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**Research Article**

# Prevalence of glucose tolerance test abnormalities in women with polycystic ovarian syndrome

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## ABSTRACT

**Background:** PCOS is the most frequent endocrine disorder, often complicated by chronic anovulatory infertility and hyperandrogenism. High prevalence of impaired glucose tolerance and type 2 diabetes is observed due to peripheral insulin resistance. Holistic approach to the disorder to prevent long-term complications is required. The objective of the study was to study the prevalence of oral glucose tolerance test abnormalities (OGTT) in PCOS women and to study the significance of risk factors contributing to glucose intolerance in women with PCOS.
**Methods:** Hospital based analytical cross sectional study was conducted for 1 and ½ years among 200 women with PCOS. Women diagnosed as PCOS according to Rotterdam's criteria. Women with other causes of anovulation, premature ovarian failure and women already diagnosed to be diabetic.
**Results:** Abnormal glucose tolerance was observed in 32 (16 %) of the 200 PCOS women. Among them 14.5% had impaired glucose tolerance (IGT) and 1.5% had diabetes. There was a significant trend towards increasing prevalence of IGT and diabetes in females with higher BMI, waist circumference, clinical and biochemical hyperandrogenism and patients with metabolic syndrome.
**Conclusions:** High prevalence of IGT and Non-Insulin Dependent Diabetes Mellitus (NIDDM) in women with PCOS was observed than expected. They have accelerated conversion from IGT to NIDDM. IGT is often asymptomatic and is a known risk factor for type 2 DM and cardiovascular disease. OGTT with 75 gms of glucose is the best screening method for glucose intolerance and a good measure to diagnose type 2 DM in PCOS women.

**Keywords:** PCOS, Oral glucose tolerance test abnormalities, Impaired glucose tolerance, Non-insulin dependent diabetes mellitus

## INTRODUCTION

Polycystic ovarian syndrome (PCOS) is a common endocrinopathy, affecting approximately 5-10% of women of reproductive age characterized by oligo- or anovulation, clinical or biochemical hyperandrogenism, and polycystic ovarian morphology on ultrasonography.[1-4] Burghen et al in 1980 reported that women with PCOS, had basal and glucose-stimulated hyperinsulinemia compared with weight-matched control women, suggesting the presence of insulin resistance (IR) and noted significant positive linear correlations between insulin and androgen levels.[5] Since then so many studies were done on PCOS and insulin resistance and found that IR affects 50% -70% of women with PCOS leading to co-morbid conditions like impaired glucose tolerance, diabetes, hypertension, dyslipidaemia and metabolic syndrome. Most of the women present at young age and IGT being asymptomatic, it is important to screen them for the prevalence of pre-diabetes and diabetes so that direct counselling regarding life style modifications which helps in decreasing the severity or delaying the onset of diabetes mellitus.

## METHODS

### *Study design*

Hospital based analytical cross sectional study

### *Study period*

One and half years from April 2014 to September 2015 .

### *Study population*

200 women and adolescents who attend the outpatient department, OBGY, ACS Medical College, Chennai.

### *Inclusion criteria*

Women diagnosed as PCOS according to Rotterdam's criteria.

### *Exclusion criteria*

1. Women with other causes of anovulation like thyroid, prolactin abnormalities, premature ovarian failure.
2. Women already diagnosed to be diabetic.
3. Women unwilling to participate or sign the informed consent.

### *Ethical considerations*

Informed consent was obtained from all the participants at the start of the study. Ethical clearance was taken from the institutional ethical committee before starting the study.

### *Proforma*

Detailed clinical history was taken and clinical examination performed. Information about age, menarche, menstrual cycles, acne, hirsutism, marital status, family history of diabetes and PCOS, anthropometric measurements of weight, height, waist circumference, blood pressure were noted. USG abdomen and pelvis, blood levels of various hormones, lipid profile and OGTT were done. The study group were categorized as normal glucose tolerance (NGT), IGT or NIDDM according to ADA criteria (2015).

Regarding hypothyroidism, the women were divided into 3 groups, as per the National Health and Nutrition Examination Survey III 2002.[3]

1. Group 1 (euthyroid): Infertile women with normal TSH level (0.39-4.6 mIU/ml).
2. Group 2 (subclinical hypothyroidism): Infertile women with raised TSH level ranging from 4.6-20 mIU/ml and normal free $T_4$ level.
3. Group 3 (overt hypothyroidism): Infertile women with TSH level > 20 mIU/ml and low free $T_4$ level.

