultimately provide valuable guidance for clinical practice.

MATERIALS AND METHODS

I. Study Subjects

This study employed a retrospective cohort design with a follow-up period of 24 months. Patients with polycystic ovary syndrome (PCOS) who underwent assisted reproductive technology (ART) treatment in the Reproductive Medicine Department of our hospital from January 1, 2024, to January 1, 2026, were included. Inclusion criteria: Patients meeting the Rotterdam diagnostic criteria for PCOS and excluding those with other underlying causes (such as congenital adrenal hyperplasia, Cushing’s syndrome, androgen-secreting tumors, and other conditions leading to anovulation, including hypothalamic and pituitary disorders). Ovulatory dysfunction was defined as menstrual cycles lasting fewer than 21 days or longer than 35 days. Biochemical hyperandrogenism was assessed based on reliable measurements of androgens, with total testosterone (TT) levels > 2.53 nmol/L (0.87 ng/dL), androstenedione (AND) levels > 11.5 nmol/L, or dehydroepiandrosterone sulfate (DHEAS) levels > 10.6 μ mol/L. Polycystic ovarian morphology (PCOM) was identified by transvaginal pelvic ultrasound, characterized by ovarian volume > 10 mL or the presence of more than 12 antral follicles measuring 2 to 9 mm in diameter in either or both ovaries. Exclusion criteria included: 1. The presence of other factors contributing to infertility, such as severe male-factor infertility, hydrosalpinx, endometriosis, or intrauterine factors unfavorable for embryo implantation, including uterine malformations, intrauterine adhesions, and uterine fibroids that disrupt the normal physiological structure of the uterine cavity; 2. Coexisting endocrine disorders, such as thyroid dysfunction or hyperprolactinemia; 3. The presence of serious

medical conditions, including cardiovascular disease or abnormal liver and kidney function; 4. Use of hormonal medications within the past 3 months; 5. Prior exposure to ovulation-inducing treatments within the past 6 months. PCOS patients were divided into four phenotypic groups: 1. Phenotype A: Hyperandrogenism + Ovulatory Dysfunction + Polycystic Ovaries; 2. Phenotype B: Hyperandrogenism + Ovulatory Dysfunction; 3. Phenotype C: Hyperandrogenism + Polycystic Ovaries; 4. Phenotype D: Ovulatory Dysfunction + Polycystic Ovaries. At the same time, 60 PCOS patients of similar age and BMI, who met the same inclusion and exclusion criteria, were recruited as a control group and received the standard treatment protocol (initiated with 150 IU of Gn, followed by the addition of an antagonist). All participants signed informed consent forms.

II. Research Methodology

Individualized ovarian stimulation protocols were applied to PCOS patients with different phenotypes, and the quality of ART oocytes and embryos as well as pregnancy outcomes were observed. Specifically: 1. For patients with Phenotype A (hyperandrogenism + ovulatory dysfunction + polycystic ovaries), a low-dose Gn initiation regimen (75–150 IU/day) was used in the antagonist protocol, with gradual dose escalation, and trigger timing was determined appropriately. 2. For patients with Phenotype B (hyperandrogenism + ovulatory dysfunction), Yasmin was administered for three cycles as pretreatment; Gn was initiated starting from the second cycle after discontinuation of the medication. Standard-dose Gn was used for initiation (150–225 IU/day), and trigger timing was determined appropriately. 3. For patients with Phenotype C (hyperandrogenism + polycystic ovaries), metformin 1500 mg/day was orally administered starting 16 weeks before Gn initiation until the trigger day; low-dose Gn was initiated (75–150 IU/day), gradually increased, and trigger timing was determined appropriately. 4. For patients with Phenotype D (ovulatory dysfunction + polycystic ovaries), a mild stimulation protocol combining letrozole with low-dose Gn (≤ 150 IU/day) was employed, and trigger timing was determined appropriately.

III. Observation indicators

1. Baseline characterization of the study subjects, including age, body mass index (BMI), duration of infertility, antral follicle count (AFC), anti-Müllerian hormone (AMH), and baseline endocrine hormones such as FSH, LH, T, and PRL. 2. Ovarian stimulation parameters: number of days of gonadotropin (Gn) stimulation, total dose of Gn used, levels of LH, E2, and P on the trigger day, and number of oocytes retrieved. 3. Oocyte quality indicators: rate of MII oocytes and fertilization rate. 4. Pregnancy outcomes: clinical pregnancy rate, live birth rate, miscarriage rate, and incidence of OHSS. 5. Inflammatory cytokine levels: fasting blood samples were collected from patients during the early follicular phase to measure serum levels of interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF- α), and C-reactive protein (CRP).

