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Original Article

Polycystic Ovary Syndrome Confers Additional Hormonal Level Abnormalities: A Study in Tertiary Care Hospital on Bengali Obese Women

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Abstract

Introduction: Polycystic ovary syndrome (PCOS) is one of the most frequently encountered endocrine disorders in women of reproductive age. Adiposity plays a crucial role in PCOS and influences the clinical and endocrine features in many women with this condition.

Purpose: This aim of the study was to compare hormonal abnormalities in women with obese Bengali PCOS cases attending in a government hospital with body mass index (BMI) matched women without PCOS in West Bengal.

Methods: A total of 75 obese PCOS patients (ethnic Bengali) were recruited and 75 BMI matched control were taken, and PCOS was diagnosis according to the Rotterdam criteria (2003). Serum follicle stimulating hormone (FSH), luteinizing hormone (LH), FSH/LH ratio, plasma glucose, insulin glucose/insulin ratio, and serum total testosterone were measured.

Results: Study serum LH, LH/FSH ratio, serum fasting insulin, and serum total testosterone levels were higher, and serum insulin/glucose ratio is lower than their obese BMI-matched controls.

Conclusion: Polycystic ovary syndrome confers additional hormonal level abnormalities in Bengali obese PCOS women in West Bengal.

Key words: Insulin resistance, Obese, Polycystic ovary syndrome

INTRODUCTION

Polycystic ovary syndrome refers to a multi-system reproductive-metabolical disorder, and it is characterized by irregular menstruation, hyperandrogenism, and polycystic ovarian morphology. It is most common endocrine disorder in women of reproductive age, and its prevalence of polycystic ovarian syndrome (PCOS) is 4–12%.[1,2] Menstrual irregularity is characterized by irregular, infrequent, or absent menstrual bleeding.

PCOS is associated with obesity whether obesity causes PCOS or PCOS cause obesity is not clearly understood.

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Obesity is a common finding in women with PCOS. Many women with PCOS (between 38% and 88%) are overweight[3,4] the relationship between PCOS and obesity is complex, not well understood.

In obesity increased androgen production has been reported especially in women with upper-body obesity. Androgens play an important role in the determination of body composition. Chronic exposure to higher testosterone levels in women with PCOS may modify body fat distribution in these women. Support for this hypothesis is provided by studies of androgen administration in non-obese female to male transsexuals that lead to increases in visceral fat and adversely impact insulin sensitivity.[5] There is considerable variation in body fat and fat-free mass among various ethnic groups. Many studies have suggested that Asian populations have more body fat relative to weight (but not in absolute terms) than white populations.

In Indians, receiver operating characteristic curve analysis showed a low sensitivity and negative predictive value of the

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conventional cutoff of body mass index (BMI) (25 kg/m^2) in identifications of overweight compared with a cutoff value based on percentage body fat, and this BMI cutoff resulted in substantial misclassification (approximately 25% of men and approximately 70% of women).[6]

Obesity also causes the metabolic syndrome, which includes insulin resistance, type 2 diabetes mellitus. PCOS is also associated with insulin resistant.[7,8] The presence of a defect in insulin action in PCOS has been described by many authors, but no clear study was done on Bengali women and few studies done in India to see the effect of obesity on PCOS with contrasting reports.[9] Hence, the aim of the study is whether obesity has an additive effect on hormonal abnormalities such as insulin resistant or hyperandrogenism in PCOS cases or not.

Aims and Objectives

This aim of the study was to compare hormonal abnormalities in women with obese PCOS cases with BMI-matched women without PCOS in West Bengal so we can understand pathophysiology of PCOS better and improve management of PCOS.

METHODS

Study Design

A community-based case–control study was conducted from 2007 to 2011 among women aged 20–35 years who were permanent residents of West Bengal. PCOS patients with BMI (≥30 <35 kg/m^2) were recruited from the OPD clinics of the Department of Gynaecology in Institute of Postgraduate Medical Education and Research (IPGME and R), Kolkata. This clinical study was approved by the Institutional Ethics Committee (IPGME and R), Kolkata. All of the participants signed informed consent to be included in the study.

Sample Size

A total of 75 obese PCOS patients between age group between 20 and 35 years were recruited. Healthy age-matched controls (n = 75) women without PCOS and matched age, BMI recruited.

- Selection of cases and control from sources
- Operational definition
- Amenorrhea.

