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ORIGINAL ARTICLE

Impaired Glucose Tolerance in Patients with Polycystic Ovarian Syndrome

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ABSTRACT

Background: Polycystic ovary syndrome first described by Stein and Leventhal, is a complex genetic trait of unclear etiology characterized by Oligomenorrhea or anovulation, biochemical or clinical hyperandrogenism and polycystic ovarian morphology on ultrasonography. Women with polycystic ovarian syndrome have an increased risk of developing impaired glucose tolerance and type 2 diabetes mellitus. This study aims to determine the prevalence of impaired glucose tolerance in patients with polycystic ovary syndrome.

Study Design: Cross-sectional study

Study Duration: This study was conducted in the Department of Endocrinology Ayub Teaching Hospital Abbottabad from 1st Nov 2021 to 30th April 2022.

Materials and Methods: All patients with age range 16 to 40 years who were diagnosed with polycystic ovarian syndrome were included in the study. Age, ovarian volume, clinical signs of hyperandrogenism, menstrual abnormalities, serum testosterone, blood glucose at baseline and following 75g of oral glucose load, Body mass index etc. were recorded. Data was analyzed using SPSS-23.

Results: Among 139 patients, 35(25.2%) were in the age range 16-25 years while 104(74.8%) were in the age range 26-40 years. Mean age was 28.6(SD±4.2) years. 69(49.6%) patients had BMI> 30 Kg/m^2, 60(43.2%) had BMI between 25-29.9 Kg/m^2, while only 10(7.2%) patients had their BMI within normal range (18.5-24.9). Mean BMI was 30.7 Kg/m^2 (SD±4.4). 47(33.8%) patients had ovarian volume less than 25ml while, 92(66.2%) had ovarian volume greater than 25ml. Mean ovarian volume was 25.5(SD±6.7). 106(76.3%) patients had serum testosterone less than 70ng/dl while, 33(23.7%) had serum testosterone greater than 70ng/dl. Mean serum testosterone was 48.8(SD±26.4). Hirsutism and Acne was observed in 92 (66.2%) and 91(65.5%) patients respectively. 75 (54%) women had positive family history of Diabetes, 56 (40.3%) had family history of polycystic ovary syndrome and 71 (51.1%) patients had past or current history of oral contraceptive pills. Impaired glucose tolerance was found in 52(37.4%) patients. Post stratification results were statistically significant.

Conclusions: The prevalence of impaired Glucose tolerance with polycystic ovary syndrome can be as high as 37.4%. Increasing age and Body Mass Index, raise serum testosterone level and increasing ovarian volume are significant predictors for developing impaired glucose tolerance in women with polycystic ovary syndrome.

Keywords: Polycystic Ovarian Syndrome, Impaired Glucose Tolerance, Predictive Factors.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a heterogeneous complex genetic trait of unclear and likely multiple etiologies. It is an important cause of menstrual irregularity and sub fertility and is clinically evident by hyperandrogenism and metabolic dysfunction. The syndrome was first described by Stein and Leventhal in 1935, although the presence of sclerocystic ovaries had been recognized for at least 90 years prior to their report.[1] The syndrome is usually characterized by Oligomenorrhea or anovulation, biochemical or clinical hyperandrogenism and polycystic ovarian morphology on ultrasonography.[2]

According to the Rotterdam 2003 criteria, PCOS is diagnosed based on the presence of two of these three features, Oligomenorrhea or anovulation, clinical and/or biochemical signs of hyperandrogenism and polycystic ovaries on ultrasound.[3] The Endocrine Society 2013 guidelines suggested using the Rotterdam criteria for diagnosing PCOS.[3] Most PCOS women present with insulin resistance and hyper insulinemia which play an important role in the pathogenesis of PCOS by modulating both ovarian and adrenal androgen production and decreasing sex hormone binding globulin (SHBG) liver synthesis and blood levels.[4] Polycystic ovary syndrome is the most common endocrinopathy affecting reproductive age women with a reported prevalence of 6%–26%, depending on the diagnostic criteria applied and population studied.[5] In the United States, it is one of the most common endocrine disorders of reproductive age women, with a prevalence of 4-12%.[6] Up to 10% of women are diagnosed with PCOS during gynecological visit. In some European studies, the prevalence of PCOS has been reported to be 6.5-8%.[7] Due to significant metabolic burden of insulin resistance; women with PCOS have an increased risk of impaired glucose tolerance (IGT) and type 2 diabetes mellitus. IGT is a known risk factor for type 2 DM and the development of cardiovascular disease.[8]