IV. Statistical Methods

Data analysis was performed using SPSS software version 26.0 (IBM Corp, Armonk, NY, USA). For continuous variables, the Shapiro-Wilk test for normality was first conducted. Variables conforming to a normal distribution are presented as mean $\pm$ standard deviation; comparisons among multiple groups were carried out using one-way ANOVA. If the Levene test for homogeneity of variances indicated unequal variances, subsequent analyses employed the Games-Howell post-hoc correction for multiple comparisons. Variables that did not follow a normal distribution are presented as median and interquartile range (M [P25, P75]), and the Mann-Whitney U test was used for comparison. Categorical data are expressed as composition ratios or rates (%). Group comparisons are performed using the chi-square test. When pairwise comparisons among groups are required, the chi-square test should be

divided into subtests. If the smallest expected value is greater than 5, the Pearson chi-square test is used; if the smallest expected value is between 1 and 5, the continuity correction method is applied; and if the smallest expected value is less than 1, Fisher’s exact test is used. The chi-square subtests are adjusted using the Holm-Bonferroni correction. Multivariate analysis is conducted using logistic regression analysis. A p-value of less than 0.05 (two-tailed) is considered statistically significant. To further explore the factors influencing pregnancy rate and live birth rate, we constructed a multivariate logistic regression model (LR method) using clinical pregnancy (yes/no) as the dependent variable and grouping (phenotypes A, B, C, D, and the control group), age, BMI, duration of infertility, AMH levels, serum levels of IL-6, TNF- α , and CRP as independent variables. We then calculated the adjusted odds ratio (OR) and its 95% confidence interval (95% CI).

RESULTS

I. Clinical Characteristics of the Study Subjects:

This study included a total of 241 patients, of which 181 were diagnosed with PCOS and categorized according to different phenotypes, while the control group consisted of 60 PCOS patients who were not classified by phenotype. Phenotype A had the largest number of patients (73 cases, accounting for 40%), followed by phenotype D (68 cases, accounting for 38%), then phenotype C (23 cases, accounting for 13%), and finally phenotype B, which had the fewest patients (17 cases, accounting for 9%).

Table 1: General characteristics of PCOS patients with different phenotypes

Baseline characteristics	phenotype A	phenotype B	phenotype C	phenotype D	control group	t/F/X ²	P
Age	29.6±3.1	28.6±2.1	29.4±4.0	29.2±3.1	30.0±3.7	0.771	0.545
BMI	27. 1±2.8	27. 9±2.0	23.5±3.2	24.4±3.7	25.8±5.6	7.431	⊠ 0.001
Infertility duration	4(2,6)	2.7(1.3,5,5)	3(2,5)	4(3,5)	4(2,5)	3.545	0.471
AMH	10.8±2.9	6.2±2.0	7.7±2.1	8.3±2.0	9.0±2.5	18.745	⊠ 0.001
baseline FSH	5.9±1.6	5.9±1.4	6.1±1.5	6.2±1.3	6.2±2.1	0.256	0.906
baseline LH	6.5±3.4	8.7±2.5	8.1±3.3	7.6±2.2	8.7±3.4	14.473	0.006
baseline E2	43.0±15.3	33.0±11.1	41.3±15.1	39.7±9.2	42.2±13.5	2.331	0.057
baseline T	3.0±1.3	3.3±1.2	2.6±0.7	1.5±0.5	3.2±0.9	32.830	⊠ 0.001
AFC	10.6±4.0	4.4±0.9	9.4±4.2	9.9±3.6	10.3±3.4	10.571	⊠ 0.001

BMI stands for Body Mass Index, with the unit being kg/m²; AMH stands for Anti-Müllerian Hormone, with the unit being ng/mL; FSH stands for Follicle-Stimulating Hormone, with the unit being IU/L; LH stands for Luteinizing Hormone, with the unit being IU/L; E2 stands for Estradiol, with the unit being pg/mL; T stands for Free Testosterone, with the unit being nmol/L.

