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Prevalence of Insulin Resistance, Dyslipidemia and Metabolic Syndrome in Infertile Women with Polycystic Ovary Syndrome

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Abstract:

Introduction: 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 with related risks of insulin resistance, dyslipidemia and metabolic syndrome. There is ethnic variation in the prevalence of obesity and its related metabolic abnormalities in women with polycystic ovary syndrome. This study was designed to explore the prevalence of insulin resistance, dyslipidemia and metabolic syndrome in infertile women with polycystic ovary syndrome in Bangladesh.

Methods: This was a cross sectional study of 126 infertile women with polycystic ovary syndrome attending the Infertility unit of the Department of Obstertrics and Gynaecology at Bangabandhu Sheikh Mujib Medical University from January 2017 to December 2017.

Results: The mean BMI was 26.58±3.18 and mean waist circumference was 91.07±9.5 cm. Regarding the prevalence of obesity, 47.6% of the women were overweight (BMI 23 - 27.5 kg/m^2), 39.7% was obese (BMI>27.5 kg/m2) and central obesity (waist circumference ≥80 cm) was in 80.2%. In infertile women of PCOS, the prevalence of insulin resistance was 27.8% , dyslipidemia 93.7% metabolic syndrome 42.9% .Median fasting insulin was higher than the cut off for insulin resistance specific for south Asian population.

Insulin resistance measured by hyperinsulinemia was much more frequent (65.9%) than that measured by HOMA-IR (27.8%).The most common lipid abnormality was low HDL cholesterol (90.5%) followed by elevated LDL-cholesterol (79.4%). Low HDL cholesterol (90.5%) and abdominal or central obesity (80.2%) were the most common criteria of metabolic syndrome. There is increasing trend in metabolic syndrome with age.

Conclusion: Screening the infertile women with polycystic ovary syndrome for insulin resistance, dyslipidemia and metabolic syndrome is important because it allows for additional counseling about long term health consequences and emphasis on weight management.

Keywords: dyslipidemia, infertility, insulin resistance, metabolic syndrome, polycystic ovary syndrome

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Introduction:

Infertility, which affects around 10-20% of the couple, means failure to reproduce even after one year of regular conjugal life. Polycystic ovary syndrome (PCOS) affects 5-10% of reproductive age women and it is a common cause of infertility in young women. PCOS is characterized by menstrual irregularities, hirsutism, acne and often enlarged polycystic ovaries.[1] Most of the infertile women with PCOS are overweight and obese and weight loss favors management of infertility in them.[2] Increased weight gain is again associated with insulin resistance, dyslipidemia and metabolic syndrome.[3]

Hyperinsulinemia and insulin resistance are inherent in the pathogenesis of PCOS and accentuates the vicious cycle of hyper-androgenemia and high LH secretion. Weight gain worsens the insulin resistance and the resultant reproductive and metabolic dysfunction of PCOS.[4] Dyslipidemia means abnormal levels of total cholesterol, trigycerides, low density lipoproteins and high density lipoproteins in blood. Metabolic syndrome is diagnosed on the basis of abdominal obesity,

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hyperglycemia, hypertension, hypertriglyceridemia and reduced high density lipoprotein cholesterol.[5]Metabolic syndrome and dyslipidemia are linked to long term risks of diabetes mellitus, coronary heart disease and cerebrovascular disease and non -alcoholic fatty liver disease. Women with PCOS who are infertile tend to be overweight. The problems related to obesity are increased insulin resistance, dyslipidemia and metabolic syndrome. The south Asian women are different in central obesity and insulin resistance from their counterparts in western world or other regions of Asia.[6]. The infertile women with PCOS in our population may have increased prevalence of insulin resistance and associated dyslipidemia and metabolic syndrome. The problems are additional to that of infertility and require extra care and counseling. Our objective was to see the prevalence of insulin resistance, dyslipidemia and metabolic syndrome in Bangladeshi women with infertility and PCOS.

Methods:

This was a cross sectional study carried out in the Infertility unit of the Department of Obstetrics and Gynecology at Bangabandhu Sheikh Mujib Medical University from January 2017 to December 2017. A total of 126 infertile women with polycystic ovary syndrome attending the Infertility unit participated in the study.The women consented for study participation and 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 any two of the following: i) infrequent menstruation (cycle length >35 days), ii) hirsutism with modified Ferriman Galway score e"8, iii) at least one enlarged (>10cm^3) polycystic ovary at TVS.

