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Association of Demographic and Clinical Factors with Ovarian Response in Subfertile PCOS Patients Treated with Letrozole

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Abstract

Background: Polycystic ovary syndrome (PCOS) is a leading cause of anovulatory subfertility. While letrozole is widely used for ovulation induction, treatment response varies and predictors beyond anti-Müllerian hormone (AMH) require further evaluation. This study aimed to investigate the association of demographic and clinical factors with ovarian response in subfertile PCOS patients treated with letrozole. ***Methods:*** A cross-sectional analytical study was conducted at the Center for Assisted Reproduction, BIRDEM-II Hospital, Dhaka, from April 2022 to September 2023. A total of 116 women with PCOS, aged 18–35 years, underwent letrozole induction (5 mg/day). Participants were categorized as responders (dominant follicle ≥16 mm, n=58) and non-responders (<16 mm, n=58). Demographic variables, BMI, type of subfertility, and baseline serum FSH and LH were compared between groups. Statistical analyses were performed using SPSS v26, with $p<0.05$ considered significant. ***Results:*** No significant associations were found between ovarian response and age ($p=0.743$), education ($p=0.121$), occupation ($p=0.356$), or income ($p=0.576$). BMI distributions did not differ significantly ($p=0.331$), nor did the type of subfertility ($p=0.550$). Serum FSH was significantly higher among non-responders (9.28±5.6 vs. 7.19±3.64, $p<0.001$), while serum LH showed no significant difference ($p=0.102$). ***Conclusion:*** Demographic and socioeconomic factors did not influence the ovarian response in patients with PCOS treated with letrozole. Elevated basal FSH levels were associated with poor responsiveness, indicating its role as a predictor. These findings support FSH assessment in individualized treatment planning for women with PCOS.

Keywords: Polycystic ovary syndrome, Letrozole, Ovarian response, Follicle-stimulating hormone.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders among women of reproductive age, affecting approximately 20% globally and accounting for nearly 80% of anovulatory infertility [1]. Characterized by hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology, the syndrome is linked with a wide spectrum of reproductive and metabolic abnormalities, including subfertility, insulin resistance, obesity, and cardiovascular risk [2,3]. The variability in phenotypic presentation complicates clinical management, making it crucial to identify factors that influence treatment outcomes.

Ovulation induction with pharmacological agents remains a cornerstone in the management of infertility associated with PCOS. Clomiphene citrate was historically the first-line therapy, but letrozole, an aromatase inhibitor, has recently emerged as the preferred drug due to higher ovulation and live birth rates, fewer anti-estrogenic effects, and more favorable

endometrial profiles [4,5]. However, ovarian responsiveness to letrozole is not uniform, and a significant proportion of women fail to achieve adequate follicular development despite treatment. This raises the need to explore predictors of ovarian response to tailor therapeutic strategies more effectively.

Anti-Müllerian hormone (AMH) has received considerable attention as a biomarker of ovarian reserve and predictor of ovarian response [6,7]. However, studies suggest that AMH alone does not fully account for the heterogeneity of response, and other demographic and clinical variables may play critical roles [8]. Parameters such as age, body mass index (BMI), type of subfertility, and baseline gonadotropin levels (FSH and LH) may contribute to treatment outcomes in women with PCOS [9]. While obesity and insulin resistance have been associated with altered follicular dynamics, the independent effect of BMI on ovarian response to ovulation induction remains debated. Similarly, elevated FSH levels have been linked with impaired ovarian function, but their predictive value in the context of PCOS treated with letrozole is less well-defined [10].

Demographic characteristics such as age, educational status, and socioeconomic indicators also warrant consideration. Although these factors may not directly influence ovarian physiology, they can reflect broader lifestyle and healthcare-related disparities that indirectly affect reproductive health [11]. Evidence from prior studies indicates that women with higher BMI and advanced age often experience reduced responsiveness to ovulation induction and require more aggressive treatment strategies [12]. On the other hand, some investigations report minimal associations, suggesting variability across populations and highlighting the importance of region-specific data [13].