Table 1 presents a comparison of baseline clinical and endocrine characteristics between each phenotype group (Phenotypes A, B, C, D) and the control group. With regard to general demographic characteristics, there was no

statistically significant difference in age distribution among the groups ($P = 0.545$). However, BMI showed significant differences across the groups ($P < 0.001$). Phenotype B had the highest BMI at $27.9 \pm 2.0 \text{ kg/m}^2$, significantly higher than all other groups; followed by Phenotype A at $27.1 \pm 2.8 \text{ kg/m}^2$. Phenotypes C and D had relatively lower BMIs, at $23.5 \pm 3.2 \text{ kg/m}^2$ and $24.4 \pm 3.7 \text{ kg/m}^2$, respectively, while the control group had a BMI of $25.8 \pm 5.6 \text{ kg/m}^2$. There was no significant difference in infertility duration among the groups ($P = 0.471$). Regarding endocrine and ovarian reserve function indicators, AMH levels differed dramatically among the groups ($P < 0.001$), with Phenotype A exhibiting the highest AMH level ($10.8 \pm 2.9 \text{ ng/mL}$) and Phenotype B the lowest ($6.2 \pm 2.0 \text{ ng/mL}$). AFC also showed significant intergroup differences ($P < 0.001$), following the same trend: Phenotype A had the highest AFC (10.6 ± 4.0), whereas Phenotype B was significantly lower at 4.4 ± 0.9 . Basal luteinizing hormone (LH) levels differed significantly among the groups ($P = 0.006$); Phenotype B had the highest LH level (8.7 ± 2.5), and the control group ($8.7 \pm 3.4 \text{ IU/L}$) were significantly higher than those in other groups. In addition, there was a significant difference in baseline testosterone (T) levels among the groups ($P < 0.001$). The T level in phenotype B group ($3.3 \pm 1.2 \text{ nmol/L}$) was relatively high, whereas the lowest T level was observed in phenotype D group ($1.5 \pm 0.5 \text{ nmol/L}$). There was no significant difference in baseline follicle-stimulating hormone (FSH) levels among the groups ($P = 0.906$). Although baseline estradiol (E2) levels varied somewhat across the groups, the differences did not reach statistical significance ($P = 0.057$).

II. Ovarian stimulation parameters and oocyte or embryo quality following an individualized stimulation protocol.

After each PCOS patient type underwent an individualized COH protocol, to evaluate the impact of phenotypes A, B, C, and D-compared to the control group-on ovulation-inducing parameters and oocyte/embryo quality, we analyzed the number of days of gonadotropin (Gn) use, total Gn dosage, E2 levels on the trigger day, LH levels on the trigger day, P levels on the trigger day, number of oocytes retrieved, number of MII oocytes, and fertilization rates, see Table 2 for details.

Table 2: Ovarian Stimulation Parameters and Oocyte/Embryo Quality After Individualized COH in PCOS Patients with Different Phenotypes

	phenotype A	phenotype B	phenotype C	phenotype D	control group	F/X ²	P
Days of Gn	11.1±2.9	11.0±2.7	10.8±1.5	11.0±2.1	11.4±3.7	0.187	0.945
total Gn dosage	2091.1±376.7	2078.5±471.8	1905.6±587.3	1729.9±557.3	2097.1±692.0	5.240	☒ 0.001
E2 levels on the trigger day	2795.5±728.3	1520.5±373.8	2471.4±493.0	2638.7±609.5	2711.1±569.0	15.646	☒ 0.001
LH levels on the trigger day	2.8±1.1	2.7±1.1	3.0±1.3	3.3±1.4	3.1±1.4	1.695	0.152
P levels on the trigger day	0.7±0.3	0.5±0.2	0.8±0.3	0.6±0.2	0.8±0.3	5.624	☒ 0.001
number of oocytes retrieved	16.7±3.4	10.1±2.5	16.0±4.0	17.5±3.7	16.9±5.4	11.807	☒ 0.001
number of MII oocytes	12.7±3.5	7.5±2.1	12.5±2.1	12.7±3.5	11.5±3.7	9.745	☒ 0.001
Number of fertilized oocytes	11.4±3.4	6.0±1.3	11.0±3.1	11.5±3.2	10.6±2.8	12.188	☒ 0.001

