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Clinical, biochemical and ultrasonographic features of infertile women with polycystic ovarian syndrome

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ORIGINAL ARTICLE

CLINICAL, BIOCHEMICAL AND ULTRASONOGRAPHIC FEATURES OF INFERTILE WOMEN WITH POLYCYSTIC OVARIAN SYNDROME

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ABSTRACT

Objective: To evaluate and compare the clinical, biochemical and ultrasonic features of infertile women with PCOS from the two infertility centers of Karachi, The Aga Khan University Hospital and Concept Fertility Centre.

Study Design: Cross-sectional, analytical study.

Place and Duration of Study: The Aga Khan University Hospital, and Concept Fertility Centre, Karachi, Pakistan, from January 2003 till December 2004.

Patients and Methods: Patients attending the Infertility Clinics of Aga Khan University Hospital, Karachi and Concept Fertility Centre, Karachi, were evaluated for their clinical features. Complete biochemical evaluation was performed by day 2 FSH, LH, serum prolactin, serum testosterone and fasting serum insulin determination. These results were recorded on the data collection form. Ultrasonic evaluation was performed with transvaginal ultrasound to check the morphological appearance of ovaries.

Results: A total of 508 patients were evaluated for epidemiological features of PCOS. Frequency of PCOS in the infertility clinic was 17.6% with high rate of obesity (68.5%) and hyperinsulinemia (59%). The highest rate of abnormal clinical, biochemical features were seen above BMI of 30.

Conclusion: High rates of obesity, hyperinsulinemia and impaired glycemic control were seen in this series. It was demonstrated that high BMI had an association and correlation with abnormal clinical and biochemical features. Obese women with PCOS need more attention for their appropriate management.

KEY WORDS: *PCOS. Obesity. Hyperinsulinemia. Tonic LH. Metabolic disturbance. Morbidity.*

INTRODUCTION

Polycystic Ovarian Syndrome (PCOS) was first recognized in 1935 by two Chicago Gynecologists - Dr. Irving Stein and Michael Leventhal. This syndrome is associated with amenorrhea, infertility, variable levels of hirsutism and obesity in the presence of bilaterally enlarged ovaries.[1,2] Despite continuous research in pathophysiology, PCOS remains a syndrome of heterogeneous disorder. The consensus conference at Rotterdam in 2003 suggested that diagnosis of PCOS would be fulfilled if 2 out of the following 3 features are present: anovulation (usually manifested as oligomenorrhea or amenorrhea), elevated levels of circulating androgens (hyperandrogenemia) or clinical manifestation of androgen excess and presence of polycystic ovaries on ultrasonographic.[3]

It is the most common endocrinopathy in women of child bearing age and has a prevalence of 4-10% in the United States .[4] Estimation of prevalence of PCOS depends on the nature of population being assessed. There are ethnic and racial differences in the clinical and biochemical features of PCOS but the question remains whether the difference in expression of this syndrome is due to dietary, life style factors or purely genetic familial expression?[5] The prevalence in British female population is 22%.[5] The prevalence of this syndrome in Caribbean-Hispanic women is twice than that in African-American and Caucasian women.[6] There has been no large scale study to gauge the burden of PCOS in South Asia. Authors clinical experience and few studies done on South Asian immigrants settled in England revealed a high frequency in the South Asian women. A recent epidemio-logical study was conducted on Austrian infertile Muslim women with PCOS, which revealed clinically severe symptomatology in them compared to Jewish and Christian counterparts,[7] attributed to inter-marriages. Although the exact role of inter-family marriages is not yet defined, however, logically, insulin resistance and polygenic pattern of inheritance of PCOS are the possible factors for aggravation of clinical and metabolic features of this syndrome and metabolic X syndrome.

An obese infertile woman with PCOS is one group who should be managed with care and caution as they carry morbidity and metabolic complications, especially during pregnancy.

Studies on demographics and prevalence of this disorder in South Asian region will be helpful to know the burden of disease and its associated complications. It is a fact that a study of these differences would not only contribute a better understanding of disease mechanism but will aid to formulate guidelines according to resources and burden of disease.

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The objective of this study was to evaluate and compare the clinical, biochemical and ultrasonic features of infertile women with PCOS from the two infertility centers of Karachi, The Aga Khan University Hospital, and Concept Fertility Centre.

