Original Research Article

Prevalence of glucose abnormalities in polycystic ovary syndrome women and evaluating the efficacy of fasting blood glucose in detecting these glucose abnormalities compared to glucose tolerance test

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ABSTRACT

Background: Polycystic ovarian syndrome (PCOS) is the most commonly prevalent endocrinopathy of reproductive age women. It is a significant public health issue with reproductive, metabolic and psychological features. Because patients with PCOS are at high risk for developing glucose abnormalities, the early identification of affected patients and institution of life style changes or pharmacological treatment may help reduce the long-term risks associated with PCOS. This study was done to assess the prevalence of glucose abnormalities and to evaluate the efficacy of Fasting blood glucose (FBG) in detecting glucose abnormalities when compared to 2 hrs oral glucose tolerance test (OGTT).
Methods: Hospital based cross sectional study carried out in 300 women diagnosed as PCOS according to Rotterdam criteria. In patients diagnosed as PCOS, Fasting Blood Glucose and OGTT were done. OGTT taken as an accurate test and FBG values compared with OGTT values to evaluate the efficacy of FBG. Prevalence of glucose abnormalities and association with age, BMI and clinical features was evaluated.
Results: Glucose abnormalities were detected in 69 (23%) women with 2 hours OGTT, but with FBG only in 49 (16.33%) women, around one third of women were missed. Sensitivity of FBG was 71.01% (95% CI 58.84% to 81.31%). Mean age of women with abnormal OGTT (27.99) was significantly higher than the women with normal OGTT (24.7). Mean BMI of women with abnormal OGTT (27.42) was significantly higher than the Mean BMI of women with normal OGTT (23.36).
Conclusions: Sensitivity of FBG was low in detecting glucose abnormalities. Increasing age, increase in a BMI, menstrual abnormalities, hirsutism/acne and family history of diabetes appear to have positive linear correlation with prevalence of glucose abnormalities.

Keywords: Fasting blood glucose, Glucose abnormalities, OGTT, PCOS

INTRODUCTION

The polycystic ovarian syndrome is the single most common endocrine disorder of reproductive age women, characterised by chronic anovulation/ oligomenorrhea, hyperandrogenism and insulin resistance. The association of amenorrohea and bilateral polycystic ovaries and obesity was first described in 1935 by Stein and Leventhal. The syndrome is present in approximately 15 to 20% of reproductive age women. These women present with diverse features including reproductive (irregular menstrual cycles, hirsutism, infertility and pregnancy complications), metabolic (insulin resistance, metabolic syndrome, pre-diabetes, type 2 diabetes and

cardio vascular risk factors) and psychological (anxiety, depression, body image).[1-4] Therefore, identifying PCOS and screening for these adjunct disorders will allow for timely institution of preventive strategies aimed at minimizing the overall health risks. Impaired glucose tolerance (IGT) is a known risk factor for type 2 diabetes and development of cardiovascular disease.[5] As most of women present at young age and IGT being asymptomatic, it is important to screen and identify pre diabetes and diabetes. Controversy around the optimal screening test to detect glucose abnormalities in PCOS is significant with proposed benefit of identifying IGT on an OGTT, requiring balance with increased inconvenience, cost and poor reproducibility with FBG which is more convenient, less costly more reproducible and easier to perform. Therefore, the present study was conducted to assess the prevalence of glucose abnormalities in patients with PCOS and to evaluate the efficacy of FBG in detecting glucose abnormalities.

METHODS

This study was conducted in SRM Medical College Hospital and Research Institute for a period of 2 years between October 2016 to December 2018. It was a hospital based analytical cross-sectional study, carried out in 300 women between age group of 18 to 35 years who were diagnosed as PCOS according to Rotterdam criteria (The Rotterdam ESHRE/ ASRM sponsored consensus workshop group 2004).[6] Two of the following criteria required to confirm the diagnosis of PCOS after exclusion of other causes.

- Oligo/anovulation (less than 8 cycles per year),
- Hyperandrogenism-clinical (hirsutism or less commonly male pattern alopecia) or biochemical (raised free androgen index or free testosterone),
- Polycystic ovaries on ultra sound (at least one ovary with 12 follicles of size 2 to 9 mm and or increased ovarian volume of more than 10 ml).

Women with PCOS already diagnosed with glucose abnormalities, women using insulin sensitizers or drugs affecting lipids, weight or insulin sensitivity within 3 months, women with prolactin and thyroid abnormalities, women with systemic illness and women who were not willing to participate were excluded. After exclusion total 300 women were enrolled for the study. Ethical clearance was obtained from the institutional ethical committee and informed consent was taken from each participant.