A patient who has been menstruating, the absence of periods for at least 3 of the previous cycle intervals or 6 months of amenorrhea.

Oligomenorrhea

Infrequent menstrual cycles at interval of more than 35 days. It is an indirect marker for anovulation in the absence of any hormonal evidence.

- Obese subjects
- Obese: BMI 30–35 kg/m^2
- Clinical hyperandrogenism
- Hirsutism, acne or alopecia.

Polycystic Ovaries

Polycystic ovaries was defined having follicles 2-9mm in diameter and ≥12 in number or ovarian volume ≥ 10 cm^3 in one or both ovaries on transabdominal pelvic ultrasonography (USG). There should be no dominant follicle with size greater than 10 mm in diameter.

Participant selected was undergone three stages of operation.

Stage I - questionnaire:

Administration of the questionnaire "Probable cases" and "probable controls" were identified during the cross-sectional survey.

A probable case: A "probable case" was defined as a woman with symptoms suggestive of PCOS (i.e., oligo/amenorrhea/ or clinical features of hyperandrogenism) as defined above.

A probable control: A "probable control" was defined as a woman with regular menses and no clinical features of hyperandrogenism. Probable control group matched for age and BMI with probable PCOS cases were selected. A detailed history of taking drugs was elucidated and all participants who were on oral contraceptive pills, oral hypoglycemic agents and antithyroid drugs were excluded from study. Desired number of control was selected.

They were then selected for Stage 2 examination.

Stage 2 - clinical examination and biochemical investigations.

Selected women were examined for the presence of hirsutism, acne, or alopecia. Hirsutism was routinely graded by two physicians independently using the common modified Ferriman -Gallway (FG) score. If the FG score differed by more than 2, re-evaluation by a third physician was done, and median values were used. Nine areas were examined - upper lip, chin, chest, upper abdomen, lower abdomen, upper back, lower back, thighs, and upper arms. Each area is scored 0–4, resulting in maximum score 36. Hirsutism was diagnosed when a score above 5 was evaluated.

Biochemical Investigations

Venous blood (5 mL) was drawn from both probable cases and probable controls. Blood samples were taken during the 3rd day of the menstrual cycle. Hemolyzed sera were discarded. Serum total testosterone was measured to diagnose biochemical

Table 1: Age and BMI of the study population

Age/BMI	Obese PCOS *n*=75	Obese controls *n*=75
Age in years		
Range	20–35	20–35
Mean	27.8	28.65
SD	3.4	2.7
BMI kg/m^2		
Range	30–35	30–35
Mean	31.08	30.98
SD	1.76	1.32

SD: Standard deviation, BMI: Body mass index, PCOS: Polycystic ovary syndrome

Table 2: Hormonal status of obese individuals with PCOS (BMI ≥30 <35 kg/m^2) in comparison to BMI match controls and their statical significance

Hormones	Mean±SD		*P* value, *P*, 0.05 significant
	Cases, *n*=75	Controls, *n*=75	
LH, miu/mL	7.6±2.23	4.094±1.2	*P*<0.01, significant
FSH, miu/mL	4.35±1.78	4.58±1.26	*P*=0.642, not significant
LH/FSH ratio	1.864±0.4	0.91±0.282	*P*<0.01, significant
Glucose, mg/dL	92±11.72	87±12.11	*P*=0.235, not significant
Insulin, uiu/mL	27.56±11.37	20.2±10.36	*P*<0.01, significant
Glucose/insulin ratio	4±2.36	5.58±2.48	*P*<0.01, significant
Total testosterone, ng/dL	99.07±34.15	18.27±11.42	*P*<0.01, significant

SD: Standard deviation, PCOS: Polycystic ovary syndrome, n: Number of cases, LH: Luteinizing hormone, FSH: Follicle stimulating hormone, BMI: Body mass index, PCOS: Polycystic ovary syndrome

Table 3: Correlation between BMI and another dependent variable in cases (*P*<0.05 is significant) *n*=75

Dependent variable	*r* value	*P* value
LH	−0.389	<0.01
FSH	−0.122	>0.1 NS
LH/FSH	−0.399	<0.01
Glucose	0.07	>0.05 NS
Insulin	0.545	<0.01
Glucose/insulin ratio	−0.38	<0.01
Testosterone	0.302	<0.01

NS: Not significant, LH: Luteinizing hormone, FSH: Follicle stimulating hormone, BMI: Body mass index

evidence of androgen excess or hyperandrogenemia. Hyperandrogenemia was diagnosed when serum total testosterone level was greater than 55 ng/dl.Upper normal level of serum total testosterone level was 55ng/dl mentioned by kit supplier. Kit was supplied by Radio-pharmaceutical and isotope technology, BARC, Mumbai.