PATIENTS AND METHODS

This study was carried out on infertile women, attending the two infertility centers of Karachi, from January 2003 to December 2004. A total of 2,884 infertile couples were seen and treated at these centers. A total of 1,476 couples were treated at Aga Khan University Hospital while 1,408 were managed at Concept Fertility Center. The diagnostic criterias adopted for PCOS were according to Rotterdam 2003 consensus workshop, its menstrual irregularity i.e. long cycle of >35 days, hirsutism (facial and truncal) acne, tonic LH levels i.e.> 10 U/L and ultrasonographic morphology of ovaries i.e. presence of more than 8 small follicles measuring less than 10 mm in subcortical region and total ovarian volume of more than 10 ml.

The clinical, biochemical and ultrasonographic features of women with PCOS were recorded on a data collection form with respect to age, type and duration of infertility, history of menstrual cycle, hair growth, weight gain, and family history of diabetes mellitus. The biochemical hormonal evaluation was performed by Day 2 FSH, LH, prolactin levels. Fasting insulin and fasting blood glucose were also checked. Reports of transvaginal ultrasound to check ovarian morphology were recorded.

The normal cutoff for FSH, LH and fasting insulin was taken less than 10 iu/l. Prolactin was taken as normal if less than 25ng/dl. BMI was calculated by dividing the weight in kilograms from height in meter square. For BMI, reference standards were taken as defined by WHO for South Asian women i.e. BMI > 25 is taken as type I obesity. In order to have more clear demarcation of lean and obese patients with PCOS, BMI was categorized from 18 or less to 35 or more.

Women who had other causes of infertility like tubal factor, uterine and male factor were excluded from the study. Data analysis was performed by SPSS version 13. Five hundred and eight women met the criteria of PCOS, making a frequency of 17.6% in those infertility clinics. Out of 508 patients, 476 women, who had a BMI of > 25, were included for univariate and multivariate analysis.

Correlations were done by Pearson test. Categorical variables were compared by using Chi-square test and for continuous variables, t-test was used for comparing women with PCOS in different group of BMI. Two tailed significance was calculated and p–value of < 0.05 was taken as significant. The association of different clinical, biochemical and ultrasonic features with BMI was analyzed at univariate and multivariate levels and adjusted R-value and p-value were calculated to show statistical significance.

RESULTS

Study population consisted of women of reproductive age group. The mean age of women was 27.1 ± 4.5. Table I describes the percentage distribution of normal and abnormal clinical, biochemical and ultrasonographic features from these two centers. Out of 508 studied women, the rate of obesity was 68.5% while 58.9% of them had varying degree of hirsutism and 59% had hyperinsulinemia. Menstrual irregularity was found in 74.2% of studied infertile women with PCOS. Almost half of them i.e. 48% had first degree inter-family marriages. Out of 508 infertile couples, 63.7% of them had primary infertility while 37.7% had a presentation with secondary infertility. Majority of studied women were from infertility clinics of Aga Khan University Hospital i.e. 80.3% compared to 17.7% from Concept Fertility Centre, Karachi. Hormonal essay revealed that 94.5% had normal FSH while 66.6% had normal LH levels. Family history of diabetes was strongly positive in 54% of infertile women, with PCOS. Out of 508 studied women, 33.5 % had impaired GTT while 10.1%

Table I: Percentage distribution of different characteristics.

Characteristics	AKU	Concept	Mean %age
Age			
22.5	36.2%	23.6%	29.4%
25-29	42.7%	43.8%	43.1%
30-34	19.6%	23.7%	21.6%
35 and above	5.2%	7.1%	6.1%
Mean age (SD)			27.1 ±4.5
BMI			
<18.5 (underweight)	1.5	2.6	1.9%
18.5-22.9 (n)	16.2	12.3	14.1%
23-24.9 (even)	14.9	16.2	15.5%
25-29.9	41.2	37.3	39.7%
30 above	30.1	27.3	28.8%
Mean BMI (SD)			27.7±5.07
FSH level			
Normal	95.6	93.2	94.5%
Abnormal	4.6%	6.3%	5.5%
LH level			
Normal	61.6%	71.4%	46.6%
Abnormal	38.4%	28.6%	33.3%
Prolactin level			
Normal	70.4	820	76.1%
Abnormal	29.6	18	23.9%
Insulin level			
Normal	46.3%	37.2%	41%
Abnormal	53.7%	62.8%	59%
PCOS detection through ultrasound			
Yes	65.2%	73.1%	69.7%
No	34.8%	26.9%	30.3%
Hirsutism			
Yes	60.1%	28.2	58.9%
No	39.9	41.8	41.1%
Family history of diabetes			
Yes	56.3	52%	54%
No	43.7	48%	46%
Inter-family marriages			
Yes	56.3	40.2%	48%
No	43.7	59.8	52%
GTT			
Normal	52.3	50.9	56.3%
Impaired	36.1	31.2	33.7%
Abnormal	11.6	8.9%	10.1%
Total sampled	408	100	508