In general population there is evidence that insulin resistance may play a major pathophysiological role in the development of IGT in PCOS women. The decreased insulin sensitivity in PCOS women appears in fact quite similar to that found in type 2 diabetic patients and to be relatively independent of obesity, fat distribution, and lean body mass. On the other hand, there is strong evidence that obesity particularly the abdominal phenotype is an important independent risk factor for IGT in PCOS women.[4] Because IGT is often asymptomatic, the screening of women with PCOS for IGT has been recommended.[9,10] Studies in American and Asian subjects have shown that women with PCOS have an increased risk for impaired glucose tolerance (IGT) & type 2 diabetes as compared to general population with a tendency toward early development of glucose intolerance (GI) states.[4] In a prospective trials, Moran et al[11] showed a prevalence of IGT of 35%, prevalence of Type 2 diabetes mellitus (T2DM) of 10%, 5-10 fold risk of progression from IGT to diabetes, and a 4-7 fold higher risk of T2DM in PCOS patients. The risk factors for impaired glucose tolerance in women with PCOS includes, obesity and central adiposity, family history of diabetes, irregular menses, use of certain oral contraceptives and advance age.[12]

IGT is underdiagnosed, even in populations at high risk because it is usually asymptomatic and its detection requires an oral glucose tolerance test. With appropriate lifestyle or pharmacological intervention, it may be feasible to delay, or possibly prevent, the progression from IGT to Non- insulin dependent Diabetes mellitus. Thus a great emphasis has been placed recently on earlier detection of IGT.[13.] Most of the data about IGT in PCOS women were available from American and European studies. Limited data is available about the prevalence

and features of IGT in PCOS women in Pakistan. This study is designed to provide information on prevalence of IGT in women with PCOS.

MATERIAL AND METHODS

This cross-sectional study was conducted in the department of Endocrinology Ayub Teaching Hospital Abbottabad from 1st November 2021 to 30th April 2022. Approval was taken from Hospital Ethical committee. Sample size was calculated by using WHO calculator with 5% level of significance and 90% power of test. Non probability sampling technique was utilized. All patients with age range 16 to 40 years who were diagnosed with polycystic ovary syndrome according to Rotterdam`s criteria were included in the study. Rotterdam`s criteria for diagnosis of Polycystic ovary syndrome require the presence of two of the following three criteria i.e. irregular menstrual cycle (Amenorrhea or Oligomenorrhea), Hyperandrogenism (clinical features and/or biochemical elevation of testosterone), and/ or PCOS morphology on ultrasound (more than 10 follicles in each ovary or ovarian volume more than 10cc). Women with history of Diabetes mellitus, non-classical congenital adrenal 21 hydroxylase deficiencies, androgen secreting tumors, Cushing's syndrome and hyperprolactinemia were excluded from the study. A standardized structured questionnaire was created. Informed written consent was obtained from each patient. Impaired glucose tolerance was confirmed by performing oral glucose tolerance test. Blood glucose level of 140-199mg/dl after 2 hours of 75g oral glucose load was considered impaired glucose tolerance. Variables including age, ovarian volume in ml as measured by ultrasound, clinical signs of hyperandrogenism (Hirsutism or acne), menstrual abnormalities (Oligomenorrhea or amenorrhea), serum testosterone level, blood glucose at baseline and following 75g of oral glucose load, Body mass index, waist circumference, use of oral contraceptive pill, family history of Diabetes mellitus and family history of polycystic ovary syndrome were recorded.

Data was entered and analyzed using statistical package for the social sciences (SPSS)-23. A descriptive analysis was done and features were presented as mean ± standard deviation for quantitative variables and number (Percentage) for qualitative variables. Data were stratified for age, BMI, waist circumference, serum testosterone level, ovarian volume and family history of Diabetes mellitus. Chi square test was applied. P value less than 0.05 was considered statistically significant.