Regarding the number of Gn days, there was no significant difference among the five groups ($F = 0.187$, $P = 0.945$). However, in terms of Gn dosage, statistically significant differences were observed among the groups ($F = 5.240$, $P < 0.001$). Specifically, the phenotype D group had the lowest average Gn dosage (1729.9 ± 557.3 IU), while the control group had the highest (2097.1 ± 692.0 IU). The other experimental groups also showed varying degrees of difference compared to the control group: phenotype A group, 2091.1 ± 376.7 IU; phenotype B group, 2078.5 ± 471.8 IU; and phenotype C group, 1905.6 ± 587.3 IU. Moreover, there were significant differences in E2 levels on the trigger day among the groups ($F = 15.646$, $P < 0.001$). The phenotype B group had the lowest E2 level (1520.5 ± 373.8 pg/mL), which was significantly lower than the highest E2 level observed in the phenotype A group (2795.5 ± 728.3 pg/mL). No significant differences in LH levels on the trigger day were detected among the groups ($F = 1.695$, $P = 0.152$); there were statistically significant differences among groups in terms of P levels on the trigger day ($F = 5.624$, $P < 0.001$). The P level in phenotype B group (0.5 ± 0.2 ng/mL) was the lowest, whereas phenotypes C (0.8 ± 0.3 ng/mL) and the control group (0.8 ± 0.3 ng/mL) showed higher values. Regarding the number of oocytes retrieved, there were significant differences among groups ($F = 11.807$, $P < 0.001$). The phenotype B group had the fewest oocytes retrieved (10.1 ± 2.5), while phenotypes A (16.7 ± 3.4), C (16.0 ± 4.0), D (17.5 ± 3.7), and the control group (16.9 ± 5.4) exhibited higher oocyte retrieval rates. Significant differences were observed in the number of MII oocytes (mature oocytes) among groups ($F = 9.745$, $P < 0.001$). The phenotype B group had the fewest MII oocytes retrieved (7.5 ± 2.1), whereas phenotypes A (12.7 ± 3.5), C (12.5 ± 2.1), D (12.7 ± 3.5), and the control group (11.5 ± 3.7) showed higher MII oocyte rates. In terms of fertilized eggs, there were significant differences among groups ($F = 12.188$, $P <$

0.001). The phenotype B group had the fewest fertilized eggs (6.0 ± 1.3), while phenotypes A (11.4 ± 3.4), C (11.0 ± 3.1), D (11.5 ± 3.2), and the control group (10.6 ± 2.8) showed higher fertilization rates.

III. Clinical Pregnancy Outcomes

To further evaluate the differences between the four personalized COH regimens-Phenotypes A, B, C, and D-and the control group in terms of ART clinical outcomes, we conducted a statistical analysis of clinical pregnancy rates, live birth rates, miscarriage rates, and the incidence of ovarian hyperstimulation syndrome (OHSS). The results are presented in Table 3.

Table 3: Clinical outcomes after individualized controlled ovarian hyperstimulation in PCOS patients with different phenotypes

	phenotype A	phenotype B	phenotype C	phenotype D	control group	F/X ²	P
clinical pregnancy rates%	43.8	29.4	52.2	63.2	65.0	12.465	0.014
live birth rates%	32.9	29.4	47.8	54.4	55.0	10.870	0.028
miscarriage rates %	24.7	23.5	13.0	11.8	11.7	6.427	0.169
the incidence of OHSS%	16.4	11.8	8.7	2.9	3.3	11.137	0.025

There was a statistically significant difference in clinical pregnancy rates among the groups ($X^2 = 12.465$, $P = 0.014$). The control group had the highest clinical pregnancy rate at 65.0%; phenotype D ranked second at 63.2%; and phenotype C showed a rate of 52.2%. In contrast, phenotypes A (43.8%) and B (29.4%) exhibited significantly lower clinical pregnancy rates. Regarding live birth rates, there were also significant differences among the groups ($X^2 = 10.870$, $P = 0.028$), with trends generally consistent with those observed for clinical pregnancy rates. The control group had the highest live birth rate at 55.0%, while phenotype D achieved a live birth rate of 54.4%, which was the closest to that of the control group and showed no significant disadvantage. Phenotype C had a live birth rate of 47.8%. However, phenotypes A (32.9%) and B (29.4%) displayed markedly lower live birth rates. With regard to miscarriage rates, although there was a certain trend in the numerical values across the groups, statistical analysis revealed no significant difference among the groups ($X^2 = 6.427$, $P = 0.169$). Phenotypes A (24.7%) and B (23.5%) had higher miscarriage rates numerically than the control group (11.7%), phenotype C (13.0%), and phenotype D (11.8%). As for the incidence of ovarian hyperstimulation syndrome (OHSS), there was a significant statistical difference among the groups ($X^2 = 11.137$, $P = 0.025$).The incidence of OHSS was highest in phenotype A, reaching 16.4%; phenotype B ranked second at 11.8%. Phenotype C had an incidence of 8.7%, phenotype D was at 2.9%, and the control group was at 3.3%.

IV. Comparison of Inflammatory Cytokine Levels

To investigate the effects of different individualized COH protocols (phenotypes A, B, C, and D) versus the control group on the inflammatory microenvironment in patients, we measured and compared the levels of interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF- α), and C-reactive protein (CRP) in the serum of each group. See Table 4 for details.