had abnormal GTT showing diabetes mellitus. Only 14% of women had normal BMI while 29.7% had BMI of 30 and 28.8% had a BMI above 30-35.

Table II and III shows analysis and association of abnormal, clinical, and biochemical features with BMI at univariate and multivariate levels. Out of 508 women, 476 were included for variate analysis having a BMI > 25 . By using appropriate co-efficient (R2 and F-Change), statistical significance was declared significant if p-value was < 0.05. Menstrual cycle irregularity, serum LH levels, hyperinsulinemia and family history of diabetes had a strong association with high BMI i.e. > 25 (p-value 0.01-0.001).

Table II: The association of different factors with BMI at univariate level.

Characteristic	Estimated Slope (SE)	Coefficient of determination (r2)	p-value
Centre			
AKU (Ref.) concept	0.04 (0.585)	9.8x10-6	0.946
Menstrual cycle			
Normal (Ref.) abnormal	1.90 (0.524)	0.027	<0.001*
FSH level in the body			
Normal (Ref.) abnormal	0.57 (1.024)	0.001	0.578
LH level in the body			
Normal (Ref.) abnormal	1.56 (0.488)	0.021	0.002*
Prolactin level in the body			
Normal (Ref.) abnormal	0.29 (0.545)	0.001	0.600
Hirsutism			
Normal (Ref.) abnormal	2.284(0.674)	0.002	0.036*
Family history of diabetes			
Normal (Ref.) abnormal	2.362(0.676)	0.001	0.021*
Total sampled (n)		476	

*Women with BMI of more than 25, i.e. 476, are included for variate analysis.

Table III: The association of different factors with BMI at multivariable level.

Characteristic	Estimated adjusted slope (SE)	p-value
Constant (intercept)	24.38 (0.509)	-
Centre		
AKU (Ref.) concept	-0.38 (0.550)	0.485
Menstrual cycle		
Normal (Ref.) abnormal	1.68 (0.499)	0.001*
LH level in the body		
Normal (Ref.) abnormal	1.16 (0.464)	0.013*
Hirsutism		
Normal (Ref.) abnormal	2.484(0.774)	0.002*
Family history of diabetes		
Normal (Ref.) abnormal	2.962(0.776)	<0.001*
F-Statistic	17.863 (p-value<0.001)*	
Total sampled (n)	476	

*Women with BMI of more than 25, i.e. 476, are included for variate analysis.

DISCUSSION

In this study, the clinical symptomatology, biochemical and ultrasonographic features of infertile patient with PCOS were evaluated. An effort was made to compare the severity of clinical, biochemical features with other investigating counterparts from the west.[10-12] One of the major difficulties in the analysis of PCOS is the great variability in clinical and biological manifestations of this condition. The spectrum of this syndrome ranges from infertility as a result of chronic anovulation and menstrual irregularities such as amenorrhea or oligomenorrhea, apple type obesity and certain dermatological manifestations such as alopecia, acne or hirsutism as a result of hyperandrogenism.[9]

Most of the research to determine the ethnic, demographic, epidemiologic, and metabolic derangements of PCOS has been performed in the women of western region. The frequency of PCOS in infertile patients, visiting the study centres was comparable to the rates mentioned from infertility centers in Britain and United States i.e. 20-25%.[8,9] The diagnostic criterias used to identify the PCOS were according to Consensus Opinion of Rotterdam 2003. Study results revealed a high frequency of obesity, hyperinsulinemia, and tonic LH levels in this group of patients compared to the rest of studies.[10-12] The WHO global data based on obesity and BMI in adults from different ethnic groups has recently redefined obesity in South Asian women: a BMI > 25 is regarded as class I obesity which is considered equivalent to BMI > 30 for Caucasian women.[5]

