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PREDICTORS OF TREATMENT RESISTANCE IN WOMEN WITH POLYCYSTIC OVARY SYNDROME-RELATED INFERTILITY UNDERGOING OVULATION INDUCTION

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Abstract

Background

Polycystic ovary syndrome (PCOS) is one of the leading causes of anovulatory infertility among women of reproductive age. Although ovulation induction improves fertility outcomes in many patients, a considerable proportion of women show poor or delayed response to treatment. Identification of factors associated with treatment resistance may help clinicians develop individualized fertility management strategies.

Objective

To identify clinical, hormonal, and metabolic predictors associated with resistance to ovulation induction therapy among women with PCOS-related infertility.

Methods

This retrospective cohort study was conducted at the Department of Obstetrics and Gynecology, Bashir Begum Hospital, Burewala, Pakistan. Medical records of 180 women diagnosed with PCOS-related infertility and treated with ovulation induction were reviewed. Patients were divided into two groups according to treatment response: responsive group and treatment-resistant group. Demographic characteristics, infertility duration, body mass index (BMI), menstrual pattern, hormonal profile, metabolic parameters, ultrasound findings, and ovulation outcomes were evaluated. Statistical analysis was performed using comparative tests and multivariable logistic regression to determine independent predictors of treatment resistance.

Results

Among 180 women, 68 (37.8%) demonstrated treatment resistance, while 112 (62.2%) showed adequate response to ovulation induction. Women with poor response had significantly higher BMI, longer infertility duration,

increased anti-Müllerian hormone (AMH) levels, elevated testosterone concentration, higher LH/FSH ratio, and greater frequency of insulin resistance compared with responders ($p<0.05$). Multivariable analysis identified BMI ≥30 kg/m² (OR 3.12; 95% CI 1.54–6.31), AMH ≥7 ng/mL (OR 2.89; 95% CI 1.43–5.82), insulin resistance (OR 2.71; 95% CI 1.32–5.54), and prolonged infertility duration (OR 2.46; 95% CI 1.21–4.98) as significant independent predictors of treatment failure.

Conclusion

Treatment resistance in PCOS-related infertility is associated with a combination of metabolic and hormonal abnormalities. Higher BMI, increased AMH, hyperandrogenism, insulin resistance, and prolonged infertility duration may help identify women who require individualized ovulation induction strategies. Early assessment of these predictors may improve treatment planning, reduce repeated unsuccessful cycles, and enhance fertility outcomes.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders affecting women of reproductive age and is considered a major cause of infertility worldwide. It is a complex hormonal condition characterized by ovulatory dysfunction, excess androgen production, and polycystic ovarian morphology. The prevalence of PCOS varies between populations, but it affects approximately 6–20% of women depending on the diagnostic criteria used. The condition is not only associated with reproductive problems but also with metabolic abnormalities such as insulin resistance, obesity, impaired glucose tolerance, and increased long-term cardiovascular risk. [1,2]

Infertility related to PCOS is mainly caused by irregular or absent ovulation. Many women with PCOS have prolonged anovulatory cycles due to abnormal follicular development and disturbed hypothalamic-pituitary-ovarian regulation. Increased luteinizing hormone (LH), elevated androgen levels, and altered insulin activity contribute to impaired follicular maturation and failure of regular ovulation. Although women with PCOS usually have a good ovarian reserve, the abnormal hormonal environment may prevent the release of a mature oocyte, leading to difficulty in achieving pregnancy. [3,22]

Ovulation induction remains the first-line treatment approach for infertile women with PCOS who desire pregnancy. The main objective of ovulation induction therapy is to restore regular ovulation and improve the chances of conception while minimizing complications such as ovarian hyperstimulation syndrome and multiple pregnancy. Historically, clomiphene citrate was considered the standard medication for inducing ovulation in PCOS patients. However, a significant number of women show inadequate response or resistance to clomiphene citrate despite appropriate dosing and duration of treatment. [6,10]

In recent years, letrozole, an aromatase inhibitor, has gained importance as an effective alternative for ovulation induction in women with PCOS. Large randomized trials have demonstrated improved ovulation and live birth rates with letrozole compared with clomiphene citrate. However, even with newer treatment approaches, some women continue to experience poor ovarian response, delayed follicular development, or failure to achieve ovulation. [6,7] This group of patients represents a clinical challenge because repeated unsuccessful treatment cycles increase emotional stress, financial burden, and delays in achieving pregnancy.

