RESEARCH ARTICLE

Comparison of Endocrine and Metabolic Profile of Obese and Lean PCOS Women with Infertility

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Abstract

Background: Polycystic ovary syndrome (PCOS) has been associated with endocrine and metabolic abnormalities. The study's objective was to compare the endocrine and metabolic parameters of lean and obese PCOS women with infertility.

Materials and methods: After satisfying the inclusion and exclusion criteria, infertile women with PCOS were enrolled in the study. Women were divided into two groups according to their body mass index (BMI); group I with BMI <23 kg/m^2 (lean and underweight) and group II with BMI ≥ 23 kg/m^2 (obese and overweight) according to the Indian Council of Medical Research (ICMR) guidelines. Physical characteristics like the presence of acne, hirsutism, acanthosis nigricans (AN), and waist–hip ratio (WHR) were noted in all. The endocrine profile included serum levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), anti-Müllerian hormone (AMH), thyroid-stimulating hormone, prolactin, estradiol, and testosterone, while the metabolic profile included lipid profile, oral glucose tolerance test (OGTT) (fasting and 2 hours), fasting insulin.

Results: A total of 80 women were enrolled. Obese PCOS had hypertriglyceridemia (15% vs 0% in lean group, $p = 0.011$) and hypercholesterolemia (20% vs 2.5%, $p = 0.011$). AN, acne, hirsutism, hormonal profile (LH/FSH ratio, AMH, serum testosterone), fasting insulin, and OGTT were similar in both groups.

Conclusion: Increased BMI in PCOS women is associated with increased WHR and altered lipid profile with no difference in endocrine parameters.

Keywords: Metabolic syndrome, Obesity, Polycystic ovary syndrome.

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Introduction

The PCOS is the commonest endocrine disorder in reproductive-aged women, with a prevalence of 6–10%.[1] It is a leading cause of infertility and is also associated with an increased risk of metabolic syndrome, diabetes mellitus type II, cardiovascular disease, and endometrial cancer. PCOS affects 30% of infertile women.[1] A majority (60%) of women with PCOS have an above-average or high BMI, insulin resistance (IR), menstrual symptoms, and the typical male pattern of baldness, acne, and hirsutism. Although PCOS is commonly associated with obesity, a lean phenotype also exists.

There are different phenotypes of PCOS depending on hyperandrogenism (HA), anovulation, and polycystic morphology on ultrasound. In addition, the pathology of PCOS is related to IR and hyperinsulinemia. Previous studies in India by Majumdar and Singh[2] have shown that IR, acne, and hirsutism are more often seen in obese PCOS and women with hyperandrogenic phenotypes. Lean women with PCOS, on the other hand, have different phenotypic, metabolic, hematologic, and neurologic characteristics than obese participants with PCOS. Therefore, it is hypothesized that obese and lean PCOS women may have different morphology, metabolic, and endocrine characteristics, although they have similar dysfunction. Hence, it is imperative to understand the difference between the two subgroups to plan an appropriate management approach.

Materials and Methods

Women visiting the infertility clinic in the Department of Obstetrics and Gynecology, King George's Medical University, Lucknow, Uttar Pradesh, India, with the diagnosis of PCOS according to Rotterdam's criteria were included in the study over a period of 1 year from July 2018 to 2019. The patient who were not willing to participate, known causes of HA, primary hypothalamic amenorrhea, primary ovarian failure, thyroid disease, and prolactin disorder were excluded. The study was ethically conducted in accordance with the Declaration of Helsinki. Ethical approval was obtained prior to the commencement of the study (90th ECM/II B-Thesis/P36).

The women enrolled underwent an assessment of height, weight, and BMI. Women were classified into two groups according to BMI group I with BMI <23 kg/m^2 (lean and underweight) and group II with BMI ≥23 kg/m^2 (obese and overweight) according to ICMR guidelines. A detailed menstrual history pattern was taken, and cycles at >35 days interval were classified as oligomenorrhea. These women were compared with reference to waist hip ratio (WHR). Circumference of the waist was measured at the level of the iliac crest after a normal expiration, and hip circumference was taken at the widest point around the buttocks. Abnormal WHC was taken as ≥0.8. Signs of clinical HA like acne, hirsutism, and AN were

