Original Article

Comparing Assisted Reproductive Outcomes in Women with Different Polycystic Ovary Syndrome Phenotypes Undergoing Frozen Embryo Transfer

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Abstract

Background: Patients with polycystic ovarian syndrome (PCOS) have unique characteristics depending on its phenotype. Therefore, prediction of controlled ovarian stimulation (COS) response and assisted reproductive technique (ART) outcome in these becomes challenging. **Aims:** To assess the outcomes of assisted reproductive technology (ART) in various polycystic ovary syndrome (PCOS) phenotypes and to evaluate the predictive value of anti-Mullerian hormone (AMH) and total testosterone on ART success. Clinical pregnancy rate (CPR) was measured as the primary outcome. **Settings and Design:** This was a prospective observational study conducted at a tertiary care centre. **Materials and Methods:** A total of 190 infertile women with PCOS (Rotterdam criteria) were enrolled and were subdivided into four phenotypes. Baseline screening and transvaginal scan were done. All patients underwent COS using antagonist protocol with recombinant follicle-stimulating hormone, and an agonist trigger was given for follicular maturation. One or two blastocysts were transferred in a frozen–thawed embryo transfer cycle. Luteal phase support was given with vaginal progesterone. **Statistical Analysis Used:** For quantitative variables, we employed the Kruskal-Wallis Test with post hoc Tukey's analysis. For continuous or ordinal variables, the Mann-Whitney U test was utilized. The analysis of categorical data was conducted using the Chi-square (χ^2) test with SPSS 21 software. **Results:** Phenotype A was the most prevalent (37%). CPR was the highest in phenotype D (57.7%), followed by phenotype C (53.06%), A (43%) and B (36%). The mean serum AMH level was the highest in phenotype A (9.7 ± 4.3 ng/dL) and the lowest in phenotype B (5.9 ± 1.8 ng/dL). The mean total testosterone level was 103 ± 15.68 ng/mL in Type A, 109.46 ± 37.08 ng/mL in Type B and 48.52 ± 17.07 ng/ml in Type D. **Conclusion:** Phenotype D showed higher CPR and lower miscarriage rate compared to other phenotypes (not significant) and was associated with good clinical outcome. No correlation could be established with serum AMH, total testosterone levels and CPR.

Keywords: *Anti-Mullerian hormone, hyperandrogenism, polycystic ovarian syndrome, polycystic ovarian syndrome phenotype*

Introduction

Polycystic ovarian syndrome (PCOS) is a highly prevalent endocrinopathy, affecting women's health in multiple aspects. The prevalence of PCOS ranges between

Received: 24-10-2023 **Revised:** 06-12-2023
Accepted: 11-12-2023 **Published:** 29-12-2023

Access this article online

Quick Response Code:

Website: www.jhrsonline.org

DOI: 10.4103/jhrs.jhrs_145_23

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How to cite this article: Patel A, Saraf A, Rao VA, Rao KA. Comparing assisted reproductive outcomes in women with different polycystic ovary syndrome phenotypes undergoing frozen embryo transfer. J Hum Reprod Sci 2023;16:340-5.

4% and 20% worldwide depending on the population where it is studied and the criteria used to define it.[1,2] Around 70%–80% of women having PCOS present with infertility as their primary complaint.[3] There are several internal (genetic influence, insulin resistance and ovarian/adrenal steroidogenesis) and external factors (lifestyle and environment) affecting its phenotypic expression.[4,5] The pathogenesis of PCOS is still not fully understood. Anti-Mullerian hormone (AMH) levels, insulin resistance and high body mass index (BMI) play a major role in the pathogenesis of PCOS.[6-9] Theories say that hyperandrogenism (HA) and high testosterone level are some of the factors affecting phenotypic expression of PCOS. Prenatal exposure of female foetus *in utero* to testosterone is a cause for adult onset of PCOS disease by epigenetic phenomenon.[10,11]

Hyper-response to gonadotropins is associated with adverse fertility outcomes.[12,13] Prediction of pregnancy and assisted reproductive technique (ART) outcome is challenging in different phenotypes of PCOS.

We undertook the present study to elucidate the effects of different phenotypes on ART outcome and to evaluate the predictive value of AMH and total testosterone levels on ART outcome.

