Original article

Obesity in relation to clinical, endocrine and metabolic parameters in infertile women with polycystic ovary syndrome: the South Asian perspective

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Abstract

Background: Polycystic ovary syndrome (PCOS) affects 5-10% of reproductive age women and it is a common cause of infertility in young women. Most of the infertile women with PCOS are overweight or obese. Obesity or excess fat aggravates the endocrine and metabolic dysfunction in women with PCOS. Weight management is the first line measure advised to infertile PCOS women who are overweight or obese. The objective of the study was to explore the association of obesity with the clinical, endocrine and metabolic parameters in infertile women with polycystic ovary syndrome in Bangladesh. ***Methodology:*** This was a cross sectional study of 126 consecutive infertile women with polycystic ovary syndrome attending the Infertility unit of the Department of Obstetrics and Gynecology at Bangabandhu Sheikh Mujib Medical University from January 2017 to December 2017.Obesity groups were defined by BMI thresholds specific for the South Asian population. ***Results:*** The mean body mass index (BMI) was 26.58±3.18 kg/m^{2}and mean waist circumference was 91.07±9.5 cm. There was highly significant association of obesity with waist circumference and fasting insulin. BMI at or above 25kg/m^2 was significantly associated with acanthosis nigricans, hyperandrogenemia and hyperinsulinemia, whereas BMI at or more than 23kg/m^2 was significantly associated, in addition, with insulin resistance and metabolic syndrome. ***Conclusion:*** Obesity is associated with hyperandrogenemia, hyperinsulinemia, insulin resistance and metabolic syndrome in infertile women with polycystic ovary syndrome.

Keywords: infertility; obesity; insulin resistance; metabolic syndrome; polycystic ovary syndrome.

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Introduction

Infertility is a condition where the couple fails to reproduce despite regular conjugal life for at least one year. Infertility has profound psychosocial consequences for the 10-15% of couples who are affected with the condition. Polycystic ovary syndrome (PCOS) is a chronic endocrine disorder that affects 5-10% of women in reproductive age. PCOS is a principal cause of anovulation, the female factor for infertility. PCOS is characterized by menstrual abnormality due to anovulation, hyperandrogenemia manifested as hirsutism and acne and sonographic evidence of at least one enlarged polycystic ovary.[1] The possible mechanisms underlying this multifactorial disease include increased secretion of luteinizing hormone (LH) from hypothalamo-pituitary system and hyperinsulinemia due to insulin resistance. Both LH and insulin stimulate intra-ovarian androgen production. Insulin resistance decrease sex hormone binding globulin which in turn leads to enhanced levels of free testosterone and androgenic features like hirsutism and acne. There is arrest of follicular development leading to anovulation and polycystic ovary.[2]

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Most of the infertile women with PCOS are overweight or obese. The excess fat in the body aggravates insulin resistance and perpetuates the vicious cycle of anovulation and hyperandrogenism. There are in-consistent reports on the effects of excess fat on clinical and biochemical parameters in PCOS women. Some found higher prevalence of menstrual problems and hirsutism in obese PCOS women compared to normal weight while others found no difference.[3] We advise weight loss in infertile women because it can minimize the menstrual abnormality and induce ovulation by itself. It would be interesting to explore the differences between the characteristics of obese and non-obese women with infertility and PCOS. The findings are likely to add meaningful dimension to the counseling of infertile women regarding the importance of lifestyle changes for weight loss. So the objective of this study was to compare the clinical, endocrine and metabolic parameters between the obese and non-obese infertile women with PCOS.

Methodology

This was a cross sectional study of 126 infertile women with polycystic ovary syndrome who attended the Infertility unit of the Department of Obstetrics and Gynecology at Bangabandhu Sheikh Mujib Medical University sequentially in the period from January 2017 to December 2017. All the women who consented for study participation were recruited at first visit. They were not exposed to metformin or the lifestyle modification in the prior three months. Being infertile women they were not exposed to oral contraceptive pills for cycle regulation or hirsutism.

The women were evaluated by clinical history, examination, TVS (transvaginal sonogram) and fasting blood samples for endocrine and metabolic parameters. Eligibility criteria were infertile women with age range 15-40 years and any two of the following: i) infrequent menstruation (cycle length >35 days), ii) hirsutism with modified Ferriman Galway score ≥8, iii) at least one enlarged (>10cm^3) polycystic ovary at TVS.