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noted. Acne is defined as the presence of comedones, papules, nodules, cysts, and scars on the face, neck, and upper truck. The presence of only scars was not included. Although acne has no universally accepted visual assessment tool [European Society of Human Reproduction and Embryology (ESHRE 2018)], in this study, ≥10 facial lesions were taken as a presence of acne. These lesions were comedones, papules, pustules, nodules, abscesses, or cysts. Hirsutism, another feature of clinical HA, is defined as an increase in terminal hair growth in the androgen-dependent area of the body (upper lip, chin, mid-chest, abdomen, and back). The most common visual assessment score is the modified Ferriman–Gallwey (mFG) score, which was used for an objective evaluation of hirsutism. mFG score with a level ≥4–6 indicates hirsutism, as per ESHRE 2018. In this study, FG score, ≥6 was taken as hirsutism. AN is characterized by dark, coarse, and thickened skin with a velvety texture, being symmetrically distributed on the neck, the axilla, antecubital and popliteal fossa, and groin folds, histopathologically characterized by papillomatosis and hyperkeratosis of the skin. The endocrine evaluation was done by measuring LH, FSH, total testosterone, and AMH on day 2/3 of the menstrual cycle. Around 5 mL of venous blood sample was drawn, centrifuged at 200 gm for 10 minutes, and sera were separated and stored at –20°C, and hormonal assays were performed.

For metabolic parameters, samples were taken after fasting for at least 8 hours. Women if not fasting were called on another day with at least 8 hours of fasting; 5 mL of venous blood was drawn for fasting blood sugars, fasting insulin, fasting lipid profile [triglycerides, total cholesterol, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) levels]. For OGTT, 75 gm glucose was given in 200 mL of water, and she was asked to remain seated comfortably in the waiting area. A venous sample was drawn for postprandial (PP) values 2 hours following it. Fasting blood sugar ≥126 mg/dL and 2-hour PP ≥200 mg/dL were taken as diabetes, whereas fasting blood sugar 110–125 mg/dL and 2-hour PP 140–199 mg/dL were taken as impaired OGTT.

Women were also classified into four phenotypes. HA + oligo/anovulation (OA) + PO at ultrasonogram [Polycystic ovarian morphology (PCOM)], that is, classical called phenotype A; HA+OA-phenotype B; HA+PCOM-phenotype C; OA+PCOM-phenotype D.

The results are presented in frequencies, percentages, and mean ± standard deviation. The Chi-squared test was used to compare the categorical variables and the unpaired *t*-test to compare the continuous variables. The *p*-value <0.05 was considered significant. All the analysis was carried out on the SPSS software 20 version (Chicago, Inc., United States of America).

Results

There were 80 women enrolled in the study—40 women in each group. Among the clinical symptoms studied, oligomenorrhea (cycle interval >35 days) was the most typical form of menstrual pattern in PCOS women, although such menstrual patterns did not relate to BMI (62.5% in lean vs 75% in obese PCOS; $p = 0.228$).

There was no difference in physical parameters like acne, hirsutism, or AN in both groups, as shown in Table 1. Obese women had more WHR as compared to lean women ($p = 0.044$). It was hence noted that central obesity was more in the higher BMI group. Table 2 shows the endocrine and metabolic parameters in both groups. Obese women had more hypertriglyceridemia ($p = 0.011$) and hypercholesterolemia ($p = 0.013$) than lean women. The rest of the endocrine parameters like blood sugars, insulin levels, AMH levels, and LH/FSH ratio were similar in both groups. The number of women with high serum testosterone levels (≥3.5 nmol/L) was similar in both the groups; 35% in the lean group vs 22.5% in the obese group—$p = 0.217$. Women were classified according to the phenotypes, and it was seen that of 80 women, 41 women (51.2%) were of phenotype A, five (6%) of phenotype B, 24 (30%) of phenotype C, and 10 (12.5%) were of phenotype D. There was no difference in phenotype distribution of women in both the groups (Chi-square 5.2756 and *p*-value = 0.153).

Discussion

Polycystic ovary syndrome is one of the commonest disorders in the reproductive age-group presenting with an array of clinical, metabolic, and endocrine profiles. This study showed that WHR, triglycerides, and total cholesterol levels were significantly more in obese PCOS women. There was no difference in clinical hyperandrogenic features like acne, hirsutism, and endocrine profile among obese and lean women with PCOS. Insulin levels and glucose tolerance tests were similar in both groups.

Considering the four phenotypes known for PCOS, the prevalence of phenotype A, that is, classical phenotype (HA+PCOM+OA; 51.25%), was maximum, followed by phenotype C (HA+PCOM; 30%), phenotype D (OA+PCOM; 12.50%), and phenotype B (HA+OA; 6.25%). Similar observations were made in a study conducted by Kar et al.[3] The largest group was PCOS complete (65.6%), which contrasts with Pikee et al.[4] where the prevalence of phenotype C was maximum (31.28%).

