

Prevalence of Polycystic Ovarian Syndrome, Phenotypes and their Ovulation Response to Sequential Letrozole Dose Escalation among Infertile Women at a Tertiary Care Centre in Southern India

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ABSTRACT

Background: Women with polycystic ovarian syndrome (PCOS) often have anovulatory infertility requiring ovulation induction with letrozole. **Aims:** This study aimed to determine the prevalence and phenotypic categorisation of infertile PCOS women and to assess ovulatory response and pregnancy rates of PCOS phenotypes with sequential letrozole dose escalation. **Study Setting and Design:** This was a prospective observational study. **Materials and Methods:** One hundred seventy-five infertile PCOS women were enrolled. One hundred fifty-six women received ovulation induction as per the protocol with sequential letrozole dose escalation in each subsequent cycle (2.5 mg, 5 mg and 7.5 mg). Responses were assessed by ovulation and/or pregnancy. **Statistical Analysis Used:** Descriptive statistics were elaborated by means, medians, frequencies and percentages. Group comparisons and linear correlation between two continuous variables were done using appropriate statistical tests. **Results:** Eighty-seven (49.7%) women were Phenotype A; 11 (6.3%) were Phenotype B; 20 (11.4%) were Phenotype C and 57 (32.6%) were Phenotype D in our study. After excluding the lost to follow up participants in each induction cycle, 33.3% (2.5 mg dose); 62.8% (5 mg dose) and 78.9% (7.5 mg dose) women responded to letrozole. A significant increase in ovulation to escalating letrozole doses was noted (Phenotype A: 35.1% to 2.5 mg, 53.7% to 5 mg and 72.7% to 7.5 mg; Phenotype B: 30% to 2.5 mg and 80% to 5 mg; Phenotype C: 35.3% to 2.5 mg and 87.5% to 5 mg and Phenotype D: 30.8% to 2.5 mg, 65.6% to 5 mg and 87.5% to 7.5 mg). Fifty-six of 156 (35.9%) infertile PCOS women achieved pregnancy; increase in pregnancy rates with escalated doses of letrozole was noted. **Conclusion:** All PCOS phenotypes show a similar response to escalating doses of letrozole. The role of phenotypic sub-categorisation for variable response to letrozole as an ovulation-inducing agent is uncertain.

KEYWORDS: Letrozole, infertility, polycystic ovary syndrome phenotypes, polycystic ovary syndrome

INTRODUCTION

Polycystic ovarian syndrome (PCOS), one of the most common endocrinopathies in women of reproductive age, is a significant public health issue with reproductive, metabolic and physiologic features. The results of epidemiological studies of PCOS largely

depend on how the study population and the PCOS phenotypes were defined. The worldwide prevalence of PCOS ranges from 4% to 21%, depending on

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the diagnostic criteria used.^[1] European Society for Human Reproduction and Embryology (ESHRE) and American Society for Reproductive Medicine (ASRM) issued guidelines for the diagnosis of PCOS (also known as Rotterdam 2003 criteria).^[2] PCOS is diagnosed if the patient demonstrates two of the following three criteria: (a) oligo or chronic anovulation, (b) clinical and/or biochemical signs of hyperandrogenism (HA) and (c) polycystic ovaries. It is necessary to exclude other causes of androgen excess and anovulatory infertility before diagnosing a patient with PCOS.^[2]

Women with PCOS often have anovulatory infertility and hence require ovulation induction. Several methods have been effective for ovulation induction and fertility treatment in women with PCOS. However, ovulation and pregnancy rates with aromatase inhibitors such as letrozole and anastrozole appear to be promising.^[3] Lately, various studies and guidelines recommend the use of letrozole as first-line therapy for all women with PCOS.^[4] Till date, no studies are available to assess the response to escalating doses of letrozole in different phenotypes among infertile PCOS women.

The present study was done to assess the prevalence of PCOS phenotypes among infertile PCOS women and their individual phenotypic response to ovulation induction with sequential letrozole dose escalation at a tertiary care hospital in Southern India.

The primary objective of the study was clinical, biochemical, hormonal and ultrasonographic evaluation of infertile women for PCOS diagnosis and phenotypic categorisation and to further assess the response of individual PCOS phenotype to ovulation induction with sequential letrozole dose escalation. The secondary objective of the study was clinical pregnancy.