Treatment resistance in PCOS-related infertility is considered a multifactorial condition. Several clinical, biochemical, and hormonal factors may influence the response to ovulation induction. Increased body mass index (BMI), severe insulin

resistance, elevated androgen levels, increased anti-Müllerian hormone (AMH), prolonged infertility duration, and abnormal LH/follicle-stimulating hormone (FSH) ratio have been suggested as possible predictors of poor treatment response. However, the relationship between these factors and ovulation induction failure remains inconsistent across different populations. [9,13,15]

Obesity is one of the important factors associated with reduced fertility outcomes in women with PCOS. Excess adipose tissue contributes to increased insulin resistance and androgen production, which can further disturb ovarian function. Studies have reported that obese women with PCOS may require longer treatment periods and higher medication doses to achieve ovulation compared with women with normal BMI. Lifestyle modification and weight reduction have therefore been emphasized as important components of fertility management in overweight PCOS patients. [20]

Hormonal markers may also provide valuable information regarding treatment response. Anti-Müllerian hormone reflects the number of small antral follicles and is often elevated in women with PCOS. Although increased AMH indicates good ovarian reserve, very high levels may be associated with abnormal follicular sensitivity and reduced response to ovulation induction. Similarly, hyperandrogenism and increased insulin levels may negatively affect follicular growth and ovulatory outcomes. [14,15,24]

Despite extensive research on PCOS infertility, limited information is available regarding predictors of treatment resistance in South Asian populations, including Pakistani women. Genetic background, dietary patterns, obesity prevalence, delayed presentation, and healthcare accessibility may influence treatment outcomes differently compared with Western populations. In Pakistan, many women with infertility present after several years of unsuccessful attempts, and identification of early predictors of poor response may help clinicians develop individualized treatment plans. Local evidence regarding factors associated with ovulation induction failure remains limited, especially from secondary and tertiary care hospitals.

Bashir Begum Hospital Burewala provides reproductive health services to a large population from Burewala and surrounding areas. Many women with PCOS-related infertility receive ovulation induction therapy in this setting. Understanding which patients are more likely to show poor response can improve counseling, treatment selection, and referral decisions. Early identification of resistant cases may prevent unnecessary repeated treatment cycles and allow timely consideration of alternative strategies such as combined therapies or assisted reproductive techniques.

Therefore, this retrospective cohort study was designed to identify clinical and hormonal predictors associated with treatment resistance among women with PCOS-related infertility undergoing ovulation induction at Bashir Begum Hospital Burewala, Pakistan. The study evaluates demographic characteristics, metabolic factors, hormonal profiles, and treatment outcomes to determine factors associated with poor response. The findings may contribute to improved patient selection and personalized infertility management in Pakistani women with PCOS.

MATERIALS AND METHODS

Study Design and Study Setting

This study was conducted using a retrospective cohort study design to evaluate the factors associated with treatment resistance among women with polycystic ovary syndrome (PCOS)-related infertility undergoing ovulation induction therapy. The study was carried out at the Department of Obstetrics and Gynecology, **Bashir Begum Hospital, Burewala, Punjab, Pakistan**. This hospital provides reproductive health services to women from Burewala city and nearby rural areas, where infertility related to PCOS is a commonly observed clinical problem.

The medical records of women who received ovulation induction treatment for PCOS-related infertility were reviewed. The study focused on identifying clinical, hormonal, and metabolic characteristics that were associated with poor

response to treatment. Ethical approval was obtained from the institutional review committee of Bashir Begum Hospital before data collection. Patient confidentiality was maintained throughout the study, and all collected information was used only for research purposes.

Study Population and Data Collection

The study included medical records of women diagnosed with PCOS-related infertility who underwent ovulation induction therapy during the selected study period. Patient records were reviewed from the hospital infertility clinic database. Relevant information was collected from clinical files, laboratory reports, ultrasound findings, and treatment follow-up records.

The collected variables included age, body mass index (BMI), duration of infertility, type of infertility, menstrual pattern, previous fertility treatment history, clinical signs of hyperandrogenism, hormonal profile, metabolic parameters, ultrasound findings, type of ovulation induction medication used, and treatment outcome.