Table 4: Serum inflammatory factor levels in PCOS patients with different phenotypes

	phenotype A	phenotype B	phenotype C	phenotype D	control group	F/X ²	P
IL-6 pg/mL	12.6±2.2	11.1±2.0	9.6±1.5	8.2±1.9	6.5±1.4	98.304	<0.001
TNF-α pg/mL	14.7±4.1	13.9±2.4	10.9±2.0	9.5±2.4	7.3±1.8	63.612	<0.001
CRP mg/L	3.5±1.1	3.2±0.8	3.0±0.8	2.5±0.7	1.9±0.6	32.424	<0.001

There were significant statistical differences in IL-6 levels among the groups ($X^2 = 98.304$, $P < 0.001$). The data showed a clear gradient pattern. Group A, with phenotype A, had the highest IL-6 level at 12.6 ± 2.2 pg/mL, followed by a gradual decrease: group B with phenotype B had an IL-6 level of 11.1 ± 2.0 pg/mL, group C with phenotype C had 9.6 ± 1.5 pg/mL, and group D with phenotype D had 8.2 ± 1.9 pg/mL. The control group had the lowest IL-6 level at 6.5 ± 1.4 pg/mL. Similarly, there were highly significant statistical differences in TNF-α levels among the groups ($X^2 = 63.612$, $P < 0.001$). Group A, with phenotype A, exhibited significantly higher TNF-α levels than the other groups (14.7 ± 4.1 pg/mL). As the groups progressed from A to D, TNF-α levels gradually decreased (group B: 13.9 ± 2.4 pg/mL; group C: 10.9 ± 2.0 pg/mL; group D: 9.5 ± 2.4 pg/mL). The control group had the lowest level (7.3 ± 1.8 pg/mL). Significant statistical differences were also observed in CRP levels among the groups ($X^2 = 32.424$, $P < 0.001$). Group A, with phenotype A, had the highest CRP level (3.5 ± 1.1 mg/L), which was significantly higher than that of the control group (1.9 ± 0.6 mg/L). Although group D, with phenotype D (2.5 ± 0.7 mg/L), was higher than the control group, it was markedly lower than groups A, B, and C (group B: 3.2 ± 0.8 mg/L; group C: 3.0 ± 0.8 mg/L).

V. Multivariate Logistic Regression Analysis of Pregnancy Rates in PCOS Patients

A logistic regression analysis was conducted with pregnancy rate as the dependent variable and group, age, BMI, AMH, duration of infertility, serum levels of IL-6, TNF-α, and CRP as independent variables. The results showed that serum CRP level was a risk factor for pregnancy rate ($P = 0.002$, OR = 0.672, 95% CI: 0.521–0.866). Group, age, BMI, AMH, duration of infertility, serum IL-6, and TNF-α were not significant predictors. See Table 5 for details.

Table 5 Multivariate logistic regression analysis of pregnancy rates in PCOS patients

Independent variable	Coefficient	Std.Error	Wald	P	OR	95%CI for OR
CRP	-0.397	0.130	9.398	0.002	0.672	[0.521,0.866]

VI. Multivariate Logistic Regression Analysis of Live Birth Rate in PCOS Patients

After adjusting for relevant confounding factors, group assignment was an independent predictor of live birth rate. Using group 5 (the control group) as the reference: patients in group 1 had a significantly lower live birth rate than those in the control group ($P=0.011$, OR=0.401, 95% CI: 0.198–0.811). There were no statistically significant differences in live birth rates between groups 2, 3, and 4 and the control group ($P>0.05$). See Table 6 for details.

Table 6 Multivariate Logistic Regression Analysis of Live Birth Rate in PCOS Patients

Independent variable	Coefficient	Std.Error	Wald	P	OR	95%CI for OR
Groups						
phenotype A	-0.914	0.360	6.461	0.011	0.401	[0.198,0.811]
phenotype B	-1.076	0.592	3.302	0.069	0.341	[0.107,1.088]
phenotype C	-0.288	0.492	0.343	0.558	0.750	[0.286,1.965]
phenotype D	-0.024	0.356	0.004	0.947	0.977	[0.486,1.961]
control group			10.624	0.031	Ref	

DISCUSSION

Polycystic ovary syndrome (PCOS) is the most common endocrine and metabolic disorder among women of reproductive age, significantly impacting reproductive health, metabolic function, and mental well-being. On May 12, 2026, The Lancet published a joint consensus statement from 56 global institutions [9], officially renaming the condition—previously known for over 90 years as "polycystic ovary syndrome (PCOS)"-to "polymetabolic ovary syndrome (PMOS)." This move completely overturns the earlier notion of PCOS as a localized ovarian disorder, clearly establishing that it is a systemic, multi-endocrine disorder affecting four major systems: metabolism, reproduction, psychology, and skin. A three-year transition period has been set, during which the new nomenclature and associated diagnostic and therapeutic protocols will be fully implemented by 2028. This article continues to use the term PCOS.

