Bangladesh J Obstet Gynaecol, 2019; Vol. 34(2): 93-98

Association of Impaired Glucose Tolerance and Insulin Resistance in Women with Polycystic Ovary Syndrome

NASIMA BEGUM[1], NUSRAT ARAYOUSUF[2], MD. SHAMIM FAROOQ[3], MD. ABUL KALAM CHOWDHURY[4], MENOKA FERDOUS[4]

Abstract:

Objective: *To find out association between impaired glucose tolerance and insulin resistance with Polycystic Ovary Syndrome (PCOS).*

Materials and methods: *This cross-sectional comparative study was carried out on women with polycystic ovary syndrome (PCOS) admitted in the department of Obstetrics and Gynaecology, SSMC Mitford Hospital and BSMMU Dhaka over a period of 2 years from July 2008 to June 2010.*

Result: *A total of 100 subjects, 50 cases and 50 controls were consecutively included in the study. The mean insulin resistance, impaired fasting glucose and impaired glucose 2 hours after 75 gm of glucose were observed to be significantly higher in cases than in controls (26.7+8.4 vs. 18.8+7.5 micro IU /ml, p<0.001) The prevalence of insulin resistance ,impaired fasting serum glucose and impaired glucose 2 hours after 75 gm of glucose also higher among study group compared to control group (70% vs. 12%;44% vs. 10% and 56% vs. 10 % respectively).*

Conclusion: *Impaired glucose tolerance and insulin resistance are useful parameter for diagnosis of PCOS.*

Key wards: *Impaired Glucose Tolerance (IGT), Insulin Resistance (IR), Polycystic Ovary Syndrome (PCOS).*

Introduction:

Polycystic ovary syndrome (PCOS) is the most prevalent endocrinopathy causing anovulatory infertility. Its association with abnormal hormonal parameters leads many affected women to attend a gynecology, endocrinology or infertility clinic[1], Jeffcott in 1987 described the pathogenesis of polycystic ovary syndrome, though the cause of PCOS remains unknown. It is accepted as a clinical entity but the starting point in the circle of endocrine disturbances is still debatable. It is suggested that initially there may be a disturbance of adrenocortical function in the pre pubertal and post-pubertal phase of life followed by a shift to the ovarian dominance, which is associated with a non-cyclical pattern of ovarian function. The end result would be an increased androgen production in the ovary and increased peripheral conversion to oestrogen. There is no real confirmation of this suggestion. Another suggestion is that there is a familial or genetic role in some cases. Recent evidence suggests that one of the underlying principal disorder is insulin resistance, with the resultant hyperinsulinaemia stimulating excess ovarian androgen production. PCOS had fasting and glucose-stimulated hyperinsulinaemia compared to weight-matched control women, suggesting the

1 Dr. Nasima Begum, Assistant Professor. Department of Obstetrics & Gynaecology, Sheikh Hasina Medical college and hospital, Jamalpur.

2 Dr. Nusrat AraYousuf , Junior Consultant Department of Obstetrics & Gynaecology, Mugda Medical College and Hospital , Dhaka .

3 Dr. Md. Shamim Farooq , Professor .Department of Pathology , National Medical college and hospital ,Dhaka .

4 Dr. Md. Abul Kalam Chowdhury, Associate Professor, Department of Surgery, BSMMU

5 Dr. Menoka Ferdous, Associate Professor, Department of Obst. & Gynae, ShSMCH

Address of Correspondence: Dr. Nasima Begum, Assistant Professor. Department of Obstetrics & Gynaecology, Sheikh Hasina Medical college and hospital, Jamalpur, email: nasima16neela@gmail.com cell 01718132222