Anthropometric measurements:

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. Cut off values were lower and specific for south Asian women: overweight,BMI 23 -27.5 kg/m^2 and obese ,BMI>27.5 kg/m2.[7]

WC: Waist circumference was measured to the nearest 0.5cm with a non stretchable measuring tape. The subject stood straight. The tape was placed, at the end of expiration, horizontally between the last floating rib or lower costal margin and the iIiac crest. Hip circumference was measured to the nearest 0.5cm at the level of pubic symphysis and the point of greatest posterior extension of the buttocks. The waist circumference was divided by hip circumference for waist hip ratio.

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 Bangbandhu 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. Fasting venous blood samples were drawn after an overnight fast of at least 8 hours. Fasting insulin was measured by Chemiluminiscent Microparticle Immunoassay (CI 4100 ARCHITECT USA). Fasting plasma glucose was measured by Hexokinase method (CI 4100 ARCHITECT,USA). High density lipoprotein cholesterol (HDL-C) was measured by Enzymatic Color test (Beckman Coulter, USA). Triglyceride was measured by Enzymatic glycerol phosphate method.

Insulin resistance: The surrogate markers of insulin resistance are fasting insulin and Homeostatic Model of Assessment of Insulin Resistance (HOMA-IR).Insulin resistance was defined at fasting insulin e" 10mIU/L or HOMA-IR e"2.Fasting insulin was 9.25 µIU/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[8]. For the sake of simplicity we rounded up the cut off value of HOMA-IR to 2 and the cut off value of fasting insulin to 10mIU/L.

Dyslipidemia: Dyslipidemia was defined as any of abnormal lipid levels: total cholesterol e"200 mg/dl, triglyceride e"150 mg/dl, Low density lipoprotein-cholesterol (LDL-C)e"130 mg/dl, high density lipoprotein -cholesterol (HDL-C) d" 50mg/dl.

Metabolic syndrome: Metabolic syndrome was diagnosed according to IDF (International Diabetic Federation) criteria.[5] The women should have waist

circumference e" 80cm plus any two of the following: i) blood pressure e" 130/85 mmHg (or receiving drug therapy for hypertension), ii) fasting glucose e" 5.6mmol/L (or receiving drug therapy for hypertension) iii) triglyceride e"150mg/dl iv) HDL-C d"50mg/dl.

*Statistical analysi*s: Statistical analysis was done using SPSS (Statistical Package of Social Science) version 23 and Microsoft excel.

Ethical issues: Consent was taken regarding participation in the study. Data collection was accomplished by maintaining adequate privacy and confidentiality.

Result:

A total of 126 infertile women with polycystic ovary syndrome was analyzed for their clinical, endocrine and metabolic characteristics. General characteristics are summarized in table I. The mean age was 25.5±3.9 years. Most of the women had oligomenorrhea.

The anthropometric, endocrine and metabolic characteristics are summarized in the Table II, III and IV.

The parameters other than BMI, waist circumference and waist hip ratio are skewed, so better described as median and inter-quartile range.

The mean BMI was 26.58±3.18 kg/m^2 and mean waist circumference 91.07±9.5 cm. Regarding the prevalence of obesity, 47.6% of the women were overweight (BMI 23 -27.5 kg/m^2), 39.7% was obese (BMI>27.5 kg/m2) and central obesity (waist circumference e"80 cm) was in 80.2%.

The endocrine parameters did not have normal distribution as expected for more severe endocrine dysfunction in infertile PCOS women. Median fasting insulin was higher than the cut off for insulin resistance specific for south Asian population.

The metabolic parameters also did not have normal distribution which may be explained by the increased prevalence of metabolic dysfunction in infertile PCOS women.

In infertile women of PCOS, the prevalence of insulin resistance was 27.8% (35/126), dyslipidemia 93.7% (118/126), metabolic syndrome 42.9% (54/126)

Table-I

Clinical parameters of the infertile women with PCOS (n=126)

Parameters	Number	Mean ± SD	Percentage
Age (years)	126	25.5±3.9	
Menstrual cycles			
Regular cycle	5		4.0
Oligomenorrhoea	70		55.6
Secondary amenorrhoea	35		27.8
Polymenorrhoea	2		1.6
Oligomenorrhoea alternating with polymenorrhoea	13		10.3
Hirsutism ± acne	56		44.4
Family history of diabetes	59		46.8
Normal weight	10		7.9
Overweight	60		47.6
Obesity	50		39.7
Central obesity	101		80.2

Table-II

Anthropometric parameters of the infertile women with PCOS (n=126)

Parameters	Mean	Standard deviation	Median	Interquartile Range
BMI(kg/m^2)	26.58	3.18	26	24.5—28.85
Waist Circumference (centimeter)	91.07	9.5	91	85-98
Waist Hip ratio	0.91	0.11	0.90	0.86-0.95