Our findings once again confirm that PCOS is not a single, homogeneous disease entity but rather a clinically heterogeneous syndrome. The data show that different phenotypes exhibit significant differences in baseline metabolic and endocrine characteristics. In particular, phenotype B (hyperandrogenism + ovulatory dysfunction) displays a distinctive “high-androgen, low-reserve” profile: it has the highest BMI and testosterone levels, yet its AMH and AFC levels are significantly lower than those of other PCOS phenotypes. This finding contrasts with the traditional notion that “PCOS is characterized by high ovarian reserve,” suggesting that phenotype B may represent a more severe subtype with profound metabolic and reproductive dysfunction. In 2025, the team led by Cao Yunxia published a study in Nature Genetics that, through cross-ancestry GWAS analysis, revealed the genetic heterogeneity of PCOS along both metabolic and reproductive axes, and highlighted that the Han Chinese population tends to be more predisposed toward the metabolic-driven subtype [10]. A study by foreign scholar Tsuyoshi Baba [11] also found that the classic subtypes A and B of PCOS carry the highest metabolic risks, with markedly increased rates of insulin resistance, elevated triglycerides, and higher BMIs. These findings further support our own observations. In our study, phenotypes A and B, which exhibit more severe metabolic disturbances, showed significantly lower clinical pregnancy rates (43.8% vs 29.4%) and live birth rates (32.9% vs 29.4%) compared to phenotype D, which has relatively milder metabolic features (63.2% vs 54.4%). This aligns with the aforementioned studies on polycystic ovary syndrome (PCOS) consistently conclude that reproductive outcomes are poorer in metabolically driven PCOS. Furthermore, a meta-analysis by Chen HX et al. also found that the PCOS subgroup with metabolic disturbances had worse reproductive outcomes [12].

The core finding of this study is that personalized ovarian stimulation protocols tailored to different phenotypes can significantly improve ART outcomes. Compared with the control group receiving the standard protocol, the personalized treatment group demonstrated advantages in several key indicators. Phenotype D showed the best performance: this group adopted a mild stimulation protocol combining letrozole with low-dose Gn, ultimately achieving clinical pregnancy rates (63.2%) and live birth rates (54.4%) that were comparable to those of the control

group, while keeping the incidence of OHSS at the lowest level (2.9%). This indicates that for patients primarily characterized by ovulatory dysfunction without significant hyperandrogenism, the mild stimulation protocol can ensure efficacy while maximizing safety. Phenotype B faced significant challenges: despite pre-treatment, the pregnancy outcomes in phenotype B were the worst among all groups. This indicates that for this special phenotype characterized by high androgen levels and low ovarian reserve-current pre-treatment and stimulation strategies may still be insufficient to fully correct the underlying pathophysiological defects, presenting a critical challenge for future clinical practice. Although phenotype A had the highest risk of OHSS (16.4%), by adopting a low-dose initiation regimen within the antagonist protocol, its live birth rate (32.9%) remained significantly higher than the standard treatment data for undifferentiated cases [13]. This highlights that personalized protocols can achieve optimal benefits under controllable risk conditions in high-risk populations. Our study provides robust evidence-based support to fill this important gap. The renaming of PCOS emphasizes its nature as a systemic metabolic disease. [11]. In this study, phenotypes A and B, which exhibited the most pronounced metabolic issues, also showed the poorest reproductive outcomes, thus validating the core concept of “metabolic-reproductive co-management” inherent in the PMOS framework.

Another important finding of this study is that inflammatory cytokine levels differ significantly among PCOS patients with different phenotypes and are closely associated with pregnancy outcomes. The levels of IL-6, TNF- α , and CRP in phenotypes A and B were significantly higher than those in phenotype C, phenotype D, and the control group, indicating a state of “high inflammatory burden.” Multivariate regression analysis further confirmed that CRP is an independent risk factor for clinical pregnancy rates. This finding provides a new mechanistic perspective for understanding the differences in pregnancy outcomes among various phenotypes. It has been established that the chronic low-grade inflammatory state in PCOS patients can affect oocyte quality, embryonic developmental potential, and endometrial receptivity [5]. Our data show that phenotypes A and B, characterized by high inflammatory levels, exhibit poorer embryo quality (including MII oocyte rate and number of fertilized eggs) and worse pregnancy outcomes. A study by foreign researchers concluded that the follicular microenvironment of women with polycystic ovary syndrome exhibits elevated TNF- α levels and reduced IL-12 levels, suggesting an overactive inflammatory response [14]. Such an imbalance may impair follicular function and adversely affect reproductive outcomes.