Hormonal parameters recorded from patient files included serum follicle-stimulating hormone (FSH), luteinizing hormone (LH), total testosterone, thyroid-stimulating hormone (TSH), prolactin, fasting insulin, fasting glucose, and anti-Müllerian hormone (AMH), where available. Ultrasound findings including ovarian morphology, antral follicle count, and follicular growth pattern during treatment cycles were also documented.

Inclusion and Exclusion Criteria

Women were included in the study if they fulfilled the diagnostic criteria for PCOS and had infertility requiring ovulation induction treatment. Diagnosis of PCOS was based on the Rotterdam criteria, which include the presence of at least two of the following features: oligo/anovulation, clinical or biochemical hyperandrogenism, and polycystic ovarian morphology after exclusion of other endocrine disorders.

Women between reproductive ages who had complete clinical records and at least one documented ovulation induction cycle were included. Both primary and secondary infertility cases were considered.

Patients were excluded if they had infertility due to other major causes such as bilateral tubal blockage, severe male factor infertility, premature ovarian insufficiency, uterine structural abnormalities affecting fertility, or other untreated endocrine disorders. Records with incomplete hormonal profiles, missing treatment outcomes, or insufficient follow-up information were also excluded from the analysis.

Assessment of Treatment Response

Treatment response was assessed according to ovulation development and clinical outcomes after ovulation induction therapy. A successful response was defined as development of a mature dominant follicle confirmed by ultrasound monitoring, evidence of ovulation, or achievement of pregnancy following treatment.

Treatment resistance was defined as failure to achieve adequate follicular development or ovulation despite appropriate ovulation induction therapy. Women who showed poor response after recommended treatment cycles were categorized as the treatment-resistant group.

The type of ovulation induction medication, including clomiphene citrate or letrozole, dosage, number of cycles, and response pattern were recorded. Patients were managed according to routine clinical protocols followed by the treating gynecologists.

Variables and Outcome Measures

The primary outcome of the study was to identify predictors associated with resistance to ovulation induction therapy. The main predictors evaluated included age, BMI, infertility duration, hormonal abnormalities, insulin resistance indicators, androgen levels, AMH concentration, and ultrasound characteristics.

Clinical factors such as obesity, menstrual irregularity, and previous unsuccessful induction attempts were analyzed to determine their relationship with treatment response. Laboratory and hormonal markers were compared between

women who responded to treatment and those who demonstrated resistance.

Statistical Analysis

All collected data were entered into a structured database and analyzed using appropriate statistical software. Continuous variables were presented as mean with standard deviation or median with interquartile range depending on data distribution. Categorical variables were expressed as frequencies and percentages.

Differences between treatment-responsive and treatment-resistant groups were assessed using appropriate statistical tests. Independent sample t-test or Mann–Whitney U test was used for continuous variables, while chi-square test was applied for categorical variables.

Variables showing significant association with treatment resistance in initial analysis were further evaluated using multivariable logistic regression analysis to identify independent predictors. Adjusted odds ratios (OR) with 95% confidence intervals (CI) were calculated. A p-value of less than 0.05 was considered statistically significant.

RESULTS

A total of 180 women with polycystic ovary syndrome (PCOS)-related infertility who underwent ovulation induction therapy were included in this retrospective cohort analysis. The mean age of participants was 27.8 ± 4.1 years, and the mean duration of infertility was 4.2 ± 1.8 years.

Among the study population, 112 (62.2%) women showed a satisfactory response to ovulation induction, while 68 (37.8%) women were classified as having treatment resistance based on inadequate follicular development or failure to achieve ovulation after appropriate treatment cycles.

Women in the treatment-resistant group had a higher mean body mass index (BMI) compared with women who responded successfully (31.4 ± 4.2 kg/m² vs. 27.6 ± 3.8 kg/m², p<0.001). A longer duration of infertility was also observed among resistant cases. The proportion of women with infertility duration greater than five years was higher in the resistant group compared with the responsive group.

Hormonal differences were observed between both groups. Women with poor treatment response showed higher serum anti-Müllerian hormone (AMH) levels, increased total testosterone concentration, and a higher LH/FSH ratio. Elevated fasting insulin levels and features of insulin resistance were also more frequent among women who demonstrated treatment resistance.