MATERIALS AND METHODS

This prospective cohort study was carried out in the department of Obstetrics and Gynaecology, a tertiary care government hospital in Southern India catering to women from different ethnic groups and cultural diversity prevailing over the Indian subcontinent. The study was approved by the institutional ethics committee vide letter number 1911/12/IEC/PG Trg dated 02 Nov 2018, and carried out from November 2018 to April 2020. Ethical principles of World Medical Association Declaration of Helsinki (2013) were adhered to while conducting the study. The sample size was calculated for estimating a 95% confidence interval with a relative error of margin of 5%. The maximum sample size worked out to be 196 for a prevalence of 15% of PCOS in population, hence planned to study 200 patients. However, in view of the

unexpected COVID-19 pandemic, only 175 participants fulfilling the inclusion criteria could be enrolled in the current study. Informed written consent was obtained from all the participants.

A total of 175 infertile women having PCOS (Phenotypes A, B, C and D) with patent Fallopian tubes and normo-zoospermic male partners were included in the study. Infertile PCOS women with severe endometriosis, diminished ovarian reserve (AMH <1 ng/ml, FSH >12 IU/L), endocrine disorders, age >40 years and congenital or acquired uterine anomaly and those with abnormal male factor (oligo-astheno-terato-zoospermia) were excluded from the study.

All participants were diagnosed with PCOS using Rotterdam criteria.^[2] Menstrual cycle history was recorded to determine the extent of menstrual cycle disturbance and/or duration of infertility. Oligomenorrhea or chronic anovulation was diagnosed in patients having less than eight menstrual cycles per year, or frequent bleeding at an interval of less than 21 days, or bleeding at an interval of more than 35 days. A physical examination was done to assess height, weight, body mass index (BMI) and acne. Hirsutism, defined as an abnormal amount of sexual hair in a male pattern, was assessed on nine regions of the body using the modified Ferriman–Gallwey score of ≥ 8 .^[5] Clinical HA was diagnosed in patients who had acne or hirsutism or androgenic alopecia (male pattern baldness). Fasting blood tests were performed to assess the levels of blood glucose, free testosterone, prolactin, thyroid hormones, dehydroepiandrosterone sulfate (DHEAS) and 17-hydroxyprogesterone (17-OHP) to evaluate for causes of anovulation other than PCOS such as congenital adrenal hyperplasia and androgen-secreting tumours (only infertile women with normal values of DHEAS and 17-OHP were included in the study). Biochemical HA was diagnosed if serum androgen level was elevated (total testosterone >600 ng/l or free testosterone >12 ng/l). Polycystic ovarian morphology (PCOM) was established by transvaginal ultrasound transducers with a frequency bandwidth of 8 MHz if more than 20 follicles of 2–9 mm in diameter were present in at least one ovary (without a cyst or follicle), and/or ovarian volume of >10 ml (Para 1.4.4 of international evidence-based guideline for the assessment and management of PCOS 2018). All study participants also underwent hysterosalpingogram to confirm tubal patency and semen analysis of spouse to exclude male factor infertility.

The study participants were classified as per the National Institute of Health (NIH) consensus panel (2012)^[6] into PCOS phenotype classification: Phenotype A: HA (clinical or biochemical presence) + ovulatory dysfunction (OD) + PCOM; Phenotype B:

HA + OD; Phenotype C: HA + PCOM and Phenotype D: OD + PCOM.

A basal scan on day 2/3 of the cycle was performed to rule out the presence of ovarian cyst and to determine the endometrial thickness (ET). Ovulation induction was started only when there was no dominant follicle of size >10 mm and ET <5 mm. If the above criteria were met, ovulation induction was done as per the ovulation induction protocol with letrozole. A sequential escalation of letrozole dose was done in each subsequent cycle if there was no response to a particular dose and ovulatory response was assessed. The starting dose was 2.5 mg/day, cycle days 3 to 7, following a spontaneous menses or progestin-induced bleed. If ovulation did not occur, the dose was increased to 5 mg/day in the next cycle, cycle days 3 to 7, with a maximal dose of 7.5 mg/day (American College of Obstetrics and Gynecology [ACOG] 194, 2018) in the subsequent cycle. Transvaginal ultrasound examination was performed on day 10 of menses and followed up every other day according to the follicular size. The primary objective of effect on ovulation in different PCOS phenotypes was assessed with regular transvaginal ultrasonography. When the mean diameter of the leading follicle measured 18 mm, ovulation was triggered with injection of human chorionic gonadotropin (hCG) 5000 Units intramuscularly. Timed intercourse was advised 24–36 h after hCG injection. Two days after giving hCG, the participants were assessed for signs of ovulation (disappearance of the pre-ovulatory follicle, fluid in the cul-de-sac and/or corpus luteum formation). Pregnancy outcomes were assessed based on a positive pregnancy test (chemical pregnancy) and clinical pregnancy was diagnosed when a gestational sac was detected on transvaginal ultrasound examination at 6-week period of gestation or amenorrhea. Response assessment was done using sonographic evidence of ovulation as the primary endpoint and positive pregnancy test as secondary endpoint respectively.