Table-III

Endocrine parameters of the infertile women with PCOS (n=126)

Parameters	Mean	Standard deviation	Median	Interquartile Range
FSH (IU/L)	5.12	1.75	1.8	4.02-6.14
LH (IU/L)	8.19	5.4	6.7	4.42-10.95
TSH(mIU/L)	2.58	1.46	2.41	1.52-3.45
Prolactin (ng/dl)	13.31	9.57	11.50	7.21-15.61
Total Testosterone (ng/dl)	65.09	54.18	53.24	24.9-80.5
Fasting insulin (mIU/mL)	16.39	12.48	13.50	8.52-19.00

Table-IV

Metabolic parameters of the infertile women with PCOS (n=126)

Parameters	Mean	Standard deviation	Median	Interquartile Range
HOMA IR	1.85	1.79	1.6	0.85-2.3
Fasting blood sugar (mmol/L)	5.07	1.20	4.8	4.4-5.4
Blood sugar 2 hrs after 75 gm glucose (mmol/L)	6.97	2.57	6.1	5.5-7.4
Total cholesterol (mg/dl)	194.70	34.93	186	157-210.7
Triglyceride (mg/dl)	147.27	65.33	137.50	102-188.5
LDL cholesterol (mg/dl)	127.86	29.68	125	107-145
HDL cholesterol (mg/dl)	38.89	6.76	39	35-43.5

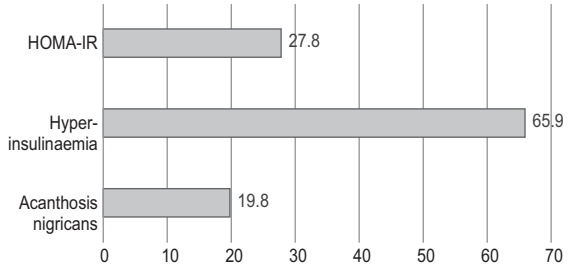

Fig.-1: *Bar chart showing prevalence of insulin resistance as defined by different markers in infertile women with PCOS (n=126)*

The cut off value of fasting insulin was at 10mIU/L and HOMA-IR at 2 according to population specifics. Insulin resistance measured by hyperinsulinemia was much more frequent (65.9%) than that measured by HOMA-IR (27.8%).

The most common lipid abnormality was low HDL cholesterol (90.5%) followed by elevated LDL-cholesterol (79.4%).

Low HDL cholesterol (90.5%) and abdominal or central obesity (80.2%) were the most common findings.

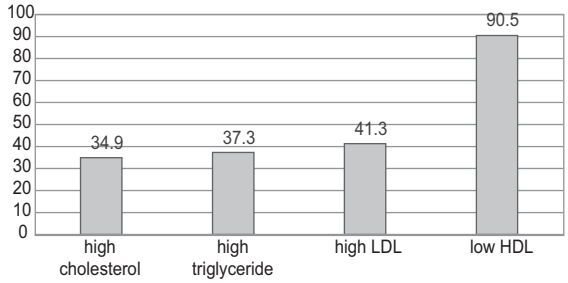

Fig.-2: *Bar chart showing frequency (percentage) of abnormal serum lipid levels in infertile women with PCOS (n=126)*

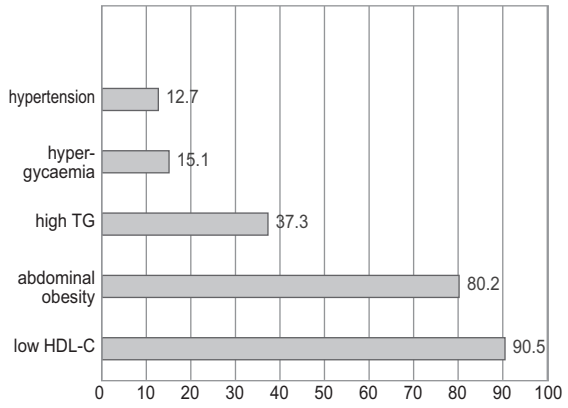

Fig.-3: *Bar chart showing frequency of individual criteria of metabolic syndrome in infertile women with PCOS (n=126).*

Women who had 1, 2, 3, 4 or all 5 criteria of metabolic syndrome comprised 12.8%, 40.8%, 34.4%, 8.8% and 3.2%.

There is increasing trend in metabolic syndrome with age stratified as groups according to percentile, inter-quartile range being 23-28 years.

