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Research Article

Impact of various PCOS phenotypes on oocyte competence in an ART cycle

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Abstract

Introduction: PCOS is a common cause of female infertility. Although PCOS patients are characterized by producing an increased number of oocytes, they are often of poor quality, leading to lower fertilization, cleavage, and implantation and higher miscarriage rates.

Aims: The present study aims to identify the effect of various PCOS phenotypes on oocyte competence in an ART cycle.

Settings and design: A retrospective observational study.

Methods and material: The study group included 102 women with PCOS as a main cause of infertility. Data was collected over a period of one year (2017-18). These women were divided into four groups on basis of PCOS phenotypes (A-D) and the relevant clinical data and the ART outcome were noted. Statistical analysis was done using SPSS statistical package. Data presented as mean ± SD which was compared using the ANOVA test. A p - value < 0.05 was considered statistically significant.

Results: Out of 102 PCOS women, 23.52% women had phenotype A, 11.76% had phenotype B, and 45.09% and 19.60% had phenotype C & D respectively. Good quality embryos formed (p - value 0.01) were lower in Group B vs. other groups. However, clinical pregnancy rates were comparable in all groups.

Conclusion: The reproductive potential of women with PCOS varies with the oocyte health and it largely depends on PCOS phenotype. Women with PCOS phenotype B might have poor IVF/ICSI outcomes with regard to the number of oocytes retrieved and embryos formed. PCO morphology might carry an advantage with regards to the number of oocytes retrieved and better quality embryos. It seems that hyperandrogenism in combination with chronic anovulation is associated with poor oocyte competence and hence, a negative impact on embryo quality and clinical pregnancy rate. Further studies with a larger sample size are required to further support it.

Key messages: Oocyte competence in various PCOS phenotypes.

Introduction

PCOS is a complex endocrine disorder characterized by hyperandrogenism, the presence of typical ultrasound features of polycystic ovaries, and chronic anovulation [1,2].

The phenotypic expression of PCOS depends on several internal (e.g. genetic influence, ovarian/ adrenal steroidogenesis, and insulin resistance) and external (e.g. quality and quantity of diet, exercise, and lifestyle) factors. It can be categorized into four types ['A'- Hyperandrogenism (HA) with ovulatory dysfunction (OD) and polycystic ovarian morphology (PCOM) (Classic PCOS), 'B'- HA and OD (Classic PCOS), 'C'- HA and PCOM (ovulatory PCOS) and 'D'- OD and PCOM (non-hyperandrogenic PCOS)]. A and B phenotypes behave similarly, with 75% to 85% demonstrating insulin resistance (IR) and some form of metabolic dysfunction [3]. Ovulatory PCOS also has some degree of metabolic dysfunction but risks somewhat less than those with classic phenotypes.

The incidence and intensity of hyperandrogenism differ ethnically and geographically [4]. Hirusitism, acne, and androgenic alopecia are clinical manifestations of hyperandrogenism. The PCOS phenotypes and comorbidities associated with PCOS contribute to oocyte health. Each of the PCOS phenotypes has its own specifics when it comes to the treatment of impaired fertility.

The role of androgens in folliculogenesis is still unclear and there are conflicting results from studies dealing with this problem. Impaired oocyte maturation and embryonic developmental competence in PCOS women are linked with abnormal endocrine/paracrine factors, metabolic dysfunction, and alterations in the intrafollicular microenvironment during folliculogenesis and follicle maturation [5]. Our study has been conducted with an aim to see the effect of various PCOS phenotypes on oocyte competence and hence its effect on embryo quality and clinical pregnancy rates.

Materials and methods

This prospective observational study was conducted at our center. The ethics committee of the Indian fertility society approved the study protocol.

Inclusion criteria

All women under 40 years of age presenting with PCOS as one of the causes of infertility who underwent IVF/ ICSI with day 3 FSH < 12 IU/L and estradiol < 50 pg/ml with normal uterine cavity and prolactin and thyroid functions before stimulation with no current/ past diseases affecting the administration of gonadotropins were enrolled in the study group.

Exclusion criteria

Women presenting with infertility with age > 40 years, poor ovarian response (FSH > 12 IU/L)/ ovarian failure, and those with other causes of infertility including severe endometriosis, hydrosalpinx, uterine factor, severe male factor (oligo-tetra to-asthenozoospermia) or with endocrine disease or systemic illness were excluded from the study group.