PCOS is a disorder in which an association exists between insulin resistance and altered ovarian function. The pathophysiology of PCOS has been explained by an insulin receptor-mediated stimulation of steroidogenesis in the ovary.[13] PCOS is most of the time co-existent with hyperinsulinemia or insulin resistance, which is the key factor for aggravation of ovulation dysfunction and metabolic derangements.[8,9] Insulin-resistant states are helpful to explain the ovarian dysfunction observed in women with type II diabetes mellitus, obesity, insulin resistance syndrome and PCOS. In this study, the infertile women with PCOS who were diabetic and had impaired glucose tolerance had more severe symptomatology of oligomenorrhea, hirsutism, tonic LH and hyperinsulinemia.[13] When women with type II diabetes and impaired glucose tolerance were evaluated for the presence of PCOS, 45-50% of them were found to have PCOS compared to the controls of non-diabetic women.[13-15]

It has been demonstrated in various studies that hyperinsulinemia and insulin resistance are independent of body weight but worsened by obesity.[6,15] Thus, a pregnancy in these PCOS patients is an additional provocating risk factor for impaired carbohydrate metabolism and placental vascular insufficiency.[15] In this study, the subjects were infertile women with PCOS, identifying their extent of metabolic problems would aid in counseling, further evaluation and management. The significant differences in insulin concentration and insulin sensitivity in South Asian women with PCOS when compared to their Caucasian and European counterparts, suggest a definite ethnic role.[5]

Although the role of hyperinsulinemia in hyperandrogenism and ovulatory dysfunction of PCOS appears most prominent in obese women, the response to insulin sensitizing agents in lean women suggest that this mechanism may be operative across a broad spectrum of patients with PCOS.[17] Studies have shown that 40% of women with PCOS have higher fasting insulin levels[15,16] but results of 508 patients of this study reveals much high rates of hyperinsulinemia i.e. 59%. It has been shown that there is an association of different groups of BMI ranging from 18-40 with the rate of cycle abnormalities, hirsutism, family history of diabetes mellitus, tonic LH levels,

extent of abnormal insulin levels and impaired glycemic controls. At univariate and multivariate analysis, a statistically significant difference of above mentioned changes was found in a group of women with BMI of over 30.

In this study, results of hypeinsulinemia were comparable with the results of Indian, Sri Lankan and a study done on South Asian immigrants in UK, which have shown the incidence of 55-60% in their respective studies.[5] The reasons could be genetic, ethnic and racial pre-disposition of insulin resistance in this population and also due to high rates of first degree marriages among families of Muslim population. These factors, most probably, have magnified the abnormal metabolic and clinical parameters of PCOS. In the Rotterdam's 2003 consensus, clinical hirsutism is one of the features of PCOS. In this study 52% of women with PCOS and infertility had varying degree of hirsutism but when a comparison was made with their LH and testosterone levels, it was not a statistically strong association. This suggests a high frequency of constitutional hirsutism in female population of this region.

Pregnancy carries considerable risk for women who are obese, and have hyperinsulinemia. This is due to increased chances of congenital anomalies (neural tube and cardiac defects), miscarriages, gestational diabetes, preeclampsia, pregnancy induced hypertension and problems during delivery.[18-20]

Pregnancy exacerbates any underlying insulin resistance and, as a result, women with PCOS having obesity and pre-existing hypeinsulinemia are at risk of carrying all the above mentioned complications.[21,22] Confidential enquiry of maternal deaths in England and Wales revealed that out of 261 maternal mortalities, 35% were morbidly obese having a BMI of > 35.[20]

Infact studies of this nature will be helpful to know the burden of disease and its associated complications. Moreover, it will aid to counsel these women and establish guidelines according to the regional burden of disease and the resources available. Counseling should be directed to reduce a weight, as studies have shown an improved endocrine profile, menstrual cycle, the rate of ovulation and the likelihood of successful pregnancy in women with enthusiastic reduction of at least 10% of body weight.[16] National guidelines in the United Kingdom for managing overweight women with PCOS, advise weight loss, preferably to BMI of less than 30 before starting drugs for ovarian stimulation.[21] The obvious question is should this rule to be applied on women with BMI of >25 from South Asian region? (WHO defines obesity as BMI > 25 in Asian population?)

Conclusion

A significant high rate of obesity and hyperinsulinemia has been observed in a studied group of infertile women with PCOS from these centers. It enables the treating clinician to anticipate the burden of metabolic complications of this syndrome while treating infertility and thereafter in pregnancy.

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