Clinical pregnancy rate (CPR) is defined as the presence of the intrauterine gestation sac with foetal cardiac activity on ultrasound. The dose of gonadotrophin required, maturity rate of oocytes, fertilisation rate, availability of good-quality embryos on day 3 and blastocysts and miscarriage rate were evaluated as secondary outcomes.

Materials and Methods

It was a prospective observational study done at a tertiary care centre between January 2020 and December 2021. The study followed the principles of the Helsinki Declaration (2013) and was approved by the Institutional Ethics Committee with approval number 083/I/21/07. All participants provided written informed consent.

Inclusion criteria

All PCOS patients, who were diagnosed as per the ESHRE/ASRM Rotterdam criteria (2003), demonstrated two of the three criteria of oligo or anovulation (AO), clinical or biochemical HA and polycystic ovarian morphology (Rotterdam criteria).[14,15]

All PCOS patients of age between 20 and 38 years undergoing conventional controlled ovarian stimulation (COS) using antagonist protocol were included.

Exclusion criteria

- Age > 38 years
- Patients with male factor infertility
- Mild stimulation protocols
- Those who received recombinant human chorionic gonadotropin (HCG) alone or dual trigger for final maturation of oocytes
- Patients with unilateral oophorectomy, severe endometriosis, hydrosalpinx and uterine factors – uterine anomalies, fibroids and adenomyosis were excluded from this study.

PCOS patients were categorised into four phenotype groups:

1. Phenotype A: the coexistence of HA, chronic AO and polycystic ovaries (HA + AO + PCO)
2. Phenotype B: chronic AO and HA without the PCO (AO + HA)
3. Phenotype C: HA and polycystic ovarian morphology (HA + PCO)
4. Phenotype D: polycystic ovarian morphology with anovulatory cycles (AO + PCO).

A routine gynaecological examination and a basic transvaginal ultrasound were performed on cycle days 2–5, and BMI was calculated. The transvaginal ultrasound (TVS) of the subjects was done by a single investigator (senior most) once it was decided that the patient would be enrolled for the study.

Baseline hormone profile, serum levels of follicle-stimulating hormone (FSH), luteinising hormone (LH), prolactin, thyroid-stimulating hormone (TSH), total testosterone and AMH were measured. In all women, COS was started with recombinant FSH on day 2/3 of the cycle. As per the patient's age, antral follicle count (AFC), BMI and previous ovarian response, the initial dose of gonadotropin was individualised. Thereafter, on the basis of ovarian response and serum E2 levels, the dose of recombinant FSH was adjusted. A flexible multiple dose protocol was followed, wherein GnRH antagonist (injection cetrorelix 0.25 mg/day, Merck Serono, Germany) subcutaneous was started when the size of the leading follicle was >13–14 mm and/or serum E2 concentration was >300 pg/mL. Antagonists and gonadotropins were continued till the day of ovulation trigger. On the day of the trigger, serum E2, LH and P4 concentrations were measured. When three leading follicles achieved 17 mm diameter, final oocyte maturation was triggered with GnRH agonist (injection decapeptyl 0.2 mg, Ferring, Germany) subcutaneously. Oocyte retrieval was performed 35 h post-trigger under transvaginal ultrasound guidance. Intracytoplasmic sperm injection (ICSI) was performed in all instances in adherence to the hospital's protocol for every patient undergoing *in vitro* fertilisation (IVF) procedures at the facility. Fertilisation was assessed 18 h after ICSI by the appearance of two pronuclei. Grading

of embryos was done as per the Istanbul Consensus.[16] Embryo culture was done in single-step culture media VitroMed-OneStep (V-ONESTEP). All embryos were electively frozen on day 5.

For frozen embryo transfer (FET), estradiol valerate tablets 2 mg thrice a day were commenced in the early follicular phase. Monitoring of endometrial thickness was done with transvaginal ultrasonography (USG) on day 9 of the cycle, and subsequent follow-up visits were planned according to the patient's response. When the endometrial lining reaches >8 mm with a triple line pattern and zone 3–4 vascularity, vaginal progesterone 400 mg twice daily was started for 5 days. One or two 'day 5 embryo' (blastocyst) was transferred in a frozen–thawed embryo transfer (ET) cycle as per patient consent. Luteal phase support was given with vaginal progesterone 400 mg twice daily along with estradiol valerate 2 mg twice daily. Serum beta HCG was done after 14 days of the ET procedure. Patients were followed up, and pregnancy outcomes were noted.