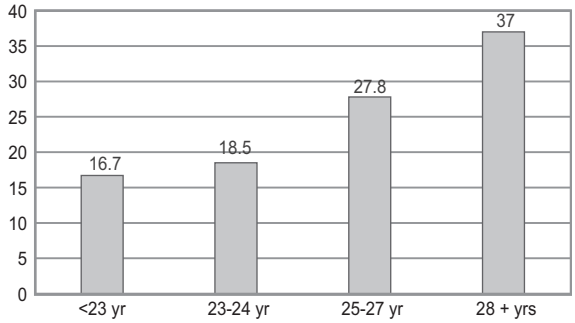

Fig.-4: *Distribution of metabolic syndrome in infertile women with PCOS grouped as quartiles of age (n=126)*

Discussion:

The objective of the study was to explore the prevalence of insulin resistance, dyslipidemia and metabolic syndrome in infertile women with polycystic ovary syndrome of Bangladesh while screening them for these risk factors of cardiovascular diseases. In infertile women of PCOS, the prevalence of insulin resistance was 27.8% ,dyslipidemia 93.7% and metabolic syndrome 42.9%.

The mean BMI was 26.5±3.1 kg/ $m^2$and mean waist circumference was 91.07±9.5 cm. In an Indian study of 80 PCOS women, the mean BMI was 29.1±4.2 kg/ m2.[9]Median fasting insulin was higher than the cut off for insulin resistance specific for south Asian population. Median fasting insulin in our study was 13.50 (8.52-19.00) mIU/L, where as in the Indian study [9] it was 13.4± 5.3 µIU/mL, both findings similar and higher than the cut off value of 0.9 mIU/L. The insulin resistance was 27.8% when we used the cut off value of HOMA-IR at 2, specific for the south Asian population. This is the value of HOMA-IR at 75th percentile of a Pakistani population.[7] This cut off value was taken because south Asian people has been found to be insulin resistant at a lower threshold than their Caucasian counterpart matched for BMI.[6] Probably due to genetic or cultural factors, PCOS women in south Asia have higher prevalence of central obesity and insulin resistance than other ethnic groups.[10]

According to the cutoff value of fasting insulin for south Asian (10 mIU/L), hyperinsulinemia was present in 65.9% of the women. This is expected as the women are infertile PCOS. Fasting insulin level appears to be more relevant to their reproductive dysfunction than HOMA IR which reflects reduced sensitivity of insulin suppression to exogenous or endogenous glucose. Hyperinsulinemia means that basal secretion of insulin from pancreatic beta cells is increased. The ovarian theca cells in PCOS women are sensitive even to physiological levels of insulin. Insulin acts via insulin receptors as well as IGF-1 receptors on theca cells of ovary to stimulate androgen production. Insulin also potentiates the stimulatory effect of luteinizing hormone on theca cells producing androgen. Insulin's action of inhibiting hepatic SHBG production further contributes to hyperandrogenemia. Insulin resistance is prevalent in women with PCOS both obese and lean. Hyperandrogenemia aggravates insulin resistance. So there is a self-propagating positive feedback loop of

hyperinsulinemia and hyperandrogenemia, increasing over time. Paradoxically in women with PCOS, the stimulatory effect of insulin on androgen production is persistent despite this apparent insulin resistance.[11] Insulin resistance occurs when peripheral tissues like liver, adipose tissues and muscle has less than normal insulin mediated response to glucose load. So there is compensatory hyperinsulinemia. Dysglycaemia and type II diabetes develop when pancreatic beta cells are incapable of insulin secretion sufficient to compensate for peripheral insulin resistance. Fasting hyperinsulinemia may result from decreased hepatic clearance of insulin as well.[12]

Dyslipidemia characterized by at least one elevated lipid levels was present in 95.2% women. Regression analysis reveals that decreased high density lipoprotein (HDL) cholesterol and elevated triglyceride levels are associated with insulin resistance and hyperinsulinemia.[13,14] Elevated low density lipoprotein(LDL) concentrations are not usually associated with insulin resistance state. The condition does not improve when insulin sensitizers are given and insulin resistance decrease.[12] They may result from hyperandrogenism[12]or may reflect genetic or dietery factors.[15]

The metabolic syndrome, previously termed syndrome X is a combination of closely related cardiovascular risk factors. The definition proposed by the International Diabetes Federation in 2005 was a consensus definition useful for identifying those at risk for developing cardiovascular disease in all populations. This is also applicable in our population because the risk of type 2 diabetes increases at much lower levels of body fat in Asians than in Europids (white people of European origin). The IDF definition includes central obesity (as defined by waist circumference) as an essential component of the metabolic syndrome. Strong evidences link waist circumference to other components of metabolic syndrome and cardiovascular risks.[16]

There are differences in the prevalence of insulin resistance in other studies which may be due to difference in threshold of HOMA-IR. In Chinese PCOS women the mean waist circumference was 75.9±10.5 cm, insulin resistance 14.7%.[17] All these parameters are much less than ours.