With regard to raised prolactin (PRL) levels, as per WHO guidelines, PRL level > 25 μg/l was considered as hyperprolactinemia.[4]

### *BMI - ICMR Guidelines (2008)[5]*

1. Normal - 18 - 22.9 kg/m$^2$
2. Overweight - 23 - 25 kg/m$^2$
3. Obese - > 25 kg/m$^2$

In our study, we have analysed the prevalence of hypothyroidism among primary infertile and secondary infertile women, potential demographic risk factors, hormonal and metabolic parameters associated with hypothyroidism.

Categorical data were analysed with the odds ratio, chi square test and the P value of < 0.05 was considered statistically significant. SPSS software was used for statistical analysis.

### *Classification of study variables*

*PCOS – Rotterdam's criteria [(6)]*

1. Oligo/anovulation
2. Clinical or biochemical hyperandrogenism (clinical hyperandrogenism - defined by more than 6 - 8 score of Ferriman Gallway scoring system)[7]
3. Ultrasound features of polycystic pattern in one or both ovaries.(Polycystic pattern is defined as more than 12 follicles of less than 10 mm diameter and ovarian volume of > 10 cm)[8]

### *ADA criteria (2015)[9]*

*Pre diabetes Diagnosis: diabetes diagnosis*

Impaired Fasting Glucose (IFG)
FBG - 100 mg/dl - 125 mg/dl FPG ≥ 126 mg/dL
Impaired Glucose Tolerance (IGT)
2 hr PG 140 mg/dl - 199 mg/dl with 75 g OGTT 2-hr PG ≥ 200 mg/dL

### *BMI - ICMR Guidelines (2008) [(10)]*

Normal: 18 - 22.9 kg/m$^2$
Overweight: 23 -25 kg/m$^2$
Obese: > 25 kg/m$^2$

In our study, we have analysed, the clinical presentation of PCOS among unmarried women, adolescents and married women, prevalence of glucose tolerance test abnormalities, potential demographic risk factors, clinical and biochemical parameters of PCOS women in relation to abnormal GTT and the prevalence of metabolic syndrome among them. Categorical data were analysed with the odds ratio, chi square test and the P value of < 0.05 was considered statistically significant. SPSS software was used for statistical analysis.

## RESULTS

**Table 1: Socio - demographic risk profile of women with PCOS.**

| Variable | Classification of variable | No. of pts. (200) | (%) |
|---|---|---|---|
| Age | 16-20 | 15 | 7.5 |
| | 21-25 | 65 | 32.5 |
| | 26-30 | 90 | 45 |
| | 31-35 | 24 | 12 |
| | 36-40 | 6 | 3 |
| BMI | <23 | 105 | 52.5 |
| | 23-25 | 45 | 22.5 |
| | >25 | 50 | 25 |
| Waist Circumference (cm) | >88 | 24 | 12 |
| | <88 | 176 | 88 |
| Family history of Diabetes | Yes | 44 | 22 |
| | No | 156 | 78 |
| Metabolic syndrome | Yes | 19 | 9.5 |
| | No | 181 | 90.5 |

Glucose tolerance was assessed by ADA criteria - 2015. Among 200 women with PCOS, normal glucose tolerance was observed in 84% (168 patients), IGT in 14.5% (29 patients) and diabetes in 1.5 % (3 patients) (Figure 1).

### *Clinical presentation of PCOS*

Among married women, 67.88% presented with irregular menstrual cycles as the chief complaint followed by infertility in 52.1% and acne, hirsutism, weight gain in 27-29% of women (Figure-2).

Among unmarried women and adolescent age group PCOS, 45.71% presented with acne as the chief complaint, 37.14% with irregular cycles, 31.43% with hirsutism and 5.71% with increased weight gain (Figure 3).

### *Age*

For the entire cohort of PCOS women, the mean age of presentation was 26.8 years. 65.52% of women with IGT and 66.67% with NIDDM were beyond 25 yrs. of age and the mean age of presentation of IGT and NIDDM patients was 27.78 years. Although the women with IGT and NIDDM tend to be slightly older, the correlation of age with abnormal GTT was not found to be statistically significant (Odds Ratio [OR], 1.33; P = 0.61) as seen in Table 3.