presence of insulin resistance. The first report of hyperisulinemia in women with classical polycystic ovary syndrome was followed by many reports with similar findings. Although obesity was a confounding factor in the early reports, latter studies found hyperinsulinaemia and insulin resistance in a proportion of non-obese women with PCOS. The exact mechanism of insulin resistance in polycystic ovary syndrome is unknown, most likely it results from a post receptor defect in the insulin pathway[2]. Despite insulin resistance in skeletal muscle and adipose tissue, the ovary remain relatively sensitive to insulin like growth factor. The relative excess of insulin or enhanced ovarian sensitivity to insulin, in combination with an elevated luteinising hormone (LH) concentration brings about thecal hyperplasia, increased androgen secretion, arrest of follicular development and therefore anovulation along with menstrual disturbances. Insulin also acts on liver and inhibits the production of sex hormone binding globulin which leads to an increase in the biologically available free testosterone. Thus, insulin resistance or hyperinsulinaemia not only increase secretion of ovarian androgen but also promotes an increase in the proportion of free or active testosterone. The identification of this association has immense value in studying the relationship between insulin resistance and PCOS[3]. Stein and Leventhal in 1935 described for the first time the association of bilateral polycystic ovary (PCO) and amenorrhoea, oligomenorrhoea, hirsutism and obesity[4]. Enlargement of ovaries or demonstration of histological abnormalities in a biopsy specimen was considered necessary for a diagnosis PCOS to be made[5]. PCOS affecting approximately 4-8% of reproductive aged women. It is associated with an increased risk of metabolic complications, including type 2 diabetes, hypertension, dyslipidemia, and cardiovascular disease[6]. Women with PCOS are at substantially higher risk for impaired glucose tolerance (IGT) and type 2 diabetes, with combined prevalence rates of 35-45% for glucose intolerance[7]. Burghen*et al*.[8] in 1998 reported that PCOS was associated with hyperinsulinaemia, it has become clear that the syndrome has major metabolic as well as reproductive morbidities. Khan et al. in 1976 described it as a distinct disorder affecting adolescent girls, which they designated a type of syndrome[9]. These girls were virilized and had extreme insulin resistance with diabetes mellitus as well as striking acanthosis nigricans. This group identified a second distinct extreme insulin resistance syndrome in postmenopausal woman with acanthosis nigricans and features of autoimmune disease, which they termed the type B syndromes and determined that it was caused by endogenous anti insulin receptor antibodies.[10] In the mid 1980s several groups noted that acanthosis nigricans occurred frequently in obese hyperandrogenic women.[11] The presence of hyperinsulinaemia in PCOS women independent of obesity, was confirmed by a number of groups worldwide.[12] Anovulation is the characteristic feature of PCOS. It manifests as menstrual disturbance with peripubertal onset.[13] Women with PCOS suffer from infertility problems significantly more often than controls[14] with hyperandrogenism hirsutism, acne, male pattern balding or alopecia[15]

Methods:

This was a cross-sectional study .It was conducted in the department of Obstetrics and Gynaecology , SSMC Mitford Hospital and BSMMU Dhaka over a period of 2 years from July 2008 to June 2010. Fifty women with PCOS admitted in the above mentioned hospitals were taken as cases, while 50 women of same hospital without PCOS were taken as controls. Inclusion criteria for the study subjects were oligomenorrhoea (menstrual cycle interval more than 35 days but less than 6 months), characteristics changes in ovaries by U.S.G, hirsutism, obesity, and infertility. Exclusion criteria for the study subjects were hyperadrenalism, hypothyroidism and overt diabetes. With all aseptic precaution, 5 cc blood was collected from all the subjects using disposable syringe. Immediately after drawing, blood transferred to a dry clean test tube to avoid haemolysis and was allowed to clot. Then the blood sample was centrifuged and serum was collected in the test tube. Then fasting serum insulin and glucose level were estimated in the laboratory, finally blood sugar 2 hours after 75gm of glucose was determined. In case of delay in carrying out the analysis, serum was preserved in the refrigerator at 20^{o}C.

Result:

The present study was intended to evaluate the association of impaired glucose tolerance and insulin resistance with polycystic ovary syndrome (PCOS). Women with polycystic ovary syndrome were study cases and without polycystic ovary syndrome were control. The findings obtained from data analysis are presented below.

Table-I
Comparison of age between case and control groups.

Age (yrs)	Group		P-value
	Case (n=50)	Control (n=50)	
<25	15 (30%)	10 (20%)	
(25-30)	10 (20%)	30 (60%)	
≥30	25 (50%)	10(20%)	
Mean ± SD	27.6± 6.1	27.3± 5.9	0.817

Table I shows the mean age was almost identically distributed between case and control groups (p = 0.817).

Table-II
Comparison of BMI between case and control groups.

BMI(kg/m^2)	Group		P-value
	Case (n=50)	Control (n=50)	
<25 (normal)	31(62%)	40(80%)	
≥25 (over weight & obese)	19(38%)	10(20%)	o.o47

Table ll depicts that over weight and obese patients were significantly higher in case group compared to control group (38%vs.20%, p=0.047).

Table-III
Comparison of menstrual profile between two groups.