Anthropometric measurements:

Body mass index (BMI): Weight was measured on a beam scale to within 0.1 kg in light clothing without shoes. Subjects stood straight with both feet in firm contact with the surface, looking ahead with hands not touching any surface. Heights were measured to 0.1 cm using a wall mounted stadiometer. BMI was calculated as weight in kg divided by the square of height in meters.

Waist circumference (WC): Waist circumference was measured to the nearest 0.1cm with a non-stretchable measuring tape. The subject stood straight. The tape was placed, at the end of exhalation, horizontally between the last floating rib or lower costal margin and the iIiac crest. Hipcircumference was measured to the nearest 0.1cm at the level of pubic symphysis and the point of greatest posterior extension of the buttocks. The waist circumference was divided by hip circumference to give waist hip ratio (WHR).

Biochemical Assay: All the women had hormone analysis, oral glucose tolerance test and fasting lipid profile. The tests were done in the Department of Biochemistry and Molecular Biology of Bangabandhu Sheikh Mujib Medical University. Fasting blood samples were drawn in follicular phase cycle days 2-5. This was to avoid any possible effects of sex steroids on insulin action. Venous blood samples were drawn after an overnight fast of at least 8 hours. Fastingblood glucose was measured by Hexokinase method (CI4100 ARCHITECT USA). All hormones were measured by Chemiluminiscent Microparticle Immunoassay (CI 4100 ARCHITECT USA).

Cut off values: BMI of 25kg/m^2 was taken as a threshold for obesity according to universal criteria. Using the BMI thresholds defined for the South Asian population,[4] the women were divided into 4 groups. Normal weight were those having BMI at 23kg/m^2 or less, overweight with BMI >23kg/m^{2}up to 27.5kg/m^2, obese I who had BMI > 27.5kg/m^{2}up to 29.9kg/m^2 and obese II who had BMI 30 kg/m^2 and above.Cut off value for waist circumference of Asian women for defining central obesity was ≥80 cm (International Diabetes Federation)[5]. Hyper-androgenemia was defined when serum total testosterone was > 60ng/ml. High LH:FSH ratio was >1.The cut off value of hyperinsulinemia was ≥10mIU/L and the cut off value of insulin resistance was HOMA IR ≥ 2. Fasting insulin was 9.25µIU/mL at 75th percentile for Pakistani population. HOMA-IR was 1.93 at the 75th percentile for Indian population and 1.82 at the75th percentile of Pakistani population[6]. For the sake of simplicity we rounded up the cutoff value of HOMA-IR to 2 and the cut off value of fasting insulin to 10mIU/L.

Metabolic syndrome: Metabolic syndrome was diagnosed according to IDF (International Diabetic Federation) criteria. The women should have waist

circumference ≥ 80cm plus any two of the following : i) blood pressure ≥ 130/85 mmHg (or receiving drug therapy for hypertension), ii) fasting bloodglucose ≥ 5.6mmol/L (or receiving drug therapy for diabetes mellitus) iii) serum triglyceride ≥150mg/dl iv) serum HDL-C (high density lipoprotein-cholesterol) ≤50mg/dl.[5]

***Statistical analysis*:** Statistical analysis was done by SPSS (Statistical Package for Social Science) version 23. Continuous variables with normal distribution were analyzed by One way ANOVA. Non parametric test (Kruskal Wallis test) was used for continuous variables which had non-Gaussian distribution. Categorical variables were analyzed for association by Fishers Exact Test and Chi Square tests. Statistical significance was defined as $p \leq 0.05$.

Ethical issues: Consent was taken regarding participation in the study. Data collection was accomplished by maintaining adequate privacy and confidentiality and without any physical harm abiding by Helsinki declaration.

Ethical clearence: Data were collected with consent from patients attending our PCOS clinic, the investigations were done as part of their routine clinical care. So no formal ethical clearance was taken.