**Table 2: Clinical and biochemical profile of PCOS patients.**

| Variable | Number | Percentage | 95% C.I |
|---|---|---|---|
| Abnormal GTT | 32 | 16 | 10.92 – 21.08 |
| Irregular menstrual cycles | 125 | 62.5 | 55.79 - 69.21 |
| Acne | 63 | 31.5 | 25.06 – 37.94 |
| Hirsutism | 58 | 29 | 22.71 – 35.29 |
| Obesity | 50 | 25 | 19 - 31 |
| Increased Androgen levels | 31 | 15.5 | 10.48 – 20.52 |

### *Anovulatory cycles*

62.5% of PCOS women among the study group had oligo/anovulatory cycles with 95% C.I: – 10.92 – 21.08 (Table 2). Among PCOS women with abnormal glucose tolerance, with the exception of 2 patients having regular menstrual cycles (IGT group), all the women with NIDDM and IGT (30 patients) were found to have irregular menstrual cycles and the relationship between anovulatory cycles with abnormal OGTT was statistically significant (OR, 11.5; P = 0.00015) as seen in Table 3.

### *Clinical hyperandrogenism*

Clinical features of hyperandrogenism like acne and hirsutism were observed in 63 (31.5%) and 58 (29%) of PCOS women with 95% C.I: 25.06 - 37.94 and 22.71 - 35.29 (Table-2). The relation between abnormal glucose tolerance and clinical features of hyperandrogenism shows a positive linear correlation. OR, 3.51; P = 0.0002 for acne and OR, 2.57; P = 0.26 for hirsutism respectively (Table 3).

### *Family history of diabetes*

Family history of diabetes was present in 22% of PCOS women (Table 1). Among abnormal glucose tolerance women, 66.65% with NIDDM and 44.83% with IGT had family history of diabetes. Conversion from IGT to NIDDM is accelerated as much as 5 to 10 fold in PCOS women and family history is considered as one of the risk factors. We found a statistically significant correlation (OR, 4.23; P = 0.0005) between family history of diabetes and abnormal GTT.

### *BMI & waist circumference*

Among the study group, 25% of PCOS women were obese (95%C.I: 19 – 31) as seen in Table-2. If we consider, women with abnormal glucose tolerance, 31 patients out of 32 were found obese. A positive

correlation between obesity and glucose tolerance abnormality was observed (OR, 243.1; P = 0.0000000*). Waist circumference >88cms was observed in 21 patients (72.41%) with IGT and all 3 patients (100%) with NIDDM.

**Table 3: Significance of clinical, demographic and biochemical characteristics of PCOS and abnormal GTT.**

| Variable | Classification of variable (total number in the group) | Number with IGT and NIDDM (out of 32) | Chi-square value | Odds ratio (95%C.I of odds ratio) | P value |
|---|---|---|---|---|---|
| Menstrual cycles | Irregular (125)<br>Regular (75) | 30<br>2 | 14.33 | 11.5<br>(2.67 –49.8) | 0.00015* |
| Acne | Acne yes (63)<br>Acne No (137) | 18<br>14 | 9.49 | 3.51<br>(1.62 –7.65) | 0.0002* |
| Hirsutism | Yes (58)<br>No (142) | 15<br>17 | 4.92 | 2.57<br>(1.18 –5.57) | 0.026* |
| Obesity | Yes (50)<br>No (150) | 31<br>1 | 100.45 | 243.1<br>(31.37 -884.27) | 0.0000000* |
| Testosterone levels | Increased ( 31)<br>Normal (169) | 30<br>2 | 171.05 | 2505<br>(220.1- 3504.12) | 0.00000000* |
| Age in years | ≤ 25 (80)<br>> 25 (120) | 11<br>21 | 0.26 | 1.33<br>(0.6 – 2.94) | 0.61 |
| Family history of diabetes | Present (44)<br>Absent (156) | 15<br>17 | 12.06 | 4.23<br>(1.9 – 9.43) | 0.0005* |

**Table 4: Components of metabolic syndrome in women with PCOS.**

| | No. of pts. | % |
|---|---|---|
| Fasting Glucose > 100 mg/dl | 32 | 16 |
| Bp > 130/85 mm of Hg | 7 | 3.5 |
| Triglycerides >150 mg/dl | 17 | 8.5 |
| HDL < 50 mg/dl | 54 | 27 |
| Waist Circumference >88 Cm | 24 | 12 |

***Androgen levels***

Among PCOS women, 15.5% had increased androgen levels with 95% C.I: 10.48 – 20.52 (Table-2). Women with glucose intolerance (IGT - 93.10%, NIDDM - 100%) had significantly higher levels of serum total testosterone which showed a positive linear correlation. (OR, 2505; P = 0.00000000 *) as seen in Table 3.