Of the 175 infertile PCOS women recruited for the study, 19 were lost to follow up. After PCOS phenotypic categorisation, 156 women were given the first cycle of ovulation induction as per the protocol, and the data were further analysed.

Statistical analysis

Data were coded and recorded in the MS Excel spreadsheet program. SPSS version 23 (IBM Corporation, USA) was used for data analysis. Descriptive statistics included documentation of means/standard deviations and medians/interquartile range for continuous variables and frequencies and percentages for categorical variables. Data were presented in a graphical manner

wherever appropriate for data visualisation. Group comparisons for continuously distributed data were made using independent sample ‘t’-test when comparing two groups. If data were found to be non-normally distributed, appropriate non-parametric tests in the form of the Wilcoxon test were used. Chi-square test was used for group comparisons of categorical data. In case the expected frequency in the contingency tables was found to be <5 for >25% of the cells, Fisher’s exact test was used instead. Linear correlation between two continuous variables was explored using Pearson’s correlation (if the data were normally distributed) and Spearman’s correlation (for non-normally distributed data). Statistical significance was noted at *P* < 0.05.

RESULTS

A total of 175 infertile PCOS women participants were enrolled for the study as per the inclusion criteria. Nineteen infertile PCOS women were lost to follow up before ovulation induction protocol could be initiated, as in Figure 1. The remaining 156 participants were given ovulation induction with letrozole starting at 2.5 mg once daily for 5 days, with sequential dose escalation by 2.5 mg (maximum dose 7.5 mg) in each subsequent cycle if there was no response as in Figure 1.

Fifty-two (33.3%) of 156 women had an ovulatory response after the first cycle of letrozole 2.5 mg, while the remaining 104 (66.7%) did not respond. Amongst

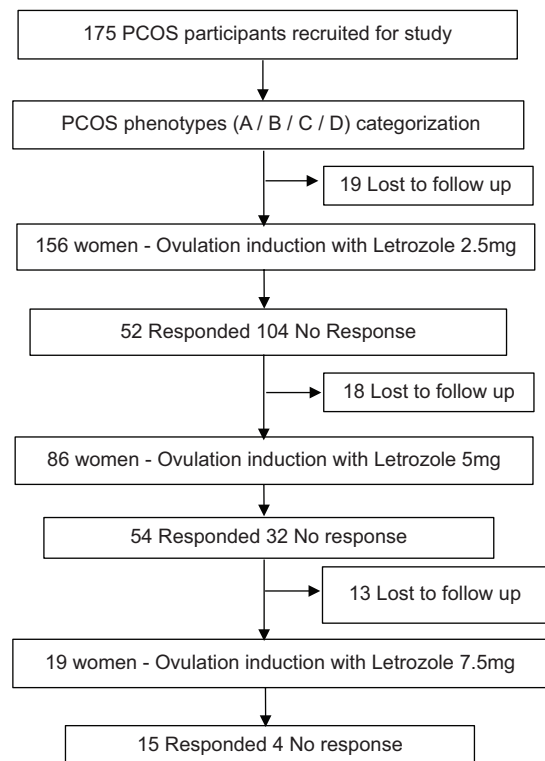


Figure 1: Flowchart of the study population and their outcome

the 104 participants who did not respond to 2.5 mg, 18 were lost to follow up. Therefore, only the remaining 86 participants underwent a second cycle of ovulation induction with an escalated dose of letrozole 5 mg. Fifty-four (62.8%) of 86 participants responded to 5 mg and 32 (37.2%) participants did not respond. Amongst 32 participants who did not respond to 5 mg letrozole, 13 were lost to follow up, leaving only 19 participants who underwent third cycle ovulation induction with an escalated dose of letrozole 7.5 mg. Fifteen (78.9%) participants responded and the remaining 4 (21.1%) did not respond.