Sample size calculation

A convenient sampling method was used, incorporating all eligible PCOS patients meeting the inclusion criteria and TVS conducted by the most senior clinician between January 2020 and December 2021.

Statistical analysis

Data were described in terms of range, mean ± standard deviation, median, frequencies (number of cases) and relative frequencies (percentages) as appropriate. Comparison of quantitative variables between the study groups was done using the Kruskal–Wallis test with *post-hoc* Tukey's. The Mann–Whitney *U* test was used for the comparison of continuous or ordinal variables. To compare categorical data, we utilized the Chi-square (χ^2) test, employing the exact test when the expected frequency was below 5. Spearman's rho correlation was employed for assessing relationships. P <0.05 was considered statistically significant. All statistical calculations were done using the (Statistical Package for the Social Sciences) SPSS 21 version (SPSS Inc., Chicago, IL, USA) statistical program for Microsoft Windows.

Immunoassay of hormones

The serum AMH concentration was measured using an automated electro-chemiluminescent immunoassay system with sensitivity: 0.01 ng/mL and linearity: 0.01–23 ng/mL (Elecsys AMH kit, Roche). Serum concentrations of FSH, LH, estradiol, progesterone, TSH, prolactin and total serum testosterone were assayed using an automated electro-chemiluminescent immunoassay system (e411 Roche Cobas).

Results

Baseline characteristics

The maximum number of patients in our cohort belonged to phenotype A (71 cases, 37%), followed by phenotype C (49 cases, 26%). Phenotype D was found in 45 (24%) cases and phenotype B in 25 (13%) cases.

Table 1 displays there was no significant difference in terms of age, basal FSH, basal LH levels, TSH, prolactin level and duration of infertility among all groups.

The mean serum AMH level was the highest (9.7 ± 4.35 ng/mL) in the group of PCOS with type A phenotype, followed by 7.5 ± 2.3 ng/mL in phenotype D, 7.10 ± 2.67 ng/mL in phenotype C and 5.93 ± 1.85 ng/mL in type B.

When the study population was stratified according to BMI categories, 112 (58.9%) were found to be overweight or obese. More number of women were in the obese category (BMI >30 kg/m^2) in phenotype A (29.6%) and B (28%) in comparison to phenotype C (8.2%) and D (11.1%).

The mean total testosterone levels were high in Type A (103 ± 15.68) and Type B (109.46 ± 37.08) compared to Type D (48.52 ± 17.07), which was expected, as phenotype D belongs to the non-hyperandrogenic PCOS group.

AFC and ovarian volume were significantly different amongst all phenotype groups. Patients with phenotype B have the lowest mean AFC and ovarian volume compared to other groups. The mean AFC was the highest in group A, and it was comparable between phenotype C and phenotype D.

Controlled ovarian stimulation and embryo transfer cycle characteristics

The data provided in Table 2 emphasizes that there were no statistically significant differences in the duration of stimulation among PCOS phenotypes. However, the total dose of gonadotrophins required during stimulation was significantly lower in phenotype D than in the other phenotypes.

Serum level of E2 on the day of the trigger was significantly lower in phenotype B; however, it was not significantly different in phenotypes A, C and D. There was no significant difference in the LH level on the day of the trigger in all four phenotypes.

The number of oocytes retrieved, the number of mature (MII) oocyte and the total number of embryos (8-cell stage and blastocyst) were significantly lower in phenotype B (non-polycystic morphology in USG)

Table 1: The baseline clinical characteristics of participants in each group

Baseline characteristics	Phenotype A	Phenotype B	Phenotype C	Phenotype D	*P*
Age	29.15±3.3	29.24±2.1	28.76±3.3	28.47±3.5	0.6
Duration of infertility	6.24±2.9	5.96±2.5	5.80±3.0	5.27±1.4	0.2
BMI	28.57±4.9	27.82±3.3	24.94±3.4	25.79±4.0	<0.001
AMH	9.73±4.3	5.93±1.8	7.10±2.67	7.50±2.3	<0.001
TSH	4.72±11.8	3.97±2.7	3.20±1.7	2.96±1.5	0.53
Prolactin	15.39±7.1	17.39±8.3	26.99±18.8	21.43±15.8	0.27
Total testosterone	103.04±15.6	109.46±37.0	93.14±8.07	48.52±17.0	0.001
Basal FSH	5.05±1.56	5.03±1.48	5.13±1.62	5.33±1.6	0.8
Basal LH	10.46±5.4	10.22±3.8	9.73±5.3	9.08±3.7	0.57
AFC	19.08±5.5	7.34±1.11	16.73±4.42	17.52±4.43	<0.001
Ovarian volume	15.43±4.85	6.33±1.15	14.22±3.70	13.92±3.68	<0.001