In infertile women of PCOS of our study, the prevalence of metabolic syndrome was 42.9%. The prevalence of metabolic syndrome was 34% in Caucasian PCOS women compared to 50% in Asian.[14] The women with low HDL was 66% in this study compared to ours which was 90.5%. The reason may be the specific population of south Asian infertile PCOS women. In another study from USA, the prevalence of metabolic syndrome was 43% in PCOS women[18] and the prevalence of low HDL was 91%, similar to our study. The metabolic syndrome has been previously reported as 1.6%, 8.2% and 43% in the PCOS women of Czech, Italian and US origin. The prevalence in Chinese women with PCOS were 19.1% and 24.9%,[16] in Korean women 16.7%.[19] The variation is probably due to ethnic and genetic factors as well as diet and lifestyle differences. The criteria of diagnosis of metabolic syndrome may differ between studies. Indian studies using the IDF criteria had prevalence of 47.5% and 52% in PCOS women.[20] This is close to our findings.

Women who had 1, 2, 3, 4 or all 5 criteria of metabolic syndrome comprised 12.8%, 40.8%, 34.4%, 8.8% and 3.2%. In an USA study [18] it was 21.7%, 25.5%, 30.2%,11.3% and 1.9% respectively. So the trend is similar to our study. Low HDL cholesterol (90.5%) and abdominal or central obesity (80.2%) were the most common findings. These two factors according to Brennan et al [20] assess cardiovascular disease risk in women with classic PCOS. Ovulatory PCOS women have lower BMI and lesser hyperinsulinaemia than classic PCOS.[20]

Our study shows increase in frequency of metabolic syndrome with age. According to a USA study, prevalence of metabolic syndrome was 44.8% in 20-29 years age group and 53.1% in 30- 49 years age group.[18] A comprehensive follow up of a cohort of Chinese women with PCOS over 10 years supports the increase in impaired glucose tolerance and development of type II diabetes mellitus and hypertension and hyperlipidaemia.[21]The meta-analysis and systematic review of metabolic syndrome and its components in PCOS women also mentioned many studies who supported the view that the condition is related with age.[21] The high prevalence of metabolic syndrome before the age of thirty is alarming for these women. They also highlight the fact the abdominal obesity and low HDL are the most prevalent criteria as found in our study. According to them, the prevalence of metabolic syndrome is higher when the IDF criteria is used rather

than WHO criteria or NCEP-ATP III (National Cholesterol Education Program Adult Treatment Panel III) criteria. The IDF criteria is more sensitive because it uses lower thresholds for waist circumference and fasting blood sugar.

Abdominal or central obesity may be an early mechanism in the pathophysiology leading to full expression of metabolic syndrome, more so in south Asian population of PCOS women. Central obesity contributes to development and maintenance of polycystic ovary syndrome and influence the severity of metabolic and cardiovascular risk profile. Central obesity is associated with high fasting insulin levels.[12] Ethnic origin or cultural habits are responsible for higher central obesity and higher prevalence of insulin resistance, dyslipidemia and metabolic syndrome in south Asian PCOS women.[23] Infertile women with PCOS are by themselves a group with more severe manifestations of PCOS.

Screening for these metabolic defects in infertile women with PCOS will allow additional counseling for lifestyle changes and diet. Orlistat and acarbose are pharmacological intervention for weight reduction. Metformin and inositol are insulin sensitizers. When dyslipidemia is diagnosed statins are not appropriate options for women who want pregnancy. Counseling about cardiovascular risk may motivate them into dietary change and exercise. Many women who do not need pregnancy are prescribed oral contraceptive pills to regularize menstruation and treat hirsutism. Oral contraceptive pills aggravate hypertension and adversely affect triglyceride levels. The screening for metabolic syndrome is appropriate before prescribing combined oral contraceptives.[22]

The study had a moderate sample size compromising precision at slightly less than 1. The sampling was purposive, not randomized and there was no comparable group. Anovulatory infertile women were recruited in a tertiary referral hospital. This is likely to introduce some potential selection bias with over-presentation of women who are more centrally obese, if inference about all PCOS women is to be made.

Conclusion:

The infertile women with polycystic ovary syndrome should be screened for insulin resistance, dyslipidemia and metabolic syndrome. This will allow those who are diagnosed to be counseled about the additional risks of diabetes mellitus, coronary heart disease and cerebrovascular disease. They will be motivated to adhere to the weight management program so vital to management of infertility.

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Conflict of Interest:

The authors declare no conflict of interest.

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