According to the Rotterdam criteria, we accepted the presence of two of the three following characteristics for inclusion in the study: 1) oligo-ovulation/anovulation (cycle length > 35 days); 2) clinical findings of clinical (presence of hirsutism evaluated by a Ferriman-Gallwey score > 8, severe acne and alopecia) or biochemical hyperandrogenism; and 3) polycystic ovaries on trans-vaginal ultrasonography (PCOM was defined as the presence of 12 or more ovarian cysts with 2 - 10 mm diameter per ovary and/or ovarian volume ≥ 10 cm^3) [after excluding other aetiologies]. Only patients with mild/moderate male factor and/or tubal factor infertility were included.

Data was collected for a period of one year (May 2017-2018). Following clinical data were recorded: age, duration of infertility, type of infertility, cause of infertility, body mass index, PCOS phenotype [hyperandrogenism (any recorded history of hirsutism or acne and testosterone levels), antral follicle count and menstrual irregularity], and cycle number. Baseline pelvic ultrasound findings, basal serum estradiol (E2), follicle-stimulating hormone (FSH), luteinizing hormone (LH), and anti-mullerian hormone (AMH) levels on a menstrual day 2 or 3, peak serum E2 level and endometrial thickness on the day of trigger administration was recorded.

Based on the physician's discretion, one of the three protocols, antagonist protocol, stop protocol (antagonist was added once the dominant follicle or endometrial thickness >6mm was noted) or AACEP (agonist-antagonist conversion protocol with estrogen priming) protocol [Described by Sher for poor responders] was chosen for ovarian stimulation.

The total number of gonadotropin units used, the number of days of stimulation, trigger used [hCG (human choriogonadotropin) or GnRH agonist], no. of transferred embryos (Day 3/5 transfer, fresh/frozen embryo transfer), the numbers of retrieved oocytes, matured oocytes, fertilized embryos, quality of embryos formed (A being the best and C being the worst), freeze-all embryos cases, embryos transferred into the uterine cavity via transvaginal ultrasonography 3 - 5 days after oocyte retrieval and development of ovarian hyperstimulation syndrome was also noted. Pregnancy result 16 days after embryo transfer was noted through a test of the serum levels of the β-hCG and transvaginal ultrasonography in women with a positive pregnancy test to determine the location of the pregnancy.

Cycle outcomes like implantation (intrauterine gestational sacs divided by a number of transferred embryos) and clinical pregnancy rate (presence of gestational sac by transvaginal ultrasonography) were also recorded.

The study group was divided into four subgroups depending on the various PCOS phenotypes (A-D) described above. The outcome among the four sub-groups was compared in terms of the requirement of gonadotropins, oocyte competence, and clinical pregnancy rates.

All the data recorded was entered into the computer using Microsoft Excel. All analyses were performed using SPSS statistical package. Each variable was presented as the mean ± SD. The mean value of the four groups was compared using the ANOVA test. A $p < 0.05$ was considered statistically significant.

Results

In total 102 women were enrolled in the study. Table 1

Table 1: Study population baseline characteristics.

Women's age in years (Mean ± S.D)	31.48 ± 3.93
Duration of infertility in years (Mean ± S.D)	6.26 ± 3.007
Type of infertility -Primary -Secondary	 77.45% (n = 79) 22.54%(n = 23)
BMI (kg/m^2)	26.72 ± 3.82
Basal FSH (IU/l) (mean ± SD)	5.74 ± 1.75
Basal LH (IU/l) (mean ± SD)	6.95 ± 3.99
Basal Estradiol (pg/ml) (mean ± SD)	43.46 ± 22.808
Basal Progesterone (ng/ml) (mean ± SD)	0.486 ± 0.52
Peak Estradiol on day of trigger (pg/ml) (mean ± SD)	3565.92 ± 2697.86
Peak LH on day of trigger (IU/l) (mean ± SD)	1.07 ± 0.64
Peak progesterone on day of trigger (ng/ml) (mean ± SD)	1.61 ± 1.55
AMH (ng/ml) (mean ± SD)	7.04 ± 3.9

shows the study population characteristics in general. Table 2 shows that most of the women 73.52% of the women underwent controlled ovarian stimulation by antagonist protocol and decapeptidyl as a trigger in 68.62% of the women to prevent OHSS. Freeze all policy was used in 58.82% while fresh transfer in 41.17% of women. Table 3 demonstrates the IVF/ICSI outcomes among the various PCOS phenotypes. The number of gonadotropin ampules and the number of days required for stimulation were not significantly different among the four groups. It also shows the lesser number of oocyte retrieval in women (p - value > 0.05) and a lesser number of embryos formed with phenotype B (p - value < 0.05) versus other phenotypes. But it did not result in a lower clinical pregnancy rate.