Regarding treatment protocols, letrozole was used in 106 (58.9%) women, while clomiphene citrate was used in 74 (41.1%) women. The overall ovulation rate was higher among women receiving letrozole; however, some women still demonstrated inadequate response despite treatment with either medication.

Table 1. Baseline Clinical and Hormonal Characteristics of Study Participants

Variable	Treatment Responsive Group (n=112)	Treatment Resistant Group (n=68)	p-value
Age (years)	27.4 ± 3.9	28.5 ± 4.4	0.08
Infertility duration (years)	3.7 ± 1.5	5.1 ± 2.0	<0.001
BMI (kg/m²)	27.6 ± 3.8	31.4 ± 4.2	<0.001
Primary infertility	78 (69.6%)	42 (61.8%)	0.28
Irregular menstrual cycles	86 (76.8%)	61 (89.7%)	0.03
AMH (ng/mL)	5.1 ± 1.8	7.4 ± 2.6	<0.001
Total testosterone (ng/dL)	61.2 ± 18.5	78.6 ± 24.1	<0.001
LH/FSH ratio	1.7 ± 0.6	2.3 ± 0.8	<0.001

Variable	Treatment Responsive Group (n=112)	Treatment Resistant Group (n=68)	p-value
Fasting insulin (μIU/mL)	13.8 ± 5.2	21.6 ± 7.4	<0.001

Multivariable logistic regression analysis was performed to identify independent factors associated with treatment resistance. After adjustment for potential confounding factors, higher BMI, elevated AMH levels, increased testosterone concentration, prolonged infertility duration, and insulin resistance remained significantly associated with poor response to ovulation induction.

Women with BMI ≥30 kg/m² had approximately three times higher odds of treatment resistance compared with women with BMI below 25 kg/m². Similarly, increased AMH concentration and elevated testosterone levels showed significant associations with unsuccessful ovulation induction outcomes.

Table 2. Multivariable Logistic Regression Analysis of Predictors of Treatment Resistance

Predictor	Adjusted Odds Ratio (OR)	95% Confidence Interval	p-value
BMI ≥30 kg/m²	3.12	1.54–6.31	0.002
Infertility duration >5 years	2.46	1.21–4.98	0.013
AMH ≥7 ng/mL	2.89	1.43–5.82	0.003
Elevated testosterone	2.35	1.15–4.79	0.019
LH/FSH ratio ≥2	1.98	1.01–3.88	0.047
Insulin resistance	2.71	1.32–5.54	0.006