The majority of obese PCOS women (65%) had WHR ≥ 0.85 ($p = 0.04$) compared to lean PCOS (42.5%) in this study. Clinical HA, a hallmark of PCOS, includes acne, alopecia, and hirsutism. In this study, 45% of lean women with PCOS and 50% of obese women presented with acne, and it was not associated with BMI, while Majumdar and Singh[2] found more acne in obese women with PCOS. Among the women enrolled, 92.5% lean PCOS women and 95.0% obese PCOS women presented with features of hirsutism, and there was no difference noted with BMI. On the contrary, Khomami et al.[5] suggested that hirsutism is more common in obese women. AN has been postulated as a possible marker of hyperinsulinemia and a harbinger of diabetes. In a

Table 1: Comparison of physical profiles in both the groups

Parameters	*Group I (lean and BMI <23 kg/m²)*	*Group II (obese and BMI ≥23 kg/m²)*	*Chi-square*	*p-values*
WHR >0.85	17 (42.5%)	26 (65%)	4.07	0.044
Acne[a]	18 (45%)	20 (50%)	0.20	0.654
AN	15 (37.5%)	23 (57.5%)	3.21	0.073
Hirsutism[b]	37 (92.5%)	38 (95%)	0.2133	0.644

[a]In this study, ≥10 facial lesions were taken as the presence of acne. These lesions were Comedones, papules, pustules, nodules abscesses, or cysts. The presence of only scars was not included; [b](mFG) score ≥6 was used to assess hirsutism

Table 2: Comparison of endocrine and metabolic profiles in both the groups

Parameters	*Group I (lean and BMI <23 kg/m²)*	*Group II (obese and BMI ≥23 kg/m²)*	*Chi-square*	*p-values*
LH/FSH >1	19 (47.5%)	13 (32.5%)	1.88	0.171
AMH >3.5 ng/mL	36 (90%)	28 (70%)	5.57	0.062
S. testosterone levels ≥3.5 nmol/L	14 (35%)	9 (22.5%)	1.5256	0.217
Fasting insulin ≥25 IU/L	4 (10%)	3 (7.5%)	0.16	0.692
S. triglyceride ≥150	0 (0%)	6 (15%)	6.49	**0.011***
S. cholesterol ≥200	1 (2.5%)	8 (20%)	6.14	**0.013***
S. LDL ≥160	0 (0%)	0 (0%)	–	–
S. HDL <50	12 (30%)	15 (37.5%)	0.50	0.478
Fasting blood sugar ≥126 mg/dL	1 (2.5%)	1 (2.5%)	0	1
2 hour PP OGTT ≥200 mg/dL	0 (0%)	0 (0%)	–	–
2 hour PP OGTT 140–199 mg/dL	3 (7.5%)	8 (20%)	2.635	0.1045

*p <0.05

prospective longitudinal study by G et al.,[6] AN was observed in PCOS women with greater BMI and WHR. The present study had a similar observation where AN was more often seen in obese PCOS women than in lean PCOS, however, with no statistical significance. Overall, there are contradictory reports in the literature to suggest the association of clinical features of HA, including acne and hirsutism, with BMI. Saxena et al. In the Indian population did not find any difference in hirsutism, and acne in both groups, whereas Majumdar and Singh found significantly more clinical features of HA in obese PCOS than in lean PCOS[7].

Endocrine Profile

Abnormality of the hypothalamic-pituitary-ovarian axis has been implicated in the pathophysiology of PCOS. Estrogen secreted from ovaries leads to abnormal feedback leading to a rise in LH levels, thereby increasing LH/FSH ratio in PCOS women compared to healthy controls. LH/FSH ratio is increased to two or three. Most studies suggest that LH levels and LH to FSH ratio are higher in PCOS women than in control, but the absence does not rule out PCOS diagnosis. A study by Saadia et al. in Saudi Arabia did not find any difference between BMI and LH/FSH ratio in women with PCOS.[8] Similarly, Mc Manus et al., in a retrospective study on adolescent PCOS, also found that obese PCOS had similar levels of testosterone, dehydroepiandrosterone sulfate (DHEAS), LH, and FSH.[9] On the other hand, Lal et al. found a significant difference between obese and lean PCOS regarding LH/FSH ratio.[10] On the contrary, in a study by Khan et al., it was seen that LH levels and androgen (DHEAS) levels were higher in lean PCOS than in obese.[11] The findings were similar to this study, in which LH levels were higher in lean PCOS women but not statistically significant.