The study response to ovulation induction with letrozole was further assessed with clinical pregnancy as the secondary endpoint. Fifty-six (35.9%) of 156 infertile PCOS women who received at least one cycle of letrozole achieved clinical pregnancy, whereas 100 (64.1%) women could not achieve the secondary objective of this study.

Demographic variables, baseline characteristics and distribution of the study participants in terms of letrozole dose at response are depicted in Table 1. The summary of association between individual PCOS phenotype and various parameters in our study and their statistical significance is depicted in Table 2.

Eighty-seven (49.7%) of 175 participants were diagnosed as PCOS Phenotype A, 11 (6.3%) of 175 as Phenotype B, 20 (11.4%) of 175 as Phenotype C and 57 (32.6%) of 175 as Phenotype D in our study. There was no significant difference noted between the various PCOS phenotypic groups in terms of distribution of letrozole dose at response amongst the total study participants ($\chi^2 = 8.622, P = 0.735$).

After excluding the lost to follow up participants in each induction cycle, the proportion of infertile women responding to escalating letrozole doses in each phenotype were calculated.

Phenotype A: Twenty-seven of 77 (35.1%) participants had ovulation response to the first cycle of induction with 2.5 mg letrozole, 22 of 41 (53.7%) participants had ovulation response to the second cycle of induction with 5 mg letrozole and 8 of 11 (72.7%) participants had ovulation response to the third cycle of induction with 7.5 mg letrozole dose.

Phenotype B: Three of 10 (30%) participants had ovulation response to the first cycle of induction with 2.5 mg letrozole, 4 of 5 (80%) participants had ovulation response to the second cycle of induction with 5 mg letrozole, whereas no participant required the third cycle with 7.5 mg dose.

Table 1: Demographic variables, baseline characteristics and distribution of the study participants in terms of letrozole dose at response

| Demographic variables (n=175) | Mean±SD |
|---|-------------------------------|
| Age (years) | 27.62±3.76 |
| Height (m) | 1.54±0.04 |
| Weight (kg) | 56.48±6.89 |
| BMI (kg/m ²) | 23.78±2.95 |
| Baseline characteristics (n=175) | Number of participants, n (%) |
| Obstetric history | |
| Primary infertility | 100 (57.1) |
| Secondary infertility | 75 (42.9) |
| Previous menstrual cycle | |
| Regular | 21 (12) |
| Irregular | 154 (88) |
| Hirsutism (present) | 99 (56.6) |
| Acne (present) | 67 (38.3) |
| Ovulatory dysfunction (present) | 154 (88) |
| Hyperandrogenism (clinical ± biochemical) (present) | 118 (67.4) |
| PCOM (present) | 163 (93.1) |
| PCOS phenotype | |
| A | 87 (49.7) |
| B | 11 (6.3) |
| C | 20 (11.4) |
| D | 57 (32.6) |
| Letrozole dose at response (n=175, all enrolled participants) | Number of participants, n (%) |
| 2.5 (mg) | 52 (29.7) |
| 5 (mg) | 54 (30.9) |
| 7.5 (mg) | 15 (8.6) |
| Not responded | 4 (2.3) |
| Lost to follow up | 50 (28.6) |
| Pregnancy (positive) | 56 (32.0) |

n=Number of study participants, BMI=Body mass index, SD=Standard deviation, PCOS=Polycystic ovarian syndrome, PCOM=Polycystic ovarian morphology

Phenotype C: Six of 17 (35.3%) participants had ovulation response to the first cycle of induction with 2.5 mg letrozole, 7 of 8 (87.5%) participants had ovulation response to the second cycle of induction with 5 mg letrozole, whereas no participant required the third cycle of 7.5 mg dose.

Phenotype D: Sixteen of 52 (30.8%) participants had ovulation response to the first cycle of induction with 2.5 mg letrozole, 21 of 32 (65.6%) participants had ovulation response to the second cycle of induction with 5 mg letrozole and 7 of 8 (87.5%) participants had ovulation response to the third cycle of induction with 7.5 mg letrozole dose.

There was a significant difference in ovulatory response noted with the individual phenotype on letrozole dose escalation, after excluding the lost to follow up

participants. Histogram depicts the individual phenotypic response to escalating doses [Figure 2].