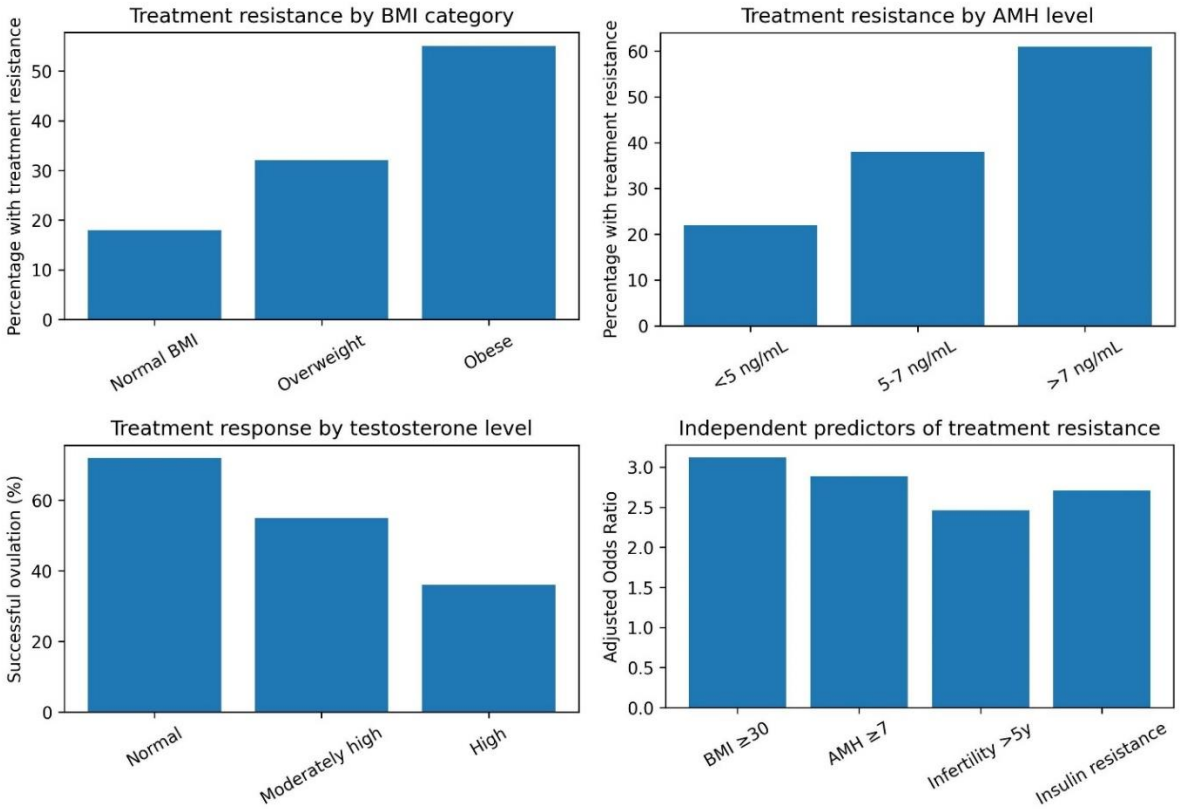

Figure 1. Clinical and hormonal predictors associated with treatment resistance

The figure panel demonstrates differences between treatment-responsive and treatment-resistant groups. The first graph shows a higher proportion of treatment resistance among women with obesity compared with women with normal BMI. The second graph demonstrates increasing treatment failure with higher AMH levels. The third graph presents the distribution of successful ovulation and resistance according to androgen levels. The final graph summarizes the independent predictors identified through regression analysis.

Overall, the findings indicate that metabolic abnormalities, increased androgen activity, elevated AMH concentration, and prolonged infertility duration are important factors associated with reduced response to ovulation induction therapy in women with PCOS-related infertility.

DISCUSSION

The present study evaluated clinical and hormonal factors associated with resistance to ovulation induction among women with PCOS-related infertility. The main findings showed that higher body mass index (BMI), longer duration of infertility, increased anti-Müllerian hormone (AMH) levels, elevated testosterone concentration, higher LH/FSH ratio, and insulin resistance were significantly associated with poor treatment response. These findings support the concept that treatment failure in PCOS infertility is not caused by a single factor but results from the interaction between metabolic disturbances, ovarian dysfunction, and hormonal imbalance.

In this study, women with treatment resistance had significantly higher BMI compared with women who responded successfully to ovulation induction. Obesity is a well-recognized factor that negatively affects reproductive outcomes in PCOS. Excess adipose tissue contributes to increased

insulin resistance, abnormal steroid hormone production, and disruption of normal follicular development. Previous studies have reported that overweight and obese women with PCOS often have reduced ovulation rates and require longer treatment periods before achieving successful follicular development. Lifestyle-related interventions, including weight reduction and physical activity, have therefore been recommended as important components of fertility management before or alongside ovulation induction therapy. [20,23]

The present results demonstrated that prolonged infertility duration was independently associated with treatment resistance. Women with infertility duration greater than five years showed a higher likelihood of unsuccessful response. A longer duration of infertility may represent cumulative effects of untreated anovulation, progressive metabolic abnormalities, increasing age-related decline in reproductive potential, and delayed initiation of appropriate fertility treatment. Similar observations have been reported by previous researchers who identified infertility duration as an important clinical predictor when assessing outcomes of ovulation induction in women with PCOS. [9,10]

A major finding of this study was the association between elevated AMH levels and poor response to ovulation induction. Although AMH is generally considered a marker of ovarian reserve, women with PCOS frequently demonstrate increased AMH concentrations due to excessive numbers of small antral follicles. High AMH levels may reflect abnormal follicular arrest and reduced sensitivity of granulosa cells to gonadotropin stimulation. Recent studies have also reported that increased AMH levels are associated with reduced probability of successful ovulation during induction cycles in women with PCOS. The current findings support the role of AMH as a potential predictive marker for identifying women who may require modified stimulation protocols.