Stage 3 - ultrasound scanning.

Pelvic ultrasound scanning on women identified as probable cases and probable controls. Polycystic ovaries on ultrasonography (USG) - multiple small follicles (>10–12) and (2–9 mm in diameter) tightly spaced along the periphery of the ovary.

Inclusion Criteria of Cases

The diagnostic criteria for PCOS were based on the unified standards formulated by the Rotterdam International Conference in 2003. Patients with any 2 of the following 3 conditions were diagnosed with PCOS: (1) Infrequent ovulation or anovulation; (2) hyperandrogenism or clinical manifestations of high blood androgen; (3) polycystic ovaries on USG - multiple small follicles (>10–12) and (2–9 mm in diameter) tightly spaced along the periphery of the ovary.

Exclusion criteria of cases included thyroid dysfunction, hyperprolactinemia, congenital adrenal hyperplasia, androgen-secreting tumors, Cushing syndrome, and other diseases.[10]

Inclusion Criteria of Controls

Patients in the control groups exhibited normal menstruation, no clinical or biochemical signs of hyperandrogenism, normal ovaries as defined by ultrasonic examination and no family history of PCOS and they should be, age and BMI matched with cases.

Participants on OCP or conceived were excluded from the study. Chronic kidney disease, liver disease, cancer patients were also excluded from the study.

75 obese PCOS patients between age group between 20 and 35 years were recruited. Healthy age-matched controls (n = 75) women without PCOS and matched age, BMI recruited.

Other Biochemical Parameters

Blood samples were taken during the 3rd day of the menstrual cycle. Hemolyzed sera were discarded. All assays were completed within 3 days. Serum glucose estimation done by GOD-POD with kit manufactured by monozyme India limited, Secunderabad, insulin by radioimmunoassay with module supplied by Radio Pharmaceutical and Isotope Technology, Mumbai. Total serum follicle stimulating hormone (FSH) and luteinizing hormone (LH) were also measured.

Statistical Analysis

Statistical analysis was done by descriptive statistics in statistical analysis were carried out using Microsoft excel 2003. Descriptive statistics are presented as the mean ± standard deviation for normally-distributed variables. Student t-test was used to compare variables with normal distribution and $P < 0.05$ was considered significant.

RESULTS

Table 1 denotes basic characteristics of study groups. Difference between mean age and BMI of 75 obese PCOS cases and mean age obese controls are not statistically significant.

In Table 2 biochemical parameters were compared between PCOS and control group. In PCOS group serum LH level is (7.6 ± 2.33 vs. 4.094 ± 1.198 miu/mL, $P < 0.0001$) higher than control. In PCOS group, serum FSH level is unaltered in relation to controls (4.35 ± 1.78 vs. 4.578 ± 1.26 miu/mL, $P = 0.642$). In PCOS group, serum LH/FSH ratio level is higher than control (1.864 ± 0.4 vs. 0.913 ± 0.282, $P < 0.001$). In PCOS group, serum fasting glucose level is unaltered in relation to control (87.4 ± 11.72 mg/dL vs. 92 ± 12.11 mg/dL, $P = 0.255$). In PCOS group, serum fasting insulin level is higher than control (27.56 ± 11.37 uIU/mL vs. 20.2 ± 10.36 ulU/mL, $P = 0.03$). PCOS group shows LOWER serum glucose/insulin ratio than control (4 ± 2.36 vs. 5.58 ± 2.48, $P = 0.044$). In PCOS group serum total testosterone level is higher than control (99.07 ± 34.15 ng/dL vs. 18.27 ± 11.42 ng/dL, $P < 0.001$).

Table 3 denotes Correlation between BMI and other dependent variables in PCOS cases. BMI is negatively correlated with serum LH ($r = -0.389$, $P < 0.01$) serum LH/FSH ($r = -0.399$, $P < 0.01$) serum fasting insulin/glucose ($r = -0.38$, $P < 0.01$). BMI has no relation with serum FSH ($r = -0.122$, $P > 0.1$) and plasma glucose ($r = -0.07$, >0.05). Serum fasting insulin is positively correlated ($r = -0.545$, $P < 0.01$) with BMI.