Discussion

PCOS is a multifaceted and heterogeneous metabolic and endocrine disorder. The ovarian stimulation in these patients can be cumbersome because of a narrowed therapeutic dose-response window, and also clinical outcomes may vary due to divergent phenotype-dependent hormone profiles and variable progesterone resistance [5]. In the present study, we studied the IVF/ICSI outcome in PCOS women and further sub-divided the study group into four on the basis of PCOS phenotypes. PCOS is characterized by clustering of hyperandrogenism, hyperinsulinemia, hypersecretion of LH, metabolic dysfunction, and menstrual irregularity. PCOS spectrum is different among the four phenotypes (A-D). PCOS women are known to produce a higher number of oocytes versus women without PCOS but the quality has been shown to be poor leading to poor fertilization and clinical pregnancy rates due to abnormal endocrine factors and metabolic dysfunction operating at the follicular level [6]. So in our study, we aimed to study the impact of various PCOS phenotypes on oocyte competence and its impact on the clinical pregnancy outcome.

Table 2: Demonstrates the treatment and the ART outcome in the study group overall.

Protocol used - Antagonist protocol - Stop protocol - AACEP protocol	 - 60.78% (n = 62) - 20.59% (n = 21) - 18.63% (n = 19)
Trigger used - Ovitrelle - Decapeptidyl	 - 31.37%(n = 32) - 68.62% (n = 70)
IVF ICSI	60.78% (n = 62) 39.22% (n = 40)
Freeze all embryos (No fresh transfer) [58.82% (n = 60)]	Day 3 Day 5
Fresh Transfer [41.17% (n = 42)]	Day 3 = 20 cases (47.61%) Day 5 = 22 cases (52.38%)
OHSS	Mild- 7.84% (n = 8) Mod – 2.9% (n = 3) Severe- 0.98%(n = 1)
Fertilization rate	91.45% (535/585)
Clinical Pregnancy rate	61.76% (63/102)

In a study by De Vos M, et al. [5], after conventional ovarian stimulation using a gonadotrophin-releasing hormone antagonist protocol, the median number of oocytes retrieved ranged between 11 and 13.5 and did not differ significantly among the studied groups. Live birth rate (LBR) after fresh embryo transfer and CLBR after transfer of all fresh and vitrified embryos were significantly lower in women with hyperandrogenic PCOS phenotypes A (LBR 16.7%, CLBR 25.8%) and C (LBR 18.5%, CLBR 27.8%) compared with women with normoandrogenic PCOS phenotype D (LBR 33.7%, CLBR 48%) and controls with a polycystic ovarian morphology (LBR 37.1%, CLBR 53.3%). Multivariate regression analysis indicated that PCOS phenotype was an independent predictor for CLBR. The authors concluded that hyperandrogenic PCOS phenotypes confer significantly lower CLBR compared with their normoandrogenic counterparts.

In our study, the number of the oocytes retrieved was lower in women with phenotype B in comparison to other phenotypes, but it was not statistically significant. This could be explained by the negative effect of hyperandrogenism and the absence of PCO morphology in phenotype, which suggests better chances of stimulation in women with higher antral follicle count. Due to the limitation of the sample size and due to lack of comparability between the groups, the difference was not found to be significant. However, a larger sample size and better study design could have resulted in a statistically significant difference. The number of the embryos formed was also found to be significantly lower in phenotype B. Grade A embryos formed were lower in women with phenotype B, but it did not reach statistical significance which could be explained by the limited sample size. However, the poor outcome with regards to clinical pregnancy rates (CPR) was not found with phenotype B. CPR was found to be comparable in all the sub-groups.

Table 3: Demonstrates the ART outcome with respect to PCOS phenotypes.