Values in the table are mean±standard deviation. BMI=Body mass index, AMH=Anti-Mullerian hormone, TSH=Thyroid-stimulating hormone, FSH=Follicular-stimulating hormone, LH=Luteinising hormone, AFC=Antral follicle count

Table 2: Characteristics of *in vitro* fertilisation cycles of participants in each group

	Mean±SD				*P*
	Phenotype A	Phenotype B	Phenotype C	Phenotype D	
Days of stimulation	9.75±1.18	9.52±1.08	9.47±0.98	9.62±1.39	0.61
Total dose of gonadotrophins	1836.26±519.3	1741.98±346.75	1672.9±407.25	1480.2±215.35	<0.001
E2 on the day of the trigger	4405.73±1988.4	2377.44±338.70	3992.0±1352.4	4081.2±1180.1	<0.001
LH on the day of the trigger	2.67±1.89	1.89±0.98	2.75±2.44	3.11±2.22	0.12
Progesterone on the day of the trigger	0.81±0.52	0.60±0.31	1.04±0.83	0.83±0.44	0.20
Number of pre-ovulatory follicles	20.83±3.86	13.04±2.46	20.35±3.73	21.04±3.54	<0.001
Oocytes retrieved	18.70±4.15	11.80±2.33	18.73±3.63	19.02±3.94	0.02
MII oocyte	14.83±3.50	9.44±2.57	14.61±3.23	14.76±3.45	0.01
Number of fertilised	13.49±3.37	8.12±2.68	13.06±3.34	13.51±3.08	0.01
Blast	3.90±1.77	2.36±1.15	3.16±1.65	3.76±2.20	0.03
8CG1	4.60±1.97	3.94±1.80	5.73±3.19	5.33±2.99	<0.001
Endometrial thickness	9.87±1.13	10.13±0.94	9.99±1.02	9.90±1.13	0.70

E2=Serum estradiol, LH=Luteinising hormone, SD=Standard deviation, MII=Mature (MII) oocyte

compared to other phenotypes, and in the rest of the groups, these were not significantly different.

However, there was no significant difference amongst all four phenotypes in relation to the number and quality of the transferred embryos and endometrial thickness on the ET day.

Pregnancy outcomes

CPR in phenotype D group was the highest with 57.7%, followed by 53.06% in phenotype C. CPR was 43.6% in phenotype A and the lowest in phenotype B with 36% of cases. However, this difference did not reach statistically significant levels in this study. The miscarriage rate in phenotype B and phenotype A was 16.1% and 14%, respectively, which is higher than phenotype C (10.2%) and phenotype D (8.9%). However, this difference is not statistically significant.

Discussion

The response of PCOS patients to ARTs varies due to their diverse clinical presentations and heterogeneity. In this study, phenotype A emerged as the most prevalent amongst PCOS patients, consistent with existing research.[17-19] However, one of the recent studies highlighted phenotype D as the most common, attributed to the exclusion of obese patients (BMI >30) from the cohort.[20]

The mean serum concentration of AMH was the highest in phenotype A and the lowest in phenotype B. Phenotype B belongs to non-polycystic morphology with a lesser number of antral follicles compared to phenotypes A, C and D (with polycystic morphology) aligning with similar findings from Sahmay *et al*., Gupta *et al*. and Ramezanali *et al*.[18,19,21]

We have found in this study that the mean BMI in phenotype A and phenotype B was significantly higher than in phenotypes C and D. Gupta *et al*. reported a significant difference in the mean BMI amongst the phenotypes, whereas Sahmay *et al*. did not find any significant difference in BMI amongst PCOS phenotypes.[17,19]