RESULTS

Among 139 patients with polycystic ovarian syndrome, 35(25.2%) were in the age range 16-25 years while 104(74.8%) were in the age range 26-40 years **(Figure-01)**. Mean age was 28.6(SD±4.2) years. 69(49.6%) patients had BMI> 30 Kg/m2, 60(43.2%) had BMI between 25-29.9 kg/m2 while only 10(7.2%) patients had their BMI within normal range (18.5-24.9). mean BMI was 30.7(SD±4.4)**(Table-01)**. 47(33.8%) patients had ovarian volume less than 25ml while, 92(66.2%) had ovarian volume greater than 25ml. Mean ovarian volume was 25.5(SD±6.7)**(Figure-02)**. 106(76.3%) patients had serum testosterone less than 70ng/dl while, 33(23.7%) had serum testosterone greater than 70ng/dl. Mean serum testosterone was 48.8(SD±26.4) **(Table-02)**. Hirsutism and Acne was observed in 92 (66.2%) and 91(65.5%) patients respectively. Out of 139 patients, 75 (54%) had family history of Diabetes, 56 (40.3%) had family history of polycystic ovary syndrome and 71 (51.1%) patients had past or current history of oral contraceptive pills. Impaired glucose tolerance was found in 52(37.4%) patients **(Figure-03)**. Out of 52 patients with impaired glucose tolerance, 15 were in the age range 16-25 years while 37 were in the age range 26-40 years **(Table-03)**. 18(34.6%) out of 52 patients were obese, 29(55.7%) were overweight while only 5(9.6%) patients have their BMI within normal range **(Table-04)**. 30(57.6%) women had family history of Diabetes, 15(28.8) had family history polycystic ovarian syndrome while 25(48.07%) had current or past history of oral contraceptive pills. Increase in waist circumference is associated with increased risk of impaired glucose tolerance (P value=0.01). Out of 52 patients with impaired glucose tolerance, 13 have waist their circumference less than 80cm while 39 patients have their waist circumference greater than 90cm **(Table-05)**. 30(57.6%) have family history of Diabetes, 15(28.8) have family history polycystic ovarian syndrome while 25(48.07%) have current or past history of oral contraceptive pills **(Table-06)**. Raised serum testosterone level to greater 70ng/dl significantly increases the risk of developing impaired glucose tolerance. In patients with serum testosterone less than 70ng/dl, 30 out of 106 had impaired glucose tolerance while those with serum testosterone greater than 70ng/dl only 11 out 33 patients have their blood glucose level within normal range following oral glucose tolerance test (P=0.000) **(Table-07)**. Increase in ovarian volume also increases the risk of glucose intolerance. In patients with impaired glucose tolerance, 40 out of 52 had combined ovarian volume greater than 25ml while only 12 had ovarian volume less 25ml(P=0.03)**(Table-08)**.

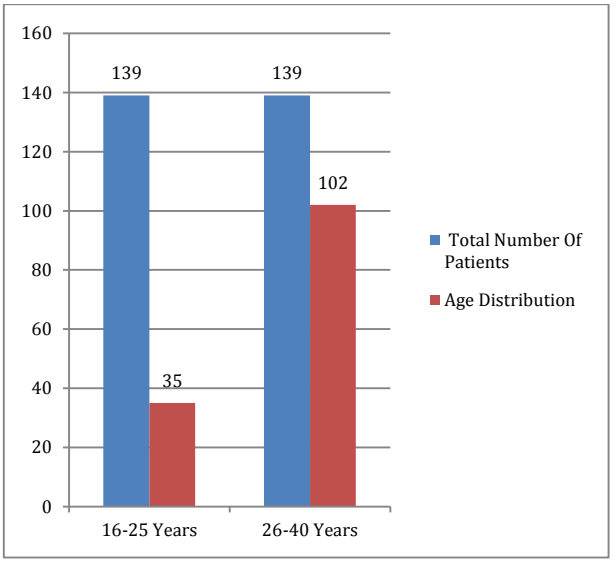

Figure-1: Age Distribution

Table-1: BMI (n=139)

BMI	Frequency	Percentage
18.5-24.9 kg/m^2	10	7.2
25-29.9 kg/m^2	60	43.2
≥30 kg/m^2	69	49.6

Mean BMI was 30.7 Kg/m^2 (SD±4.4)
Mean Height was 159.2 cm (SD±7.0)
Mean Weight was 78.4 kg (SD±11.0)

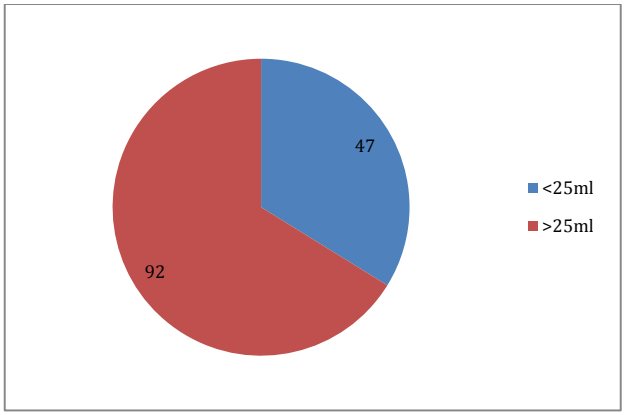

Figure-2: Ovarian Volume (n=139)
Mean Ovarian Volume was 25.5ml (SD±6.7)