The interplay between demographic variables, baseline hormonal milieu, and ovarian responsiveness in subfertile PCOS patients remains insufficiently addressed in South Asian populations. Bangladesh, with its high burden of PCOS and rising rates of subfertility, provides a relevant context for such an investigation. Data focusing on demographic and clinical predictors can inform individualized treatment protocols, enhance cost-effectiveness, and reduce the risk of overtreatment or under-treatment in women undergoing ovulation induction.

The present study was designed to evaluate the association of demographic (age, education, occupation, socioeconomic indicators) and clinical (BMI, type of subfertility, serum gonadotropin levels) factors with ovarian response in subfertile PCOS patients treated with letrozole. By examining these associations independently of AMH, this research offers a broader perspective on determinants of ovarian responsiveness, contributing to a more comprehensive framework for personalized fertility care.

METHODOLOGY & MATERIALS

This cross-sectional analytical study was conducted at the Center for Assisted Reproduction (CARE), Department of Obstetrics & Gynaecology, BIRDEM-II General Hospital, Dhaka, Bangladesh. The study was carried out over 18 months, from April 2022 to September 2023. A total of 116 subfertile women with PCOS who received letrozole for ovulation induction were included in the analysis.

Study population:

The study population comprised women of reproductive age diagnosed with PCOS according to the Rotterdam criteria (2003), which requires the presence of at least two of the following: oligo- or anovulation, clinical or biochemical features of hyperandrogenism, and polycystic ovarian morphology on ultrasound. After letrozole induction, participants were divided into two groups based on their ovarian response, as assessed by transvaginal ultrasound:

Group I (Responders): Women who developed at least one dominant follicle measuring ≥16 mm on day 12/13 of the cycle.

Group II (Non-responders): Women whose follicles remained <16 mm despite induction with letrozole.

Sample selection

Inclusion criteria:

- Women aged 18–35 years.
- Diagnosed with PCOS based on the 2003 Rotterdam criteria (two out of three: oligo/anovulation, clinical or biochemical hyperandrogenism, and polycystic ovarian morphology).
- History of subfertility.
- Undergoing ovulation induction with letrozole (5 mg daily).

Exclusion criteria:

- Thyroid dysfunction.
- Hyperprolactinemia.
- Premature ovarian failure.
- History of ovarian surgery.

Data collection and study procedure

Participants underwent baseline evaluation at day 2 of the menstrual cycle, including measurement of serum FSH, LH, TSH, prolactin, and AMH. For this study, only demographic parameters (age, educational status, occupation, income), BMI, type of subfertility, and gonadotropin levels (FSH, LH) were considered. A transvaginal ultrasound was performed on day 12/13 to assess follicular development. Patients were categorized into two groups based on ovarian response: responders (dominant follicle ≥16 mm) and non-responders (<16 mm). Data were recorded using a predesigned questionnaire and validated through cross-checking with medical records to ensure reliability and accuracy.

Ethical considerations

Ethical approval was obtained from the Institutional Review Board of BIRDEM. Written informed consent was collected from all participants before enrollment. Confidentiality was maintained by assigning unique identifiers to each participant, and data were used solely for research purposes.

Statistical analysis

Data were analyzed using SPSS version 26 (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean ± standard deviation (SD), and categorical variables as frequencies and percentages. Independent sample t-tests were applied to compare means, while chi-square or Fisher's exact tests were used for categorical data. A p-value <0.05 was considered statistically significant.