Phenotype B showed the highest mean serum total testosterone concentration, followed by phenotype A,

consistent with Ramezanali *et al*.'s results.[18] However, Sahmay *et al*. found no significant differences in total testosterone and DHEA-S levels amongst the four groups.[17] This is apparent as they did not find any significant difference in BMI as well. Nayar *et al*. found higher testosterone levels in phenotype C compared to other phenotypes, possibly linked to the exclusion of obese PCOS cases, where higher BMI is often associated with increased insulin resistance and HA.[20,22-24]

While the duration of stimulation remained comparable across groups, variations in the total dose of gonadotropins required for stimulation were significantly different amongst all phenotypes. Phenotype D required the lowest dose due to its PCO morphology without HA, which is in coherence with findings from other authors.[19,25] Varying gonadotropin doses impact IVF cycle costs, crucial for patient counselling before stimulation.

Phenotypes A, C and D, displaying PCO morphology, yielded more oocytes leading to increased blastocysts compared to Phenotype B. Phenotype D showed the highest CPR and the lowest miscarriage rate, followed by phenotype C. HA in phenotypes D and C is milder than in A and B, potentially explaining higher CPR. However, no significant difference was observed in the CPR amongst the groups depicting that phenotype may not have say in the pregnancy outcome. Eftekhar *et al*. found no significant differences in ART outcomes amongst PCOS phenotypes during frozen–thawed ET cycles, which is similar to the findings in this study. They suggested that phenotype D might be a significant prognosticator, although it did not reach statistical significance in their study too.[26] De Vos *et al*. observed a notably lower cumulative live birth rate in hyperandrogenic PCOS compared to normoandrogenic PCOS in their retrospective cohort study.[27]

Ramezanali *et al*. found that the combination of chronic AO with HA in phenotypes A and B was linked to lower CPR.[18]

Some studies suggest androgen's positive association with ART outcomes by enhancing FSH receptor expression in developing granulosa cells. Conversely, other research indicates negative effects of higher androgen levels on folliculogenesis and embryo development. Chappell *et al*. reported altered embryo development in pre-implantation stages linked to hyperandrogenemia in PCOS.[13] Yang *et al*. highlighted testosterone's role in aromatase down-regulation and disrupted folliculogenesis in PCOS.[28] In studies by Wissing *et al*. and Chappell *et al*., it was observed that there is slower embryo cleavage kinetics in hyperandrogenic PCOS cases and potential mitochondrial dysfunction impacting fertilisation and embryo development, respectively.[29,30]

Literature presents conflicting views on androgen's impact on ART outcomes, with studies suggesting both favourable and adverse effects. This disparity may be explained by the threshold and ceiling effects of androgen (like LH), where optimal concentrations are essential for adequate steroidogenesis and follicular development while higher levels hinder it. This study lays a foundation for future research to identify the androgen range negatively impacting ART outcomes. The potential conversion of classical phenotypes into milder forms through lifestyle modifications could yield more favourable pregnancy outcomes post-treatment.

Limitations of the study

The study's limitation lies in its small sample size. Some of the procedures like ICSI in every case may be debatable, but it was done as per the hospital protocol.

Conclusion

This study revealed the influence of PCOS phenotype on ovarian stimulation cycles and their outcomes. In this study, phenotype D represents a milder form of PCOS requiring the lowest gonadotropin dosage and displaying the highest CPR and the lowest miscarriage rate amongst all phenotypes. Phenotype B (hyperandrogenic state) exhibited the lowest CPR and a higher miscarriage rate compared to others. However, there was no statistically significant difference in CPR across the groups. The miscarriage rate was also not significant across groups. Although this study revealed notable differences in AMH levels and serum testosterone amongst groups, no correlation was observed between these factors and the CPR. A well-designed controlled study, encompassing a larger sample size, is necessary to determine the specific serum androgen levels that may lead to adverse ART outcomes. Classifying and identifying PCOS phenotypes could assist clinicians in anticipating a woman's ovarian response in IVF cycles. This categorisation would aid in outcome prognosis, counselling and the administration of personalised treatments.

Author's contributions

AP - Concept and design, definition of intellectual content, manuscript writing; AS - Definition of intellectual content and manuscript writing; VAR - Concept and design, and definition of intellectual content; KAR - Concept and design. All authors have critically reviewed the manuscript.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Data availability

Data are available with the corresponding author on reasonable request.

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