DISCUSSION

In the present study, we evaluated the clinical and biochemical characteristics of women with polycystic ovary syndrome in West Bengal. To the best of our knowledge, this study is among few reports about clinical and biochemical features of PCOS in West Bengal. Multiple hormonal and metabolic abnormalities in PCOS are (1) gonadotrophin abnormality, (2) insulin resistance, and (3) sex steroid abnormalities.

Gonadotrophin Abnormality

In our study serum LH, LH/FSH ratio was higher than obese control. Elevated LH/FSH was found only 45% of obese cases. LH was negatively correlated ($r = 0.389$, $P < 0.01$) and LH/FSH was also negatively correlated ($r = 0.399$, $P < 0.01$). In our study, BMI is inversely correlated with serum LH concentration. In one study by Fulghesu *et al.* observed that altered basal concentration of serum LH was present on the obese patient, but no relation with BMI is present. Negative correlation between BMI and LH which has been found by some authors suggest that leptin acting on a hypothalamic or pituitary level may dampen LH secretion in the obese state. Moreover, increased opioid tone and reduced dopaminergic tone have also described.

Insulin Resistance

Contrasting data exist about the importance of obesity in determining the insulin resistance in PCOS. Dunaif *et al.* demonstrated that insulin resistance in PCOS is associated with a unique cellular glucose transport defect independent of, but amplified by obesity. Earlier several articles also reported reduced insulin sensitivity in lean PCOS subjects[11] whereas other authors reported that insulin resistance was entirely related to the adiposity in obese PCOS women and that hyperinsulinemia was secondary to other factors in lean patients (Mahabeer *et al.*, 1990p; Siegel *et al.,* 1990, Ciampelli *et al.,* 1997).[12] It was demonstrated that the reduced response of glucose transport to a given concentration of insulin was greater in obese than in non-obese PCOS patients. Silfen 2003, observed that fasting insulin was significantly increased in the obese compared with the non-obese PCOS subjects. The obese adolescents with PCOS also demonstrated a greater insulin response to an oral glucose load compared with the non-obese PCOS group. All measures of insulin sensitivity, the I/G ratio was significantly reduced in the obese group compared with the non-obese PCOS group. The obese PCOS subjects compared with the obese controls, no statistically significant differences in glucose- and insulin-related parameters or the measures of insulin sensitivity were detected between the two obese groups. Hence, this study does not show an additive response. In another study, obese patients with PCOS have been shown to exhibit significantly more severe insulin resistance than obese women.[13]

The bulk of these observations indicate that hyperinsulinemia in obese PCOS subjects is due to two factors: One characteristic of PCOS and the other obesity-specific. The mechanisms by which obesity may induce an insulin-resistance is enlargement of adipose tissue mass, in particular of the visceral fat depot, increases the availability of several metabolites, i.e. free fatty acids, lactate, etc., which are able to affect the secretion and the metabolism of insulin as well as its peripheral action.[14] Insulin resistance in obesity can also be related to tumor necrosis factor (TNF-alpha) and leptin, both products of adipose tissue. TNF - mediates serine phosphorylation of IRS-1, which has been shown to interfere with the action of both insulin and IGF-I, by inhibiting insulin.

BMI does not accurately predict overweight in Asian Indians. Fat mass is high, so the endocrine response is exaggerated in obese PCOS cases. Further study is needed.

Sex Steroid Abnormality

PCOS patients with higher BMI seemed more likely to suffer hyperandrogenism or to exhibit the clinical signs of androgen excess.[15] That is consistent with our study.

CONCLUSIONS

PCOS has been one of the most explored and controversial areas in reproductive medicine. It is a subject of continuous studies concerning both pathogenesis, diagnostics methods, and therapeutic procedures. It is associated with following endocrine abnormalities.

- Serum LH in obese PCOS is higher obese control while serum FSH level between two group. LH and LH/FSH ratio are positively correlated with BMI.
- Serum fasting insulin and total testosterone are higher in obese PCOS than obese control From above data, we can conclude PCOS has an additive effect on endocrine abnormalities than obese control in Bengali women. PCOS *per se* has evolved as a risk factor for endocrinal derangements irrespective of the BMI status.

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