RESULTS

Table I: Socio-demographic characteristics of participants by ovarian response

Variable		Responders (n=58)	Non-responders (n=58)	p-value
Age (years)	≤20	0 (0.0%)	2 (3.4%)	0.334
	21–30	31 (53.4%)	32 (55.2%)	
	>30	27 (46.6%)	24 (41.4%)	
	Mean ± SD	30.2 ± 3.7	29.9 ± 5.1	0.743
Education	Graduate	29 (50.0%)	18 (31.0%)	0.121
	Secondary or below	12 (20.7%)	19 (32.8%)	
	Postgraduate	17 (29.3%)	21 (36.2%)	
Occupation	Homemaker	27 (46.6%)	26 (44.8%)	0.356
	Service holder	22 (37.9%)	21 (36.2%)	
	Business/student/others	9 (15.5%)	11 (19.0%)	
Monthly income (BDT)	≤50,000	28 (48.3%)	25 (43.1%)	0.576
	>50,000	30 (51.7%)	33 (56.9%)	
	Mean ± SD	55,020 ± 13,130	60,830 ± 21,031	0.077

Table I shows socio-demographic characteristics by ovarian response. Most women in both groups were between 21-30 years (53.4% responders, 55.2% non-responders). Mean age was similar (30.2 ± 3.7 vs. 29.9 ± 5.1 years, p=0.743). Among responders and non-responders, 50.0% and 31.0% were graduates, while 29.3% and 36.2% had postgraduate education. Occupation was mainly homemaker (46.6% vs. 44.8%) and service holder (37.9% vs. 36.2%). Monthly income showed no significant difference, with mean income being 55,020 ± 13,130 BDT in responders and 60,830 ± 21,031 BDT in non-responders (p=0.077).

Table II: Comparison of BMI by ovarian response

BMI category	Responders (n=58)	Non-responders (n=58)	p-value
18.5–24.9 (Normal)	19 (32.8%)	12 (20.7%)	0.357
25.0–29.9 (Overweight)	31 (53.4%)	34 (58.6%)	
≥30 (Obese)	8 (13.8%)	12 (20.7%)	
Mean ± SD	26.7 ± 3.7	27.4 ± 3.4	0.331

Table II presents BMI distribution by ovarian response. Most women were overweight (53.4% responders, 58.6% non-responders). Normal BMI was seen in 32.8% of responders versus 20.7% of non-responders, while obesity affected 13.8% and 20.7%, respectively. Mean BMI was similar between groups (26.7 ± 3.7 vs. 27.4 ± 3.4, p=0.331).

Table III: Type of subfertility by ovarian response

Type of subfertility	Responders (n=58)	Non-responders (n=58)	p-value
Primary	38 (65.5%)	41 (70.7%)	0.55
Secondary	20 (34.5%)	17 (29.3%)	

Table III describes subfertility types among participants. Primary subfertility was more common, affecting 65.5% of responders and 70.7% of non-responders. Secondary subfertility occurred in 34.5% of responders and 29.3% of non-responders, showing no significant difference between groups (p=0.550).

Table IV: Serum gonadotropin levels by ovarian response

Parameter	Responders (n=58)	Non-responders (n=58)	p-value
Serum FSH (Mean ± SD)	7.19 ± 3.64	9.28 ± 5.60	<0.001
Serum LH (Mean ± SD)	9.41 ± 9.05	11.49 ± 6.51	0.102

Table IV compares baseline gonadotropin levels. Mean serum FSH was significantly higher in non-responders (9.28 ± 5.60 IU/L) than in responders (7.19 ± 3.64 IU/L, p<0.001). Serum LH was slightly higher in non-responders (11.49 ± 6.51 IU/L) than responders (9.41 ± 9.05 IU/L), though not statistically significant (p=0.102).

DISCUSSION

This study examined the association of demographic and clinical factors with ovarian response in subfertile women with PCOS treated with letrozole. The findings demonstrated no significant association between ovarian responsiveness and socio-demographic parameters. Similarly, BMI and type of subfertility did not significantly differ between responders and non-responders. In contrast, serum FSH levels were significantly higher in non-responders compared to responders, while serum LH levels did not show a statistically meaningful difference.

The lack of association between age and ovarian response is consistent with the unique reproductive profile of PCOS patients. Unlike the general population, where increasing age is associated with a decline in ovarian reserve, PCOS women often maintain a larger pool of small antral follicles well into their reproductive years [1]. Stracquadanio *et al.,* reported similar findings, noting that ovarian function in PCOS does not decline as steeply with age as in women without the condition [7]. Thus, within the relatively young cohort studied (mean age ~30 years), age may not be a strong determinant of responsiveness to ovulation induction.