Table-2: Serum Testosterone (n=139)

Serum Testosterone Level	Frequency	Percentage
<70ng/dl	106	76.3
>70ng/dl	33	23.7

Mean serum Testosterone was 48.8ng/dl (SD±26.4)

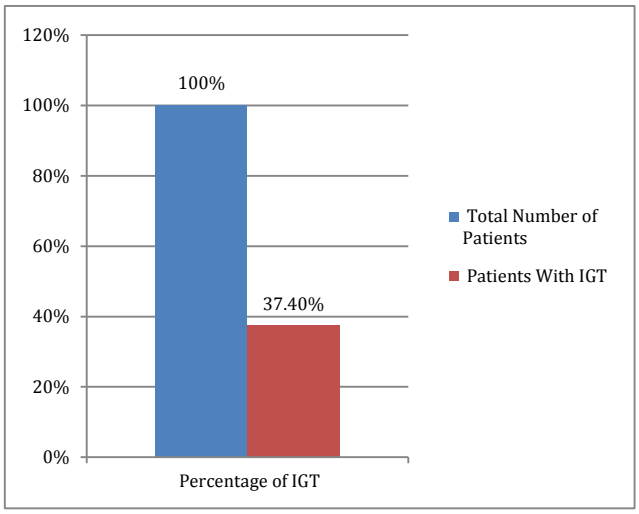

Figure-3: Frequency of Impaired Glucose Tolerance (n=139)

Table-3: Stratification for age.

Age	Impaired Glucose Tolerance		Total	P value
	Yes	No		
16-25	15	21	36	
26-40	37	66	103	0.3
Total	52	87	139	

Table-4: Stratification for BMI.

BMI	Impaired Glucose Tolerance		Total	P value
	Yes	No		
Normal	5	5	10	
Overweight	29	31	60	0.02
Obese	18	51	69	
Total	52	87	139	

Table-5: Stratification for Waist Circumference

Waist Circumference	Impaired Glucose Tolerance		Total	P value
	Yes	No		
< 80cm	13	40	53	
>80cm	39	47	86	0.01
Total	52	87	139	

Table-6: Stratification for Family History of Diabetes.

Family History of Diabetes	Impaired Glucose Tolerance		Total	P value
	Yes	No		
Yes	30	45	75	
No	22	42	64	0.4
Total	52	87	139	

Table-7: Stratification for Serum Testosterone Level.

Serum Testosterone Level	Impaired Glucose Tolerance		Total	P value
	Yes	No		
<70ng/dl	30	76	106	
>70ng/dl	22	11	33	0.000
Total	52	87	139	

Table-8: Stratification for Ovarian Volume.

Ovarian Volume	Impaired Glucose Tolerance		Total	P value
	Yes	No		
<25ml	12	35	47	
>25ml	40	52	92	0.03
Total	52	87	139	

DISCUSSION

Polycystic ovary syndrome affects 4-12% of women in their reproductive age and is more common between 15-25 years of age.[14, 15] It is usually associated with menstrual abnormalities, hyperandrogenism, anovulation, infertility, anxiety, depression, cardiovascular disease and metabolic abnormalities.[2] Women with polycystic ovary syndrome are at increased risk of insulin resistance, impaired glucose tolerance and even type 2 diabetes mellitus.[16]

This study aims to determine the prevalence of impaired glucose tolerance in patients with PCOS. This study found that 37.4% of women with PCOS have impaired glucose tolerance. Younas B et al [17] in her study of 120 patients conducted in department of Gynecology Murshid Hospital Karachi reported a frequency of 16.7%. According to some clinical studies the prevalence of IGT in women with PCOS is 31-35%. [18, 3]

Compared to previous studies we found a little bit higher association of IGT with polycystic ovarian syndrome. This may be due to lack of awareness in general population or late detection of PCOS. Insulin resistance is a major risk factor for the development of impaired glucose tolerance, type 2 Diabetes and subsequent cardiovascular disease. [19, 20] most of the PCOS women are obese which is well known risk factor for insulin resistance and account for 30% cause of insulin resistance in patient with polycystic ovary syndrome.[21]