Results

A total of 126 women with infertility and polycystic ovary syndrome were studied. Of all the continuous variables age, BMI, WC and WHR had normal distribution. Variables without normal distribution are described as median values rather than mean± SD. The mean age was 25.5±3.9 years. The mean BMI was 26.58±3.18 kg/m^2. The BMI at 25th, 50th and 75th percentile was 24.5kg/m^2, 26kg/m^2 and 28.8kg/m^2.They were divided into 4 obesity groups according to the BMI thresholds of 23 kg/m^2, 27.5kg/m^2 and 30 kg/m^2. The groups were normal weight (n=14), overweight (n=62), obese I (n=26) and obese II (n=19). Table I summarizes the anthropometric, endocrine and metabolic parameters in different groups. The mean age increased through the groups, from normal weight to overweight and obese as did the waist circumference, total serum testosterone, fasting insulin and serum triglyceride. More women were in overweight (49.2%) or obese (35.7%) group. Mean waist circumference in overweight women was 88.6±9.2cm (95%CI 86.6-90.6), in obese I women 94.6±6.4 cm (95% CI 92-97.4), in obese II women 100±9.6cm (95%CI 95.4-104.7).

Table 1. Anthropometric, endocrine and metabolic parameters in different groups defined by obesity thresholds for the South Asian women

Parameters	Total (n=126)	BMI ≤23 kg/m^2 Normal weight (n=14)	BMI >23,≤27.5 kg/m^2 Overweight (n=62)	BMI >27.5,<30 kg/m^2 Obese I (n=26)	BMI ≥30 kg/m^2 Obese II (n=19)
Age, (years) mean±SD	25.65±3.78	24.57±4.43	25.60±3.74	25.92±3.84	26.53±3.79
BMI (kg/m^2), mean±SD	26.58±3.17	21.63±1.25	25.29±1.13	28.63±0.81	31.64±1.75
WC (cm), mean±SD	91.07±9.50	81.46±9.21	88.60±7.47	94.65±6.43	100.05±9.62
WHR, mean±SD	0.91±0.11	0.87±0.08	0.90±0.66	0.93±0.19	0.92±0.05
LH (IU/L), median	6.70	5.9	7.01	6.15	4.87
LH:FSH, median	1.3	1.3	1.3	1.3	1.2
Total testosterone(ng/ml), median	49.45	35.28	50.34	56.90	67.00

Parameters	Total (n=126)	BMI ≤23 kg/m² Normal weight (n=14)	BMI >23,≤27.5 kg/m² Overweight (n=62)	BMI >27.5,<30 kg/m² Obese I (n=26)	BMI ≥30 kg/m² Obese II (n=19)
Fasting Insulin(mIU/L), median	13.5	9.90	13.35	15.35	18.47
HOMA-IR, median	1.60	1.15	1.60	1.55	2.40
Fasting blood glucose (mmol/L), median	4.80	4.96	4.81	4.52	5.18
Blood glucose 2 hours after (mmol/L), median	6.10	5.90	6.1	6.1	6.80
Total cholesterol (mg/dl) median	186	176	121	193	192
Triglyceride (mg/dl) median	137	113.5	136	138	147
LDL-cholesterol (mg/dl) median	125	121	123	134	131
HDL-cholesterol (mg/dl) median	39	39.50	40	38	35

The variance between groups was examined by the Oneway ANOVA and Kruskal Wallis test. Waist circumference and fasting insulin showed highly significant difference between the groups, but serum total testosterone and HOMA-IR did not. Figure 1 and 2 represent the line graph showing increase in waist circumference and fasting insulin through obesity groups.

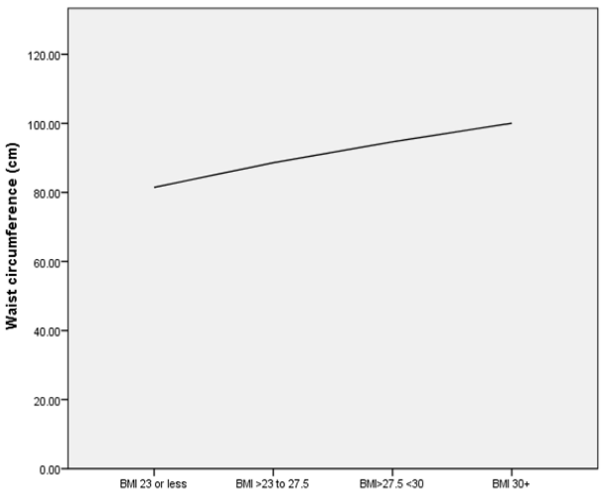

Figure 1. Line graph showing an increase in waist circumference through obesity groups.