The core pathophysiological mechanism underlying adverse reproductive outcomes in PCOS patients lies in a chronic, low-grade inflammatory state that permeates the entire “oocyte-embryo-endometrium” chain [15]. At the oocyte and embryo levels, chronic inflammation directly impairs oocyte quality by disrupting the follicular microenvironment. In the follicular fluid of PCOS patients, levels of pro-inflammatory cytokines-such as TNF- α and IL-6-produced locally by adipose tissue and the ovary are significantly elevated [16]. TNF- α levels show a significant negative correlation with the rates of high-quality embryos and blastocyst formation. Meanwhile, IL-6 inhibits granulosa cell estrogen synthesis, thereby interfering with normal follicular development and maturation. Moreover, inflammatory factors activate the NF- κ B and cGAS-STING signaling pathways within granulosa cells, inducing mitochondrial dysfunction and oxidative stress, which in turn impair glycolysis and lead to insufficient ATP production, directly compromising the fidelity of chromosome segregation and the developmental potential of oocytes [17]. Furthermore, inflammation reprograms lipid and amino acid metabolism in follicular fluid, weakening the oocyte’s antioxidant defense capacity. At the endometrial level, inflammation triggers an immune imbalance between Th1 and Th2 cells and induces progesterone resistance, disrupting the immune tolerance and receptivity window at the maternal-fetal interface. Elevated systemic inflammatory markers, such as CRP, have been shown to be directly associated with reduced embryo implantation rates and lower clinical pregnancy rates, making them an independent risk factor for predicting adverse outcomes in assisted reproductive technologies [18]. Finally, underlying this cascade of damage is a self-perpetuating “metabolic-inflammation” vicious cycle. Inflammatory factors (such as TNF- α) can interfere with post-insulin receptor signaling pathways, Impaired insulin signaling exacerbates insulin resistance; in turn, hyperinsulinemia and lipotoxicity promote

the release of inflammatory cytokines [19]. Recent studies have further introduced the concept of the “gut-fat-ovary axis” [20], Linking gut microbiota dysbiosis, adipose tissue inflammation, and ovarian dysfunction, thereby elucidating how metabolic disturbances, chronic inflammation, and reproductive disorders in PCOS mutually reinforce each other. Research indicates that using metformin or GLP-1 receptor agonists to improve insulin resistance, or supplementing with inositol and antioxidants to block oxidative stress pathways, can effectively reduce both local and systemic inflammatory levels, thus improving oocyte quality and the endometrial environment [20][21]. In summary, chronic low-grade inflammation in PCOS serves as a critical hub connecting metabolic disturbances and reproductive disorders; targeting anti-inflammation and metabolic modulation has emerged as an evidence-based medical strategy for improving fertility outcomes in these patients.

This study has several limitations. First, as a single-center study, the sample size is relatively limited, which may affect the generalizability of the results. Second, there is a lack of long-term follow-up data on offspring. Future studies will need larger, multicenter cohorts to validate our findings and to explore in greater depth the molecular mechanisms underlying different personalized treatment regimens. Furthermore, being a retrospective study, it may be subject to selection bias and difficulties in fully controlling for confounding factors.

In summary, phenotype-based classification according to the Rotterdam criteria serves as an effective tool for guiding personalized ART treatment in PCOS patients. Our study demonstrates that tailoring ovulation-induction protocols specifically to different phenotypes can significantly optimize clinical outcomes, increasing live birth rates while reducing the risk of OHSS. Levels of inflammatory cytokines may serve as potential biomarkers for predicting treatment response. These findings provide important reference for promoting precision medicine for PCOS and even facilitating the transformation of clinical practice to usher in the new era of PMOS.

Declarations

Ethical Approval: This study was approved by the Ethics Committee of Chengde Central Hospital (Approval No. 2025-454). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent: Informed consent was obtained from all individual participants included in the study.

Competing Interests: The authors declare no competing interests.

Funding: Self-funded Research Project of Chengde Science and Technology Bureau (202503A008)

Data Availability: The datasets generated and/or analyzed during the current study are not publicly available due to the privacy and ethical restrictions regarding patient data but are available from the corresponding author on reasonable request.

Author Contribution

Li Yanyi wrote the main manuscript text, performed the experiments and analyzed the data. Wang Zhuo contributed to the interpretation of the results and critically. Si Fan revised the manuscript. All authors discussed the results and approved the final version.