In our study 49.6% of women were obese, 43.2% were overweight while only 7.2% of patients have their BMI with in normal range. Following stratification for BMI we found that most of the patients with impaired glucose tolerance are overweight (55.7%) and obese (34.6%) with only 9.6% of them having BMI within normal range. Younas B et al[17] reported that 75% of PCOS women with impaired glucose tolerance have their BMI greater than 25 Kg/m^2. Bu et al[16] compared the effect of body mass index on glucose metabolism in women with PCOS. The mean BMI in his study was significantly higher in patients with impaired glucose tolerance (25.5±3.1), compared to those having normal glucose tolerance (21.8±2.7). A study by Flannery et al[15] reported equal prevalence of IGT in both obese and non-obese women with polycystic ovarian syndrome.

The relationship between serum testosterone and impaired glucose tolerance is controversial. Some studies reported a higher serum testosterone level in PCOS patients with either impaired glucose tolerance or type 2 diabetes mellitus compared to those with normal glucose tolerance.[22] Ganie et al[23] in his study did not found correlation between serum testosterone level and impaired glucose tolerance in women with PCOS. In our study mean serum testosterone was 48.8±26.4ng/dl. Most of the patients have serum testosterone level greater than 70ng/dl (76.3%). Following stratification we found significant correlation between testosterone level and impaired glucose tolerance. In our study 30 out of 106 with impaired glucose tolerance have serum testosterone less than 70ng/dl, while 22 out of 33 women with IGT have their serum testosterone level greater than 70ng/dl.

Excessive androgen secretion with associated risk of insulin resistance and metabolic syndrome is a defining feature of polycystic ovary syndrome.[24] Zhang B et al[25] found free androgen index to be an independent risk factor for high prevalence of impaired glucose tolerance in patients with PCOS. Increase in free androgen index is associated with decreased insulin sensitivity and Beta cell function.[25] There is evidence that PCOS women with positive family history of diabetes are at greater risk of developing type 2 Diabetes mellitus.[3,18] Furthermore PCOS women with positive family history of type 2 Diabetes and PCOS have highest prevalence of hyperandrogenism and impaired glucose tolerance or frank Diabetes mellitus.[26] PCOS women with positive family history of type 2 diabetes have 1.7 fold increased risk of pre-diabetes and insulin resistance.[26] We did not found similar relationship between family history of diabetes and impaired glucose tolerance. In our study 30 out 75 PCOS women with abnormal glucose metabolism had positive family history of diabetes compared to 22 out of 64 with no family history of diabetes (P=0.4).

Ntyintyane L et al[27] reported a considerable correlation between waist circumference and insulin resistance. Increase in

waist circumference to greater than 80cm has been shown to be associated with impaired glucose tolerance in women polycystic ovary syndrome.[28] We found a statistically significant correlation between waist circumference and impaired glucose tolerance (P=0.01). In our study 39 0ut of 52 patients with impaired glucose tolerance had their waist circumference greater than 80cm while only 13 patients had their waist circumference less than 80 cm. Clinically, waist circumferences is the most relevant approach for the measurement of insulin resistance. [29] It is a marker of visceral adiposity, commonly used in medical practice to detect insulin resistance clinically. Increase in waist circumference is associated with wide range of metabolic abnormalities including reduced insulin sensitivity, impaired glucose tolerance and deranged lipid profiles, which are risk factor for type 2 diabetes and cardiovascular disease. We did not found any previous study which studied the impact of ovarian volume on glucose metabolism in women with PCOS.

We observed that women with increased ovarian volume are more prone to develop abnormal glucose metabolism. In our study 40 out 52 patients with impaired glucose tolerance had combined ovarian volume greater than 25ml. This may be to excess androgen secretion which is well known risk factor for insulin resistance.

The main limitation of this study is its inability to determine the prevalence of Type 2 Diabetes in addition to IGT as impaired glucose tolerance puts the PCOS women at a higher risk for development of Diabetes mellitus. Another limitation includes lack of measurement of serum hormone binding globulin (SHBG) and free androgen index, which is more sensitive than serum testosterone level.

CONCLUSION

The prevalence of impaired Glucose tolerance with polycystic ovary syndrome can be as high as 37.4%. Increasing age and BMI, raise serum testosterone level and increasing ovarian volume are significant predictors for developing impaired glucose tolerance in women with polycystic ovary syndrome. Metabolic evaluation should be done while managing Hirsutism, menstrual abnormalities and subfertility in patients with PCOS.

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