About 16.9%, 24.4% and 36.4% of PCOS Phenotype A participants achieved clinical pregnancy with letrozole 2.5 mg, 5 mg and 7.5 mg dose, respectively. In

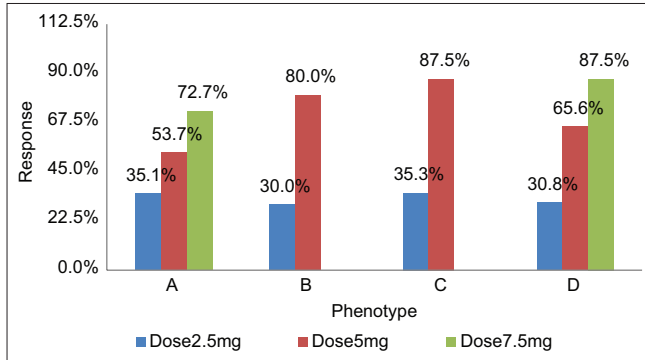


Figure 2: Histogram depicting the individual phenotypic response to escalating doses. (The coloured bars represent proportion of polycystic ovarian syndrome women in phenotypes a-d, showing ovulatory response to assigned protocol dose in each successive cycle)

Phenotype B, no participants achieved pregnancy with 2.5 mg dose, 20% achieved pregnancy with 5 mg dose and no participants were there for 7.5 mg dose. In Phenotype C, 17.6% of participants achieved pregnancy with 2.5 mg dose, 37.5% achieved pregnancy with 5 mg dose and no participants were there for 7.5 mg. In Phenotype D, 15.4%, 31.2% and 50% achieved pregnancy with letrozole 2.5 mg, 5 mg and 7.5 mg dose, respectively. It was noted that there was an increase in pregnancy rates with escalating doses of letrozole, as in Figure 3. The cumulative success rate of pregnancy was 44.8% (56 of 125) among infertile PCOS women who completed the study protocol of three cycles. The percentages of pregnancy with respect to ovulatory response at each escalating letrozole dose in different PCOS phenotypes are depicted in Table 3.

DISCUSSION

To the best of our knowledge, this is the first study comparing the ovulation induction response and

Table 2: Association between individual polycystic ovarian syndrome phenotype and various parameters in our study and their statistical significance (n=175)

| Parameters | PCOS phenotype, mean±SD | | | | P |
|--|-------------------------|-----------------|-----------------|-----------------|---------------------|
| | A (n=87) | B (n=11) | C (n=20) | D (n=57) | |
| Age (years) | 28.14±3.98 | 27.27±4.63 | 26.85±3.50 | 27.16±3.26 | 0.423 ^a |
| Height (m) | 1.54±0.04 | 1.55±0.05 | 1.54±0.04 | 1.54±0.04 | 0.505 ^a |
| Weight (kg)*** | 56.57±6.23 | 58.00±5.83 | 52.70±5.40 | 57.37±8.11 | 0.039 ^a |
| TSH (µIU/mL)*** | 2.32±0.96 | 3.10±0.93 | 2.58±0.81 | 7.10±33.31 | 0.030 ^a |
| S. Prolactin (ng/mL)*** | 9.03±2.75 | 13.27±1.63 | 9.97±1.95 | 9.82±2.52 | <0.001 ^a |
| Free testosterone (ng/l)*** | 12.88±7.62 | 1.06±0 | 13.88±4.10 | 1.97±0.69 | <0.001 ^a |
| BMI (kg/m ²) | 23.86±2.94 | 23.99±1.98 | 22.29±2.85 | 24.12±3.07 | 0.097 ^a |
| Parameters | Number of participants | | | | P |
| | A (n=87), n (%) | B (n=11), n (%) | C (n=20), n (%) | D (n=57), n (%) | |
| Obstetric history | | | | | |
| Primary infertility | 48 (55.2) | 4 (36.4) | 14 (70.0) | 34 (59.6) | 0.311 ^b |
| Secondary infertility | 39 (44.8) | 7 (63.6) | 6 (30.0) | 23 (40.4) | |
| Menstrual cycle*** | | | | | |
| Regular | 0 | 0 | 20 (100.0) | 0 | <0.001 ^c |
| Irregular | 87 (97.7) | 11 (100.0) | 0 | 57 (100) | |
| Hirsutism (present)*** | 75 (86.2) | 9 (81.8) | 15 (75.0) | 0 | <0.001 ^b |
| Acne (present)*** | 51 (58.6) | 6 (54.5) | 10 (50.0) | 0 | <0.001 ^b |
| Ovulatory dysfunction (present)*** | 87 (100.0) | 11 (100.0) | 0 | 57 (100.0) | <0.001 ^c |
| Hyperandrogenism (present)*** | 87 (100.0) | 11 (100.0) | 20 (100.0) | 0 | <0.001 ^b |
| PCOM (present)*** | 86 (98.9) | 0 | 20 (100.0) | 57 (100.0) | <0.001 ^c |
| Dose at response (all enrolled participants) | | | | | |
| 2.5 mg | 27 (31.0) | 3 (27.3) | 6 (30.0) | 16 (28.1) | 0.735 ^b |
| 5 mg | 22 (25.3) | 4 (36.4) | 7 (35.0) | 21 (36.8) | |
| 7.5 mg | 8 (9.2) | 0 | 0 | 7 (12.3) | |
| Not responded | 3 (3.4) | 0 | 0 | 1 (1.8) | |
| Lost to follow up | 27 (31.0) | 4 (36.4) | 7 (35.0) | 12 (21.1) | |
| Pregnancy (positive) | 27 (31.0) | 1 (9.1) | 6 (30.0) | 22 (38.6) | 0.276 ^b |