Menstrual profile	Group		p-value
	Case (n=50)	Control (n=50)	
Age at menarche (years)			
11-12	44(88%)	40(80%)	0.275
13-14	6 (12%)	10(20%)	
Average length of menstrual cycle			
<4 weeks	17(34%)	39(78%)	<0.001
>4 weeks	33(66%)	11 (22%)	
Average duration of menstrual period			
<3 days	46(92%)	26(52%)	<0.001
>3 days	4(8%)	24(48%)	

Table lll. Majority of the subjects in case and control groups (88% and 80% respectively gave the history of menarche between 11 – 12 years of age (p = 0.275). Two-third (66%) of the cases had average length of menstrual cycle more than 4 weeks compared to 22% of controls (p < 0.0010. Forty six (92%) of 50 cases had average duration of menstruation <3 days compared to 52% of controls (p= 0.001)

Table-IV
Comparison of parity between groups.

Number of pregnancy	Group	
	Case(n=50)	Control(n=50)
Para 1	14(28%)	9 (18%)
Para 2	00	15(30%)
Para 3	00	5(10%)

Out of 50 cases only 14 (28%) were para 1 others were nill parity. Whereas out of 50 controls, 9 (18%) were para 1, 15(30%) para 2 and the rest 5(10%) were para 3 (Table IV).

Table-V
Distribution of Cases by clinical characteristics. (n=50).

Clinical characteristics	Frequency	Percentage
Oligomenorrhoea	33	66%
Amenorrhoea	17	34%
Hirsutism	38	76%
Infertility	25	50%
Hypertension	09	18%
Enlarged Polycystic Ovary	43	86%

Table V showing the clinical characteristics revealed that two- third (66%) of the cases had history of Oligomenorrhoea, 34% Amenorrhoea, 76% Hirsutism, 50% Infertility, 18% Hypertension, 86% enlarged Polycystic Ovary.

Table-VI
Comparison of hormone profile between groups

Hormone profile	Group		p-value
	Case (n=50)	Control (n=50)	
Serum LH (micro IU/ml	25.8 ± 10.4	6.9 ± 2.9	<0.001
Serum FSH (micro IU/ml	12.5 ± 3.2	6.3 ± 2.4	<0.001
LH-FSH Ratio			
<2	20(40%)	47(94%)	<0.001
≥2	30(60%)	3(6%)	

Table VI showing hormone profile of study subjects. The mean serum levels of LH and FSH were significantly raised in the case group than in the control group (p<0.001). Altered LH & FSH ratio (≥2) was significantly higher (60%) in case group than that in the control group (6%) (P < 0.001).

Table-VII

Comparison of insulin resistance and impaired glucose tolerance between two groups

Variables	Group		p-value
	Case(n=50)	Control(n=50)	
Fasting Serum insulin (micro IU/ml)	26.7 ± 8.4	18.8 ± 7.5	<0.001
Fasting Serum glucose (m mol/L)	5.8 ± 0.7	4.9 ± 0.4	0.001
Serum glucose 2 hrs after75 gm of glucose (m mol /L)	8.7 ± 1.6	6.7 ± 0.7	<0.001

Table-VIII

Risk of developing PCOS in subject with insulin resistance and impaired serum glucose

Variables	Groups Case(n=50)	Odds Ratio Control(n=50)	p-value (95% CI)	
Fasting serum insulin				
≤25 micro IU/ml	15(30%)	44(88%)	5.3(2.4-12.8)	<0.001
>25 micro IU/ml	35(70%)	6(12%)		
Fasting serum glucose				
≤6.1 mmol /L	28(56%)	45(90%)	7.1(2.4-20.8)	<0.001
>6.1 mmol /L	22(44%)	5910%)		
serum glucose 2 hours after 75 gm of glucose				
≤7.8 mmol /L	22(44%)	45(90%)	11.3(3.9-20.80	<0.001
>7.8 mmol /L	28(56%)	5(10%)		

Table VII showing insulin resistance and impaired glucose tolerance among the study group. The mean fasting serum insulin, fasting serum glucose and serum glucose 2 hours after 75 gm of glucose ingestion were significantly higher in cases compared to control group (P < 0.001).

Table VIII showing the serum fasting insulin, impaired fasting glucose and serum glucose 2 hours after intake of 75 gm of glucose in subjects with PCOS are 5.3, 7.1 and 11.3 times higher than the control group.

Discussion:

The present study aimed at finding the association of PCOS with insulin resistance and impaired glucose tolerance. The mean age of women with and without PCOS were almost similar 27.6 ± 6.1 in cases and 27.3 ± 5.9 in controls. Lin (2006)[16] reported the mean age 26.3 ± 5.4 years in PCOS and 24.6 ± 3.9 years in normal women which is consistent with our study. Seow (2007)[17]and his associates reported a similar findings with mean age of the women with PCOS being 29.5 ± 4.9 years and that of the controls 28.3 ± 4.9 years.