***Metabolic syndrome***

Out of the 5 components, (Fasting Glucose > 100 mg/dl, BP > 130/85 mm of Hg, Triglycerides >150 mg/dl, HDL < 50 mg/dl, Waist Circumference > 88 cm) at least 3 features should be present to consider a patient to have metabolic syndrome. 19 patients (9.5%) out of 200 PCOS women were found to have this syndrome and all these women belong to abnormal glucose tolerance group (Table 4).

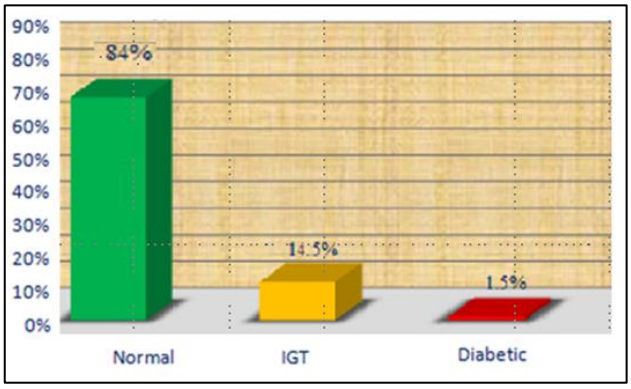


**Figure 1: GTT results by ADA criteria (N=200).**

## DISCUSSION

Women with PCOS are at high risk of developing abnormal glucose tolerance. Although the nature of insulin resistance in PCOS is currently unclear, defects in insulin receptor or post-receptor signal transduction, altered adipocyte lipolysis, decreased glucose transporter 4 in adipocytes, and impaired release of a d-chiro-inositol mediator have all been implicated. Furthermore, many women with PCOS exhibit β-cell dysfunction, rendering insulin response to a glucose load insufficient for the degree of insulin resistance in PCOS.

In two of the largest studies (Ehrmann DA et al, Legro RS et al study) to date that documented the prevalence of IGT and type 2 DM in women with PCOS, it was

estimated that IGT was present in 31–35% of women and type 2 DM in 7.5-10% compared with the prevalence of IGT (1.6%) and DM (2.2%) found in U.S.[11,12] Preeti Dabadghao et al study on 372 Australian women with PCOS had prevalence of 4% DM, 15.6% IGT and 80.4% NGT.[13] In Kanchana Devi et al study on 149 South Asian PCOS women, 14.09% had IGT and 2.01% had NIDDM.[14] In addition, IGT and type 2 DM were also highly prevalent among adolescents with PCOS. In Palmert MR et al study, IGT was present in eight of 27 (29.6%), and type 2 DM was present in two of 27 (7.4%) adolescent girls with PCOS.[15] The conversion from NGT to type 2 DM can occur in as little as 5 yrs, most likely because of the strong correlation of PCOS and insulin resistance.[16]

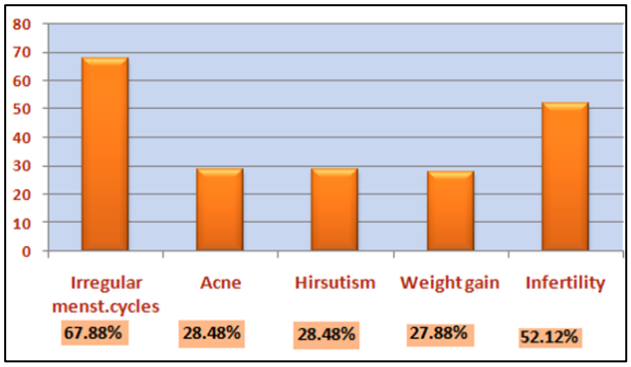


**Figure 2: Clinical presentation of married PCOS women in percentage.**

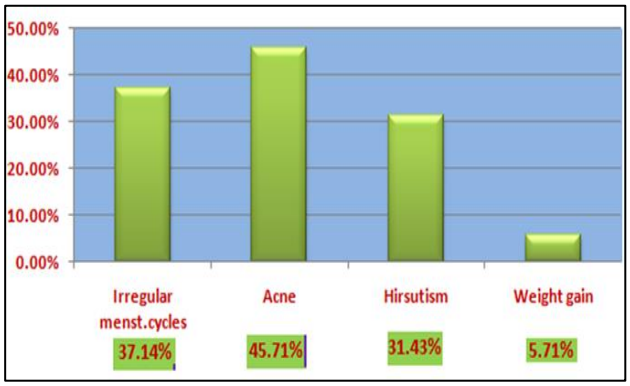


**Figure 3: Clinical presentation of unmarried PCOS women in percentage.**

In our study, among 200 women with PCOS, normal glucose tolerance was observed in 84% (168 patients), IGT in 14.5% (29 patients) and diabetes in 1.5 % (3 patients). Though the South Asian population was considered to have increased preponderance to impaired glucose metabolism, the prevalence was much lower than the American studies.