***Significant at P<0.05, ^aKruskal-Wallis test, ^bChi-square test, ^cFisher's exact test. BMI=Body mass index, SD=Standard deviation, PCOS=Polycystic ovarian syndrome, PCOM=Polycystic ovarian morphology, TSH=Thyroid-stimulating hormone, SD=Standard deviation

pregnancy rates with letrozole induction within PCOS phenotypes.

Our study showed a significant increase in ovulation and increase in pregnancy rates with escalated doses of letrozole across all PCOS phenotypes.

PCOS is a common hormonal disorder in women of reproductive age. Several sets of diagnostic criteria

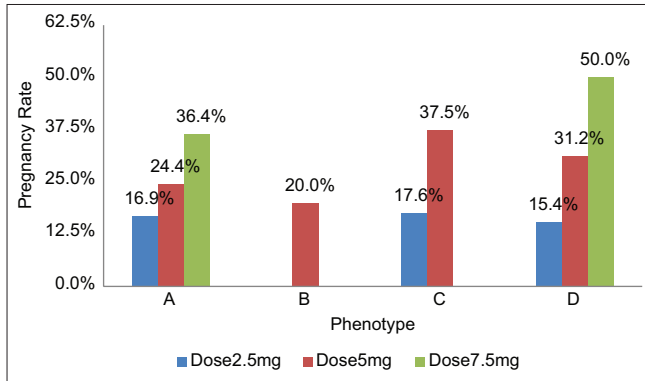


Figure 3: Histogram depicting Pregnancy rates of phenotypes to various doses. (The coloured bars represent the proportion of polycystic ovarian syndrome women in phenotypes a-d, showing ovulatory response to assigned protocol dose in each successive cycle)

have been proposed in the past.^[2] In our study, the recommendations of ESHRE/ASRM (Rotterdam 2003 criteria) were used for the diagnosis of PCOS,^[2] and the participants were classified into various PCOS phenotypes based on the NIH consensus panel evidence-based guidelines (2012).^[6]

PCOS is one of the main causes of infertility resulting from chronic anovulation. Several methods have been effective for ovulation induction. The ACOG and various international associations have now recommended the use of letrozole as first-line therapy for all women with PCOS.^[3,4]

The worldwide prevalence of PCOS ranges from 5% to 20% among different geographic regions when the ESHRE/ASRM 2003 criteria were applied, as shown in Table 4.^[1,7-17] Overall, it seems that the classic form of PCOS (i.e., Phenotypes A and B) constitutes approximately two-third of the total PCOS participants identified within the clinical setting.^[18] PCOS phenotypes present differently in their clinical, metabolic and hormonal profile which can alter their response to ovulation-inducing agents like letrozole. It could be the