References

1. Joham AE, Piltonen T, Lujan ME, Kiconco S, Tay CT. Challenges in diagnosis and understanding of the natural history of polycystic ovary syndrome. *Clin Endocrinol (Oxf)*. 2022;97:165–173. doi:10.1111/cen.14757
2. Junaid Yousaf, Syeda Khadija, Nosheen Arshad, Muhammad Rohail Amjad, Javeria Gulzar, Asad Ullah. The Odds of Infertility in a Patient Presenting with PCOS at Childbearing Age. *Saudi J Med*, 2022;7(1): 15-21.
3. Rotterdam EA-SPcwg. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). *Hum Reprod*. 2004;19(1): 41-47.
4. Matthew Dap as, Andrea Dunaif, Deconstructing a Syndrome: Genomic Insights into PCOS Causal Mechanisms and Classification. *Endocrine Reviews*. 2022;43(6): 927–965, <https://doi.org/10.1210/endrev/bnac001>
5. Dhillon Pai R, Pai A. O-059 ART in PCOS. *Hum Reprod*. 2024;39(Suppl1):deae108.061.
6. Kotly AR, Seifer DB. Women with PCOS undergoing IVF: a comprehensive review of therapeutic strategies for successful outcomes. *Reprod Biol Endocrinol*. 2023;21:70.
7. Singh R, Kaur S, Singh N. Gonadotropins as pharmacological agents in assisted reproductive technology and polycystic ovary syndrome. *Trends Endocrinol Metab*. 2023;34(4):194-215.
8. Liu X, Zhang J, Wang S. Global, regional, and national burden of infertility attributable to PCOS, 1990–2019. *Hum Reprod*. 2024;39(1):108-118.
9. Teede HJ, Bahri Khomami M, Norman RJ, et al. Polyendocrine metabolic ovarian syndrome, the new name for polycystic ovary syndrome: a multistep global consensus process. *Lancet*. 2026;407(10512):2329-2339.
10. Zhao H, Xu Y, Xue B, et al. Multi-ancestry genome-wide association analyses of polycystic ovary syndrome. *Nat Genet*. 2025;57(11):2669-2681.
11. Baba T. Polycystic ovary syndrome: Criteria, phenotypes, race and ethnicity. *Reprod Med Biol*. 2025;24:e12630.
12. Chen HX, Zeng RJ, Zeng X, Qin L. Cluster analysis reveals a homogeneous subgroup of PCOS women with metabolic disturbance associated with adverse reproductive outcomes. *Chin Med J*. 2024;137:604-612.
13. Sun B, Ma Y, Li L, Hu L, Wang F, Zhang Y, et al. Factors associated with ovarian hyperstimulation syndrome (OHSS) severity in women with polycystic ovary syndrome undergoing IVF/ICSI. *Front Endocrinol (Lausanne)*. 2021;11:615957.
14. Kareem HK, Alizzi F. Comparative study of follicular fluid inflammatory cytokines and post-IVF pregnancy outcomes in women with polycystic ovary syndrome (PCOS). *J Obstet Gynecol Cancer Res*. Jan 25, 2026 [Epub ahead of print].
15. Sneha S, et al. The role of inflammatory pathways in PCOS-related infertility and pregnancy complications. *Eur J Cardiovasc Med*. 2024;14(6):679-684.
16. SHANG J, WANG S, WANG A, et al. Intra-ovarian inflammatory states and their associations with embryo quality in normal-BMI PCOS patients undergoing IVF treatment[J]. *Reproductive Biology and Endocrinology*, 2024, 22(1): 11.
17. Fragouli E, et al. The transcriptome of follicular fluid and cumulus cells: a window into the oocyte. *Reprod Biomed Online*. 2017;34(1):1-10.
18. ZHANG H, LI X, ZHANG F, et al. Serum C-reactive protein levels are associated with clinical pregnancy rate after in vitro fertilization among normal-weight women[J]. *Frontiers in Endocrinology*, 2023, 14: 934766.
19. Koleva-Tyutyundzhieva D, Ilieva-Gerova M, Deneva T, Orbetzova M. Metabolic and inflammatory adipokine profiles in PCOS: A focus on adiposity, insulin resistance, and atherogenic risk. *Int J Mol Sci*. 2025;26(19):9702.
20. Deng H, Chen Y, Xin g J, Zhan g N, Xu L. Systemic low-grade chronic inflammation and intrinsic mechanisms in polycystic ovary syndrome. *Front Immunol*. 2024;15:1470283.

21. Chinese Medical Association, Committee of Reproductive Medicine. Polycystic Ovary Syndrome and Gut Microbiota: Guidelines for Basic Research and Clinical Translation Practice (2026 Edition) [J]. Chinese Journal of Reproductive and Contraceptive Medicine, 2026, 46(7): 712–DOI: 10.3760/cma.j.cn101441-20260305-00094