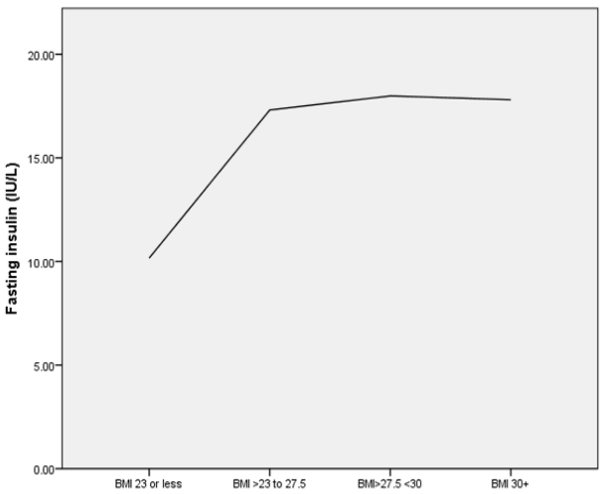

Figure 2. Line graph showing increase in fasting insulin through obesity groups. There is sharp rise in fasting insulin from normal weight (BMI 23 kg/m^{2}or less) to overweight and obese (BMI >23 kg/m^2).

The women were divided again into two obesity groups according to different thresholds. The obese group was either ≥25kg/m^2 or ≥23kg/m^2 and non-obese <25kg/m^2 or <23kg/m^2. Clinical, endocrine or metabolic variables were analyzed by 2x2 contingency tables with the obesity groups. The significant and non-significant associations are summarized in table II. Insulin resistance and metabolic syndrome were associated with obesity when the thresholds were 23 kg/m^2 or 25 kg/m^2. Acanthosis nigricans, hyperandrogenemia and hyperinsulinemia were associated with obesity when the threshold was 25kg/M^2. The prevalence of insulin resistance was 34.9% in obese group versus 15.8% in non-obese group and the prevalence of metabolic syndrome was 53% in obese group versus 23.7% in non-obese group when the threshold was 25kg/M^2. There was no women with insulin resistance or metabolic syndrome when the BMI was 23kg/m^2 or less.

Table II. Association of clinical, endocrine and metabolic parameters with obesity defined by different thresholds

Parameters	P value when obesity threshold BMI 25 kg/m^2	P value when obesity threshold BMI 23 kg/m^2
Regular cycle or polymenorrhea	0.836	1.00
Oligomenorrhea	0.246	0.601
Secondary amenorrhea	0.335	0.326
Central obesity	<0.001	<0.001
Hirsutism and/or acne	0.804	0.888
Acanthosis Nigricans	<0.001	0.225
Hyperandrogenemia	<0.05	0.102
High LH:FSH ratio	0.425	0.705
Hyperinsulinemia	<0.05	0.167
Insulin resistance	<0.001	<0.05
Metabolic syndrome	<0.001	<0.001

Discussion

The objective of the study was to see the association of obesity defined by BMI thresholds specific for the South Asian population with clinical, endocrine and metabolic parameters in infertile women with PCOS. There was highly significant association with waist circumference and fasting insulin. BMI at or above 25kg/m^2 was significantly associated with acanthosis nigricans, hyperandrogenemia and hyperinsulinemia, whereas BMI at or more than 23kg/m^2 was significantly associated, in addition, with insulin resistance and metabolic syndrome.

The mean age was 25.5±3.9 years. The women were young in their mid- twenties because the presenting symptom was infertility and early marriage is prevalent in Bangladesh. The mean BMI was 26.58±3.18kg/m^2, above the threshold of 25kg/m^2 for defining overweight. The interquartile range of BMI was 24.5-28.8kg/m^2, which means 75% of the women were above the threshold of 23kg/m^2, the cut off for defining overweight in the South Asian women.[4] Mean age was higher in obese women than in overweight women, higher in overweight than in normal weight women. It appears that infertile PCOS women tend to put on weight as they grow older. There is increasing trend in waist circumference, fasting insulin and serum triglyceride from normal to overweight through obese groups I and II. So with increase in BMI, there is increase in waist circumference or central obesity which reflects both subcutaneous and visceral fat in abdomen. Insulin resistance and lipid levels are increased exaggerating the risks of diabetes mellitus and cardiovascular disease. However significant difference between groups was marked in waist circumference and fasting insulin. So response to weight loss measures are better verified with changes in waist circumference and fasting insulin. There should be additional thresholds of waist circumference for defining central or abdominal obesity in women with PCOS especially those of the South Asian origin.[4,5]