Table 3: Distribution of different polycystic ovarian syndrome phenotypes with ovulatory response and pregnancy with escalating letrozole doses after excluding the lost to follow up participants (n=125)

| PCOS phenotype | A | | | B | | | C | | | D | | |
|---------------------------------------|--------|------|--------|--------|------|--------|--------|------|--------|--------|------|--------|
| | 2.5 mg | 5 mg | 7.5 mg | 2.5 mg | 5 mg | 7.5 mg | 2.5 mg | 5 mg | 7.5 mg | 2.5 mg | 5 mg | 7.5 mg |
| Participants exposed | 77 | 41 | 11 | 10 | 5 | - | 17 | 8 | - | 52 | 32 | 8 |
| Ovulatory response | 27 | 22 | 8 | 3 | 4 | - | 6 | 7 | - | 16 | 21 | 7 |
| Percentage (%) ovulation/participants | 35 | 53.7 | 72.7 | 30 | 80 | - | 35.3 | 87.5 | - | 30.8 | 65.6 | 87.5 |
| Pregnancy positive | 13 | 10 | 4 | - | 1 | - | 3 | 3 | - | 8 | 10 | 4 |
| Percentage (%) pregnancy/participants | 16.9 | 24.4 | 36.4 | - | 20 | - | 17.6 | 37.5 | - | 15.4 | 31.2 | 50 |
| Percentage (%) pregnancy/ovulation | 48 | 45.5 | 50 | - | 25 | - | 50 | 42.9 | - | 50 | 47.6 | 57.1 |

PCOS=Polycystic ovarian syndrome

Table 4: Prevalence of polycystic ovarian syndrome in different countries

| Country | Population | n | PCOS (%) based on ESHRE/ASRM 2003 | First author, year [reference] |
|-----------|--|-------|-----------------------------------|---|
| China | Stratified sample of women in Beijing | 2111 | 6.11 | Ma et al., 2010 ^[1] |
| Australia | Indigenous women, DRUID study | 248 | 21.3 | Boyle et al., 2012 ^[7] |
| Australia | Birth registry in a single hospital | 728 | 11.9 | March et al., 2010 ^[8] |
| Brazil | Women undergoing cervical cancer screening | 859 | 8.5 | Gabrielli and Aquino, 2012 ^[9] |
| China | Residences from 10 provinces | 15924 | 5.6 | Li et al., 2013 ^[10] |
| China | Residents of Chengdu | 1645 | 11.2 | Zhuang et al., 2014 ^[11] |
| Denmark | Employees at Copenhagen University | 447 | 16.6 | Lauritsen et al., 2014 ^[12] |
| Sri Lanka | Four areas in Gampaha region | 2915 | 6.3 | Kumarapeli et al., 2008 ^[13] |
| Iran | Four random provinces of different geographic regions | 929 | 14.6 | Tehrani et al., 2011 ^[14] |
| Iran | Females attending pre-marriage clinic in Isfahan | 820 | 15.2 | Mehrabian et al., 2011 ^[15] |
| Turkey | Pre-employment medical assessment in General Directorate of Mineral Research and Exploration | 392 | 19.9 | Yildiz et al., 2012 ^[16] |
| Iran | Randomly selected women from Southwest Iran | 602 | 14.1 | Rashidi et al., 2014 ^[17] |

PCOS=Polycystic ovarian syndrome, ESHRE=European Society for Human Reproduction and Embryology, ASRM=American Society for Reproductive Medicine

interplay between genetic and environmental factors which affect the pathogenesis of PCOS.^[19] Another possible explanation given is the intrauterine exposure to maternal androgens which might be responsible for a particular phenotype.^[20]

Across the phenotypic spectrum of PCOS, there was no significant difference in the distribution range of BMI (kg/m²) in our study ($P = 0.097$). However, Welt *et al.*^[21] and Moran *et al.*^[22] observed an increased BMI and increased prevalence of obesity in Phenotypes A and B.

Regarding the prevalence of individual phenotypes, overall published data indicate that more than half of PCOS participants identified within the clinical setting demonstrate Phenotype A, whereas the other three phenotypes (B, C and D) have almost equal prevalence. Sachdeva *et al.*^[23] observed that Phenotype A was most common with 67.7% (111 patients), followed by Phenotype C with 17.7% (29 patients), Phenotype B with 11% (18 patients) and Phenotype D with 3.6% (6 patients). Comparative relative prevalence in our study shows Phenotype A with lower prevalence (49.7% vs. 67.7%), and higher prevalence of Phenotype D (32.6% vs. 3.6%) by Sachdeva, *et al.*^[23] It was also noted that the prevalence of PCOS Phenotype C was also relatively less (11.4% vs. 17.7%). Zhang *et al.*^[24] and several other studies, as shown in Table 5,^[1,8,10,12,14,16,25,26] observed a relatively higher prevalence of Phenotype D in the general population, and not amongst infertile females. There is a paucity of literature with respect to PCOS phenotype prevalence amongst infertile patients.