In the present study women with PCOS had a significantly higher frequency of overweight and obesity compared to their controls counterpart (38% vs. 20%, p = 0.047). Lin and associate (2006) also observed higher body mass index (BMI) (average BMI: 28.5 ± 6.0 kg/$m^{2)}$ compared to that observed in normal women (average BMI: 21.7 ± 3.2 kg/$m^{2)}$.

In our study, majority women with PCOS (88%) and control (80%) experienced their first menstruation between 11-12 years of age. Two–thirds (66%) of the cases had menstrual cycle >4 weeks and 92% of the women had shorter period. Prolonged menstrual cycle and scanty menstruation is the characteristic feature of women with PCOS which are once again evident in the present study.

The present study demonstrated that two –thirds (66%) of cases had history of oligomenorrhoea, 34% amenorrhoea, 76% hirsutism, 50% infertility and 86% enlarged polycystic ovary. Franks (1995)[1] showed that 30% had a menorrhoea, 75% Oligomenorrhoea and more than 60% of their study cases were hirsute. These findings are almost consistent with the findings of the present study.

In the present study the mean serum fasting insulin level was observed to be significantly higher in cases

than in controls (26.7 ± 8.4 vs. 18.8 ± 7.5 micro IU / ml, p<0.001). The prevalence of insulin resistance, fasting serum glucose and glucose 2 hours after 75 gm of glucose also higher in the former group compared to later group (70% vs. 12%; 44% vs. 10% and 56% vs. 10 % respectively).Lin (2006)[16] reported serum fasting insulin and serum fasting glucose to be significantly higher in PCOS women compared to normal women (24.4 ± 17.2 vs. 7.9 ± 6.7 ng/dl , p<0.05 and 91.3 ± 18.1 vs. 86.3 ±17.6 ng/dl , p<0.05 respectively). Seow et al (2007)[17] reported similar findings regarding each of these parameters. However Goke (1988)[18] reported that there was no significant difference in fasting glucose levels between women with PCOS and control. Their opinion is that significantly higher fasting insulin levels are found among women with PCOS. This significantly higher fasting insulin levels indicates that the normal fasting glucose value is due to the effect of compensatory hyper insulinaemia, i.e. increased insulin secretion to overcome the insulin resistance. Furthermore, the significant difference in the 2 h glucose and 2 h insulin levels in normal women and with PCOS indicates that insulin sensitivity was decreased, since higher serum insulin levels failed to normalize the 2 h glucose levels[19]. Legro and associates (2002)[20] also reported that women with PCOS had a higher incidence of insulin resistance. Ara in Bangladesh (2000)[21] also found the similar findings (19.01 ± 5042 vs. 7.27- 2.47 µu/ ml. p<0.05).

Recent studies have suggested that the progression of IGT to type 2 diabetes mellitus (DM) is 5-to 10 fold accelerated in women with PCOS , especially in those with obesity and family history of type 2 DM[22]. Dunaif et al, (1987)[23] reported that only obese PCOD women had glucose intolerance. The prevalence of glucose intolerance in PCOS as 31.1% and 7.5% in non-diabetic are substantially higher than those found in a major population-based study (second national health and nutrition survey)

A preliminary report by Ehrmann et. El., (1996)[24] found similar prevalence rates in an ethnically mixed PCOS population from Chicago. These observations suggest that PCOS is important risk factor for glucose intolerance in young women than race or ethnicity.[25] As there is no such study in our country, the results could not be compared regarding race and ethnicity.

Conclusion:

The study concludes that chance of developing insulin resistance, impaired fasting glucose and glucose intolerance, 2 hours after 75 gm glucose is much higher in women with PCOS than in women without PCOS.

References:

1. Franks S. 1995. Polycystic ovary syndrome, N engl J Med, vol.333, no.21, pp. 1435.
2. DunaifA.1997. Insulin resistance and the Polycystic ovary syndrome: mechanism and implications for pathogenesis, Endocr Rev, vlo.18s; pp.774-800.
3. Poretsky I. 1991.On the paradox of insulin-induced hyperandrogenism in insulin-resistant states, EndocrEV, vol.12; pp3^{-13}.
4. Stein IF &LeventhalML.1935. Amenorrhea associated with bilateral polycystic ovaries, Am J ObestetGynecol, vol29;pp181-6
5. Rosenfield, R.L.1997. Current concepts of polycystic ovary syndrome, bailleres clin obestet gynaecol, vol.11; pp.307-33.
6. Wild RA.2002. Long-term health consequences of PCOS. Hum Reprod Update, vol.8; pp.231-41
7. EhrmannDA, BarnesRB, RosenfieldRL, Cavaghan MK &Imperial J. 1999 Prevalence of impaired glucose tolerance and diabetes in women with Polycystic ovary syndrome , Diabetes Care , vol 22; pp.141-6.
8. Burghen GA, givens JR &KitabchiAE.1980. Correlation of hyperandrogenism with hyper insulinism in Polycystic ovary disease, J ClinEndocrinolMetab, vol .50;pp113-16.
9. Khan CR, Flier JS, Bar RS, Archer J A, Gorden P & Martin MM .1976.The syndromes of Insulin resistance and acanthosisnigricans , N Engl J Med, vol.294;pp.739-45.
10. O´Rahilly S, Woong HC, Patel P, Turner RC, Flier JS& Moller DE. 1991. Detection of mutations in insulin receptor gene in NIDDM patient by analysis of single –stranded conformation polymorphisms, Diabetes, vol.40, pp.777-82.
11. Peters EJ, Stuart CA & Prince MJ. 1986. acanthosisnigricans and obesity: acquired and

intrinsic defects in insulin action, Metabolism, vol.35; pp.807-13

12. Chang RJ, Nakamura RM, judd HL, Kaplan SA. 1983 Insulin resistance in non obese patient with polycystic ovarian disease, J Clin Endocrinal Metab, vol.57; pp.177-269.
13. Pasquali R, Antenucci D, Casimirri F, Venturoli, S,Paradisi R, &Fabbri R. 1989. Clinical and hormonal characteristic of obese amenorrheicHyperandrogenic women before and after weight loss , J Clin Endocrinal Metab, vol .68; pp. 173-9.
14. Dahlgren E, Johansson S, Lindstedt G, Knutsson, F, Oden A &JansonPO.1992b. Women with polycystic ovarian syndrome wedge resected in 1956 to 1965: a long- term follow up focusing on natural history and circulating hormones,FertilSteril ,vol .57; pp.177-269.
15. Tailor AE. 1998a. Polycystic ovarian syndrome, Endocrinal MetabClin N Am, vol .27; pp.877-902.
16. Lin TC, Yen JM, gong KB, KuoTC, Ku DC & Liang SF et.al. 2006. Abnormal glucose tolerance in polycystic ovarian syndrome amongst the Taiwanese population not correlated with insulin receptor substrate -1 Gly972Arg/Ala513Propolymorphism, *BMC Medical Genetics*, vol .7;pp.36.
17. Seow KM, Juan CC, Hsu YP,HwangLW& LT. 2007. Amelioration of insulin resistance in women with PCOS via reduced insulin receptor substrate -1 Ser phosphorylation following laparoscopic ovarian electrocautery , Human Reproduction ,vol .22,no.4;pp.1003-10.
18. Goke B. 1998. Implication of blood glucose, insulin resistance and beta – cell function in impaired glucose tolerance, Diabetes Res ClinPract, vol .12; pp.2641-8.
19. Dunaif A. Insulin resistance and ovarian dysfunction. In: Moller D, ed Insulin resistance, New York: john Wiley, 1993:301-25.
20. Legro RS,Kunselman AR, Dodson WC &Dunaif A. Prevalence and predictor of risk for type 2 diabetes mellitus and impaired glucose tolerance in polycystic ovarian syndrome : a prospective controlled study in 254 affected women, j clinEndocrionalMetab, vol 84; pp.165-9
21. Ara G Study on Insulin resistence in Polycystic Overy Syndrom, BIRDEM, 2000.
22. Ehrmann DA, Barnes RB, RosenfieldRL, Cavaghan MK & Imperial J. Prevalence of impaired glucose tolerance and diabetes in women with polycystic ovarian syndrome. Diabetes Care, vol. 22; pp.141-6.
23. Dunaif A. Graf M, Mandeli J, LaumasV & Dobrjansky A. 1987. Characterization of groups of hyperandrogenic women with acanthosisnigricans, impaired glucose tolerance and/or hyperinsulinemia, j clin endocrional Metab, vol.65;pp.499-507
24. Ehrmann DA, RosenfieldRL, Barnes RB&KarrisonT.A Longitudinal study of glucose tolerance in women with polycystic ovarian syndrome.Prog 78th Annual Meeting of the Endocrine Society, 1996.
25. Haffner SM. 1995.Risk factor for non – insulin-dependent diabetes mellitus, J HypertensSuppl, vol 12; pp.464-74.