Insulin resistance and metabolic syndrome had significant association with obesity defined by the threshold of 23kg/m^2.There are many studies in support of this finding which concludes that compared to other ethnic populations with similar BMI, the South Asian women have higher lifetime risks of diabetes mellitus and cardiovascular disease .[7] Initial and periodic screening for these metabolic abnormalities is recommended in all these women with PCOS in addition to infertility treatment. However, obesity defined by the threshold of 25kg/m^2 has significant association with hyperandrogenemia and hyperinsulinemia. So the women should be encouraged weight reduction beyond this threshold to address these basic changes in the pathophysiology of PCOS. Enhanced exposure of ovarian tissue to insulin lead to excess androgen synthesis. Obesity related hyperinsulinemia induce and aggravate hyperandrogenemia in infertile women with PCOS.

Our study did not find any significant difference in clinical features across obesity categories except for acanthosis nigricans. However some of the

studies have shown that obese women have more severe hyperandrogenism and related features like menstrual abnormality or hirsutism.[8,9] This was not the finding in our study because of referral bias.[10]Our women presented primarily to us with infertility. Those PCOS women who had menstrual problems presented to gynecologists and those with hirsutism presented to dermatologists.

There is a similar study on Mexican infertile PCOS women divided into groups by different BMI threshold levels: normal weight 18.5-24.9 kg/m^2, overweight 25-29.9kg/m^2, obese ≥30kg/M^2. There was no difference in the levels of LH, LH:FSH ratio or testosterone between the groups.[11] Fasting insulin was significantly higher in overweight and obese women above the threshold of 25 kg/m^2 as in our study. Some studies display higher prevalence of insulin resistance in both obese and non-obese women. The Mexican study has the prevalence of insulin resistance of 19.3% in normal weight, 56.7% in overweight and 78.2% in obese. Another Jordanian study of infertile PCOS women had the prevalence of insulin resistance at 23.4%, 36.7% and 39.9% in normal, overweight and obese women.[8] One Iranian study of PCOS women of age range 15-45years, not infertile had insulin resistance at 91.7% among the over-weight, obese and 8.3% among the lean.[12] Another Iranian study however found no significant difference in the prevalence of insulin resistance between obese and non-obese.[13] The prevalence of insulin resistance in our study was 34.9% in obese group versus 15.8% in non-obese group when the obesity threshold was 25 kg/m^2.The difference may be due to ethnic variation, difference in diet and lifestyle, different age group or different thresholds of HOMA IR used for defining insulin resistance.

The strength of this study is that it explores the characteristics of PCOS women by analyzing them in multiple groups defined by lower obesity thresholds suggested for the South Asian people. We used cut off levels of fasting insulin and HOMA-IR specific for the South Asian population for defining hyper-insulinemia and insulin resistance in our women. There are some limitations. Insulin resistance was not measured by the gold standard method Euglycemic hyperinsulinemic clamp. Results cannot be generalized to PCOS women without infertility.[10] Further studies with controls will clarify whether the high prevalence of insulin resistance or metabolic syndrome is due to PCOS or the obesity itself.

Conclusion

The study investigates the clinical, endocrine and metabolic parameters of infertile PCOS women in relation to obesity. There is significant increase in waist circumference and fasting insulin in women with normal weight to overweight and obese. The hyperandrogenemia and hyperinsulinemia are significantly associated with BMI above 25kg/m^2. Insulin resistance and metabolic syndrome are significantly associated with BMI above 23 kg/m^2, a threshold lower than other ethnic population. Women with PCOS should be screened for insulin resistance and metabolic syndrome when they come with the problem of infertility. Adequate counseling and early intervention will help minimize their risk of diabetes mellitus and cardiovascular disease in older age.

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Authors's contribution:

Study concept and design, Analysis and Interpretation of data, Drafting of the manuscript: Dr Shakeela Ishrat

Acquisition of data: Dr Marufa Hossain

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