Only 20 of 175 participants were detected to have no OD. As they did not spontaneously conceive despite the natural occurrence of ovulation, we attempted ovulation induction with letrozole. Six women exposed to 2.5 mg of letrozole and 7 women exposed to 5 mg of letrozole responded. The failure to conceive despite

spontaneous ovulation could be also due to other causes of infertility.

Results were further categorised into individual PCOS phenotypic responses to escalated doses of the ovulation-inducing agent. Overall, it was noted that 33.3% of all participants with 2.5 mg, 62.8% with 5 mg and 78.9% women with 7.5 mg of letrozole responded to ovulation induction.

It was further noted that within each PCOS phenotype class, there was an equally improved response to an escalating dose of letrozole. However, it cannot be conclusively said with statistical certainty in view of the dwindling number of participants at each subsequent cycle of induction reducing the sample size thereof. Loss to follow up was mainly due to intercity transfer of our clientele coupled with unforeseen COVID-19 pandemic situation.

The overall pregnancy rates for all PCOS participants without phenotypic categorisation in our study were higher in comparison to the study by Badawy *et al.*^[27] and Bayar *et al.*^[28] (35.9% vs. 15.1% vs. 9.1%, respectively). However, our results are quite similar in comparison to Indian studies by Roy *et al.*^[29] and Kar *et al.*^[30] (35.9% vs. 43.8% vs. 21.96%, respectively).

An important observation of our study is that PCOS phenotypic categories responded equally to the ovulation induction with similar doses of letrozole and an improved response was seen with subsequent dose escalation across all phenotypes. Hence, the clinical usefulness of phenotypic categorisation as far as ovulation induction is concerned is uncertain.

Limitations of the study

The study population is small in our study with progressive loss to follow up in subsequent visits. There was a drop in participant attendance due to the prevailing COVID-19 pandemic. The present data are of the mixed Indian population, so it does not take into account the ethnic differences.

CONCLUSION

PCOS is one of the most common endocrinopathies in women of reproductive age. Understanding the prevalence and distribution of PCOS phenotypes is essential in defining the epidemiology of PCOS in a population, considering that geographic factor and ethnic/racial variations can also shape their clinical presentation. All PCOS phenotypes respond in a similar fashion to escalating doses of letrozole with improvement in achieving ovulation and pregnancy rates as well. Hence, whether PCOS phenotypic categorisation has an advantage in terms of difference in

Table 5: Distribution polycystic ovarian syndrome phenotypes in unselected population in various countries

| Country | N (PCOS) | Phenotype (%) | | | | First author, year, [reference] |
|-----------|----------|---------------|------|------|------|--|
| | | A | B | C | D | |
| China | 129 | 31.0 | 16.3 | 27.1 | 25.6 | Ma <i>et al.</i> , 2010 ^[1] |
| Australia | 129 | 21.2 | 27.5 | 18.9 | 32.5 | March <i>et al.</i> , 2010 ^[8] |
| China | 886 | 28.7 | 19.0 | 37.3 | 15.0 | Li <i>et al.</i> , 2013 ^[10] |
| Denmark | 86 | 4.7 | 4.6 | 72.1 | 18.6 | Lauritsen <i>et al.</i> , 2014 ^[12] |
| Iran | 136 | 8.8 | 39.7 | 31.6 | 19.9 | Tehrani <i>et al.</i> , 2011 ^[14] |
| Turkey | 78 | 25.6 | 5.1 | 46.2 | 23.1 | Yildiz <i>et al.</i> , 2012 ^[16] |
| Mexico | 10 | 70 | 20 | 0 | 10 | Moran <i>et al.</i> , 2010 ^[25] |
| Iran | 85 | 12.9 | 22.4 | 49.4 | 15.3 | Tehrani <i>et al.</i> , 2014 ^[26] |

PCOS=Polycystic ovarian syndrome

response to letrozole as an ovulation-inducing agent is of questionable value according to our study. Larger and pooled data are needed to validate our study in view of the limitations of our study.^[31,32]

Data availability statement

The data set used in the current study is available with corresponding author and will share upon reasonable request.

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Conflicts of interest

There are no conflicts of interest.

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