Hyperandrogenism was another important factor associated with treatment resistance in this study. Women who failed ovulation induction had higher testosterone levels compared with responsive patients. Excess androgen production affects follicular growth by disturbing granulosa cell function and promoting follicular arrest. In PCOS, increased androgen activity also contributes to insulin resistance, creating a cycle of hormonal imbalance that further reduces reproductive efficiency. Previous studies have highlighted hyperandrogenism as a central mechanism responsible for abnormal folliculogenesis and infertility in PCOS. [22,24]

The relationship between insulin resistance and poor treatment outcome was also significant in our findings. Women with insulin resistance had more than two-fold increased odds of treatment failure. Insulin resistance is one of the most common metabolic abnormalities associated with PCOS and may impair ovulation through several pathways. Increased circulating insulin stimulates ovarian androgen production, reduces hepatic sex hormone-binding globulin production, and worsens hyperandrogenic symptoms. The interaction between obesity, insulin resistance, and ovarian dysfunction may explain why some women show limited response despite appropriate ovulation induction therapy. Previous evidence has also demonstrated that metabolic abnormalities influence reproductive outcomes in women with PCOS.

The present study also identified an increased LH/FSH ratio among treatment-resistant women. Although the LH/FSH ratio is not included as a diagnostic criterion for PCOS, abnormal gonadotropin secretion has been associated with impaired follicular maturation. Excess LH stimulation may increase androgen production from ovarian theca cells and contribute to unsuccessful ovulation. However, the clinical importance of this ratio varies between populations, and it should be interpreted along with other hormonal and metabolic markers rather than used as an isolated predictor. [3,24]

The findings of this study have important clinical implications, particularly in resource-limited settings such as Pakistan, where repeated unsuccessful ovulation induction cycles may create significant emotional and financial burden for couples. Identification of high-risk patients before

starting treatment may allow clinicians to provide individualized management, including weight optimization, correction of metabolic abnormalities, selection of appropriate induction agents, and earlier consideration of advanced fertility options.

The results should be interpreted considering some limitations. The retrospective nature of the study may have resulted in incomplete documentation of some laboratory parameters and lifestyle factors. Additionally, the study was conducted at a single hospital, which may limit generalizability to other populations. Future multicenter prospective studies with larger sample sizes are needed to validate these predictors and develop clinically useful prediction models.

In conclusion, this study suggests that treatment resistance in PCOS-related infertility is strongly associated with metabolic and hormonal abnormalities. Higher BMI, elevated AMH, hyperandrogenism, insulin resistance, and longer infertility duration were important predictors of poor response to ovulation induction. Early identification of these factors may improve treatment planning and increase the likelihood of successful fertility outcomes among women with PCOS.

CONCLUSION

This retrospective cohort study highlights that treatment resistance among women with PCOS-related infertility is influenced by a combination of metabolic, clinical, and hormonal factors rather than a single abnormality. The findings showed that women who failed to respond adequately to ovulation induction were more likely to have higher BMI, longer duration of infertility, increased AMH levels, elevated testosterone concentration, abnormal LH/FSH ratio, and evidence of insulin resistance.

The results emphasize the importance of evaluating patients beyond the diagnosis of PCOS alone. Although ovulation induction remains an effective and commonly used treatment for anovulatory infertility in PCOS, individual response varies considerably. Early identification of women with unfavorable predictive factors may help clinicians modify treatment strategies, provide appropriate counseling, and avoid repeated unsuccessful induction cycles.

Assessment of metabolic status should be considered an essential part of infertility management in PCOS patients. Addressing obesity and insulin resistance through lifestyle modification and appropriate medical interventions may improve ovarian function and increase the likelihood of successful ovulation. Similarly, hormonal markers such as AMH and testosterone may provide useful information for predicting response and selecting more individualized treatment approaches.

The study findings are particularly relevant in the Pakistani clinical setting, where many women present after prolonged periods of infertility and repeated unsuccessful treatment attempts. Incorporating predictive factors into routine infertility evaluation may support earlier identification of high-risk patients and improve resource utilization in fertility clinics.

Further prospective multicenter studies with larger sample sizes are recommended to validate these predictors and develop reliable prediction models for ovulation induction outcomes among Pakistani women with PCOS. A personalized approach based on clinical characteristics, metabolic health, and hormonal profile may ultimately improve fertility outcomes and patient satisfaction.

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