Clinical characteristics of the study subjects in Ehrmann et al study shows the women with NIDDM tended to be slightly older than other group of PCOS patients but this difference in age was not statistically significant which was similar to our study.[11] It has been suggested that a family history of diabetes worsens insulin secretion and glucose tolerance in PCOS. When compared to normal glucose tolerance group, PCOS women with type 2 DM had a 2.6-fold higher prevalence of diabetes among first degree relatives ( $P < 0.01$) and were significantly more obese.(BMI 41.0 ± 2.4 vs. 33.4 ± 1.1 kg/m2, P = 0.01 ). In another study conducted by Preeti Dabadghao et al 98% of PCOS women with abnormal GTT were overweight or obese, predominantly abdominal obesity and a significant higher waist circumference (P = 0.001) than those in the NGT group.[13] Women with diabetes were significantly older (P = 0.003) and family history of diabetes (44%) had a positive correlation (P = 0.014).

In our study, risk factors for glucose intolerance were BMI >23, waist circumference >88 cms, obesity and family history of diabetes. Strong correlation of obesity and family history of diabetes with glucose intolerance were found which was statistically significant. (P = 0.00000000*, P = 0.0005)

A life style modification is the most important aspects of treating IGT and reduces the progression to NIDDM. Lifestyle intervention comprising low-fat diet and 150-min exercise per week reduced the progression from IGT to type 2 DM by 58% in a study done by Knowler WC et al.[16]

Another contributing factor to the glucose intolerance of PCOS relates to elevated androgen concentrations. A dynamic interaction exists between hyperinsulinemia and hyperandrogenemia. It has been reported that there was a higher frequency of clinical androgenic features in PCOS women with IGT. The prevalence of menstrual irregularities, hirsutism and acne were 75%, 65% and 40% respectively in Preeti Dabadghao et al study.[13] In our study positive correlation between clinical androgenism and glucose intolerance was observed.

Ehrmann et al study on PCOS women with glucose intolerance had significantly higher levels of both total and free testosterone which was statistically significant (P = 0.0002, P = 0.0006). Our study finding of PCOS women with IGT or diabetes having significantly higher levels of total testosterone when compared to normal glucose tolerance women indicate that hyperandrogenemia contributes to the development of glucose intolerance. (OR, 171.05; P = 0.00000000 *). Hence addressing hyperandrogenism is important.

Women with PCOS have increased cardiovascular risk factors such as obesity, hyperandrogenism, hyperlipidemia (raised triglycerides and low-density lipoproteins) and hyperinsulinemia. IGT is a strong predictor for DM, as well as risk of cardiovascular disease and premature mortality. The prevalence of DM was significantly higher in women with features of metabolic syndrome. A meta-analytic study with BMI-matched controls showed a high prevalence of metabolic

syndrome in women with PCOS than in women without PCOS (OR 2.20, 95% CI 1.36–3.56).[17] In our study, all the PCOS women who had metabolic syndrome were in abnormal glucose tolerance group. Screening of high risk family members for metabolic abnormalities can be considered.

Thus, PCOS adversely affects endocrine, metabolic, and cardiovascular health. Evidence - based studies suggest that lifestyle-based multidisciplinary approach is optimal to manage PCOS and prevent long-term complications. A range of dietary strategies which are nutritious, sustainable in the long term and exercise which instead of focusing on weight loss, concentrating on overall health benefits is important. Regarding pharmacological therapy, OC pills improve hyperandrogenism and insulin sensitizers like metformin reduce insulin resistance. Medical therapy is targeted to symptoms and should not be an alternative to life style therapy in PCOS. Management should focus on education, support and strongly emphasizing the importance of healthy lifestyle with targeted medical therapy as required to prevent long-term complications.

## CONCLUSIONS

Women with PCOS are at high risk of developing abnormal glucose tolerance. Impaired glucose tolerance is often asymptomatic and is risk factor for NIDDM and cardiovascular disease. Hence regardless of BMI, all PCOS women should be screened for the presence of abnormal glucose tolerance using a 2-h OGTT using 75 gm glucose. OGTT is a simple test and can be performed easily in the laboratory. Based on current evidence, majority of PCOS women have normal fasting plasma glucose, hence the 2-h OGTT is the best screening method for glucose intolerance and a good measure to diagnose type 2 DM in PCOS women.

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