IVF/ICSI outcomes	Phenotype A (n = 24) 23.52%	Phenotype B (n = 12) 11.76%	Phenotype C (n = 46) 45.09%	Phenotype D (n = 20) 19.60%	*P* - value
Gonadotropin dose	3120 ± 111.52	3567.85 ± 1242.87	3114.42 ± 730.99	3569.44 ± 1029.16	0.07
Days of stimulation	10.81 ± 1.88	11 ± 2.38	11.03 ± 1.75	10.88 ± 1.26	0.96
No. of oocytes retrieved	14.81 ± 8.81	9.14 ± 4.05	14.46 ± 6.24	13.11 ± 4.07	0.06
No. of MII oocytes retrieved	12 ± 6.89	7.57 ± 3.25	11.34 ± 5.99	9.88 ± 3.55	0.12
No. of embryos	11.90 ± 5.41	6.42 ± 1.51	10.5 ± 5.05	9.55 ± 3.77	0.01
Grade A embryos	7.36 ± 3.74	4.14 ± 1.95	5.57 ± 3.81	6.22 ± 3.59	0.07
Grade B embryos	3 ± 2.02	1.28 ± 1.60	2.38 ± 1.89	1.88 ± 1.69	0.05
Grade C embryos	1.54 ± 2.16	1.0 ± 1.0	2.42 ± 3.63	1.44 ± 1.87	0.30
Clinical pregnancy rate	16(66.67%)	8(66.67%)	26(56.52%)	12(60%)	0.83

Androgens have been suggested to have a modulating effect on FSH activity in developing granulosa cells, and studies on PCOS have shown that androgens have a positive and negative effect on folliculogenesis [7]. Despite the changing effects of androgens and PCO morphology among groups, the endpoint is similar in terms of biochemical, clinical, and ongoing pregnancy rates.

In a study conducted in Iran by Ramezanali, et al. [8], PCOS patients were categorized into four phenotype groups according to the Rotterdam criteria: (i) phenotype A (43.5%) (ii) phenotype B (26.6%) (iii) phenotype C (21.5%) and (iv) phenotype D (8.2%). This study evaluated 386 PCOS women. There were no statistically significant differences among PCOS phenotypes groups in terms of stimulation duration, the total number of retrieved and metaphase II (MII) oocytes, the number, and quality of the transferred embryos, and endometrial thickness on the embryo transfer day. Clinical pregnancy rate (CPR) in the phenotype D group (53.3%) was higher than in other groups (32.5%, 26.4%, and 36.8%, respectively, in phenotypes A, B, and C), but not to a significant level. This suggested that a combination of hyperandrogenism and chronic anovulation is associated with a negative impact on the CPR in these patients.

In a study by Kar [9] in the Indian population, Phenotype A is the most common phenotype encountered i.e. in 65.6% followed by phenotype D at 22.2%, phenotype B at 11.2%, and phenotype C at only 0.9%. Therefore, the prevalence and severity of the various PCOS phenotypes vary in our population depending on various factors this study was conducted at a private center that caters to populations belonging to higher socioeconomic status and so the outcome of IVF/ICSI needs to be evaluated. This explains the difference in the prevalence of PCOS phenotypes.

A recently published study on the effect of PCO morphology on oocyte quality in intracytoplasmic sperm injection cycles compared with a control group showed neither positive nor negative effects and the MII oocyte number was found to be higher in the group with PCO morphology, whereas the ratio of MII oocyte was similar, the number of top-quality embryos was comparable between groups but the implantation and clinical pregnancy rates were found significantly higher in the PCO morphology group [10].

The effect of basal testosterone levels in IVF cycles of patients without PCOS was evaluated in a study by Sun, et al. [11], the authors concluded that although basal testosterone did not predict pregnancy outcomes, it was associated with the large follicles on the day of trigger, FSH dosage, and also that lower levels of basal testosterone might be related with poor ovarian response [11]. The difference in the results could be explained by the study design and the small sample size of our study. PCOS women had different responses to stimulation in a wide range, and to the best of my knowledge, different phenotypes were not assessed separately.

Conclusion

Women with hyperandrogenemia in absence of PCO morphology have poor IVF/ICSI outcomes with regard to the number of oocytes retrieved and embryos formed. PCO morphology might carry an advantage with regards to the number of oocytes retrieved and better quality embryos. This implies the need for appropriate counseling and tailored approaches when treating PCOS women with hyperandrogenism who need ART. Further studies with a larger sample size are required to further support/refute the results.

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