Socio-demographic factors, including education, occupation, and income, also did not influence ovarian response in the present study. While such variables may indirectly affect health-seeking behaviors and access to fertility care, their direct biological impact on ovarian physiology is limited. Previous reviews have emphasized that although disparities in reproductive outcomes exist across socioeconomic groups, these differences are often mediated by access to healthcare and lifestyle rather than inherent biological variations [11]. The absence of significant socio-demographic effects in this study is likely attributable to the hospital-based design, where participants had comparable access to treatment and monitoring.

BMI has been widely studied as a potential determinant of ovarian response, with obesity linked to reduced ovulation and conception rates in some populations. Kloos et al. reported that in PCOS patients, increased BMI was negatively associated with AMH levels, suggesting that obesity may impair ovarian reserve [14]. In the current study, although the non-responder group had a slightly higher mean BMI than responders, the difference was not statistically significant. This aligns with observations that the impact of BMI on ovarian responsiveness may vary depending on ethnicity and the therapeutic regimen employed [3]. It is possible that letrozole, by reducing peripheral estrogen production and improving gonadotropin release, mitigates some of the adverse effects of obesity on ovarian function.

Type of subfertility, whether primary or secondary, showed no significant relationship with ovarian response. This finding echoes the observations of Ashrafi *et al.,* who noted that baseline reproductive history is not always predictive of ovarian stimulation outcomes [15]. The similarity between groups in the present study suggests that the underlying follicular dynamics in PCOS, rather than reproductive history per se, are more critical determinants of treatment responsiveness.

The most notable finding of this study was the significantly higher mean serum FSH levels in non-responders compared to responders. Elevated basal FSH has long been regarded as a marker of diminished ovarian reserve and poorer outcomes in assisted reproduction. Although PCOS patients typically present with relatively normal or low FSH, variation within this range may still influence ovarian responsiveness. Ashrafi *et al.,* previously demonstrated that higher FSH was associated with lower follicular response during controlled ovarian hyperstimulation, supporting the present results [15]. By contrast, serum LH levels did not differ significantly between the two groups. While hypersecretion of LH is characteristic of many PCOS phenotypes, its predictive value for ovarian response remains inconclusive, with studies reporting conflicting results [6].

Taken together, these findings suggest that in women with PCOS undergoing letrozole treatment, demographic and socioeconomic variables exert minimal influence on ovarian responsiveness. Instead, clinical and hormonal parameters, particularly serum FSH, appear to play a more important role. This has practical implications: while AMH remains a strong predictor of responsiveness, FSH may serve as an additional marker to identify patients less likely to respond to standard letrozole protocols. Early recognition of such patients could allow clinicians to individualize treatment strategies, such as adjusting

letrozole dosage or considering alternative induction regimens.

Limitations of the study

This study was conducted at a single tertiary care hospital, limiting the external validity of the findings. The sample size, though adequate, may not fully represent the broader population of subfertile PCOS patients. The use of a fixed letrozole dose (5 mg) also restricts the ability to evaluate dose-response variability. Additionally, confounding factors such as insulin resistance and metabolic parameters were not assessed, which may have influenced ovarian response.

CONCLUSION

This study demonstrated that demographic and socioeconomic characteristics did not significantly influence the ovarian response in patients with PCOS who were treated with letrozole. BMI and type of subfertility were also not predictive factors. However, elevated basal serum FSH levels were significantly associated with poor ovarian response, whereas serum LH levels showed no significant relationship. These findings suggest that hormonal assessment, particularly FSH levels, may be more informative than demographic variables in predicting the treatment outcomes. Personalized treatment strategies incorporating both AMH and FSH levels could optimize ovulation induction in patients with PCOS.

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Conflicts of interest: There are no conflicts of interest.

Ethical approval: The study was approved by the Institutional Ethics Committee.

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