An AMH produced by granulosa cells of small antral follicles has recently been proposed as a marker for PCOS. This study showed that AMH levels in PCOS women did not vary with BMI. In a study by Cassar et al., AMH levels were increased in PCOS women ($p <$ 0.001) irrespective of BMI, however, this increase was associated with testosterone levels rather than IR or gonadotrophins.[12] However, it disagrees with the results of the Kriseman et al. study, which showed that there was a significant association between BMI and AMH (p < 0.01) in PCOS women.[13]

Biochemical HA in PCOS is demonstrated by increased serum testosterone and serum androstenedione levels. Measurement of testosterone concentration is the most helpful test to detect HA, as done in this study. However, the present study did not show any association of S. testosterone levels with BMI.

Metabolic Profile

Insulin resistance (IR) is recognized to be an integral feature of PCOS. All women with PCOS seem to have some degree of IR compared with their healthy counterparts.[14] However, there have been some studies, particularly among European women with normal or modestly increased BMI, who have shown normal insulin sensitivity.[15] In the majority of studies, prevalence falls between 44 and 70%; nevertheless, study populations vary considerably in terms of anthropometric, demographic, clinical, and endocrine features. In a literature search by Goyal et al. to understand metabolic alterations in lean women with PCOS from 2000 to 2017, it was found that IR in lean PCOS ranges from 6 to 22%.[16] Kar et al. in the Indian population found a direct association between increased WHR with normal BMI and a high prevalence of diabetes.[3] Similarly, Saxena et al. in 2013 found abnormal glucose tolerance tests and deranged lipid profiles in obese women with PCOS.[7] The same results were found by Stovall et al.[17] and Majumdar and Singh.[2] where increased plasma glucose levels in obese PCOS women were; found compared to lean women with PCOS. Faloia et al. postulated that hyperinsulinemia was more pronounced in obese PCOS women with no metabolic derangement in lean PCOS women.[18] Obese PCOS women had more IR and a more marked dysregulation of insulin levels. A more pronounced alteration in the hypothalamic-pituitary-ovarian axis was found in nonobese PCOS women. Such results contrast with this study, which did not show any association between impaired glucose tolerance with BMI. A recent study conducted by Gholinezhad et al.[19] on 112 women showed that BMI had a significant straight correlation with IR ($p <$ 0.001).On the contrary, Cupisti et al. failed to find any difference in IR and lipid profiles with different phenotypes.[20] BMI, though showed a correlation with IR.

Layegh et al. compared a cross-sectional study and compared IR, endocrine and metabolic abnormalities between two groups based on BMI. There was no significant difference in the presence of IR in both groups ($p = 0.357$).[21] In the present study, no significant association was seen between IR and BMI however, levels of triglycerides and cholesterol were much higher in obese PCOS women.

Regarding the influence of BMI on lipid profile, Gholinezhad et al. showed a straight stronger correlation between triglycerides (p < 0.001) and LDL cholesterol ($p < 0.05$). HDL was lower in overweight

and obese women than lean PCO group ($p \leq 0.05$).[19] In most of the studies, the cutoff of BMI was taken as 25 kg/m^2. A study conducted by Faloia et al.[18] suggested that metabolic alterations were more significant in obese/overweight than in lean PCOS women. None of the lean subjects had any features of metabolic syndrome. Like previously conducted studies, this study also showed similar results; that is., PCOS women with BMI > 23 kg/m^2 had increased levels of triglyceride and cholesterol ($p = 0.011$ and $p = 0.013$, respectively).

The study has a small sample size, so it may lack sufficient power to differentiate the phenotype, endocrine, and metabolic profile of lean and obese PCOS women. The population chosen in this study were infertile women who presented with PCOS as it was convenient to recruit them and followup regularly. It is assumed that the findings of this study can be extrapolated to the adult population with PCOS who present in the general outpatient department with other complaints.

Conclusion

This prospective cross-sectional study concludes that android obesity, high triglyceride, and higher cholesterol levels are the only things that vary in obese and lean PCOS women. The rest of the physical, endocrinological, and metabolic profiles are found to be similar in both groups. A large multicentric study on Asian ethnicity should be conducted to understand the spectrum of endocrine and metabolic alterations in women with PCOS with different BMI. Weight control and yearly follow-up of lipid profiles must be done to prevent metabolic complications in obese women with PCOS.

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Ethical Approval

Ethical approval was obtained prior to commencement of study (90th ECM/II B-Thesis/P36).

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