Detailed history regarding menstrual cycles, acne, hirsutism, marital status, parity, duration of infertility, history of gestational diabetes, drug history, family history of Type 2 diabetes taken from each patient. Standard anthropometric data including height, weight, blood pressure was measured. Degree of hirsutism was assessed by modified Ferriman- Gallwey- Lorenzo score. A score of more than or equal to 4-6 was considered as abnormal.[7] BMI was calculated and women were categorized according to ICMR guidelines in the following way.[8] Normal between 18 to 22.9 kg/m^2, overweight between 23 to 24.9 kg/m^2, and obese if BMI is more than 25 kg/m^2. FBG was obtained, then 2 hours OGTT was performed with 75 gm anhydrous glucose dissolved in 200 to 300 ml of water and the blood sample was taken after 2 hours. Glucose abnormalities were diagnosed according to ADA criteria.[9]

- FBG <100 mg/dl- Normal, 100 to 125 mg/dl- Impaired fasting blood glucose, ≥126 mg/dl- Type 2 diabetes.
- 2 hours OGTT <140- Normal, 140 to 199 mg/dl- impaired glucose tolerance, ≥200 mg/dl- Type 2 diabetes.

Descriptive analysis was carried out by mean and standard deviation for quantitative variables. Data was also represented by appropriate diagrams like bar diagrams. The efficacy of FBG in detecting glucose abnormalities considering OGTT as gold standard was analysed by calculating sensitivity, specificity, predictive values and diagnostic accuracy of FBG with 95% CI.

RESULTS

Demographic features

The mean age of study population was 25.5±5.6, the mean age of women with normal OGTT was 24.7±3.2 and the mean age of abnormal OGTT was found to be higher 27.99±4.3 (Table 1).

Table 1: Age and BMI.

Variable	Mean±SD of study population (n=300)	Mean±SD of women with normal OGTT (n=231)	Mean±SD of women with abnormal OGTT (n=69)	P value (One-way ANOVA)
Age	25.5±5.6	24.7±3.2	27.99±4.3	P <0.01
BMI	24.29±0.9	23.36±0.7	27.42±0.88	P <0.01

Among 300 women in this study, 133 women had normal BMI. 61 women had over weight BMI and 106 women were obese. Abnormal OGTT was found in 6 (4.5%) of women with normal BMI (n=133), 16 (26.22%) of

women with overweight BMI (n=61) and 47 (44.33%) of women with obesity respectively (Figure 1).
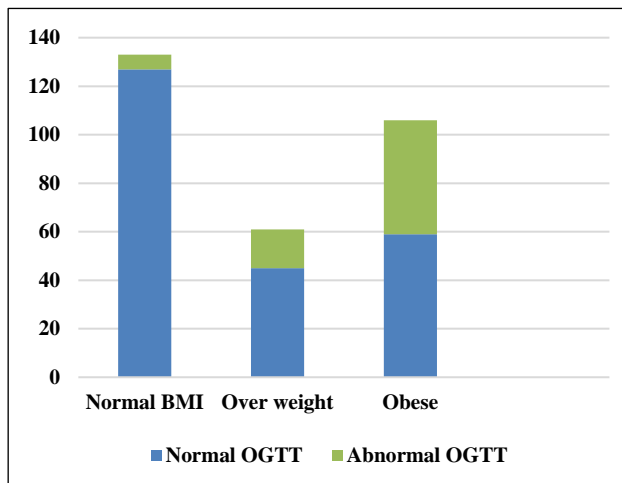

Figure 1: BMI and abnormal OGTT.

The mean BMI of total study population was 24.29±0.9, the mean BMI of women with normal OGTT was 23.36±0.7 and the mean BMI of women with abnormal OGTT was higher 27.42±0.88. Mean BMI values are depicted in Table 1.

Clinical presentation

In this study, 198 women were presented with menstrual irregularities out of which 135 women (68.18%) had normal OGTT, 63 women (31.81%) had abnormal OGTT. Hirsutism was present in 117 of study population out of which 30 (25.64%) women had abnormal OGTT, the remaining 87 women (74.35%) had normal OGTT. Family history of diabetes was present in 71 women out of which 35 women (49.29%) had abnormal OGTT and 36 women (50.70%) had normal OGTT. There appear to be a positive linear correlation between menstrual irregularities, hirsutism/ acne and family history of diabetes (Figure 2).

Table 2: Clinical presentation and OGTT.

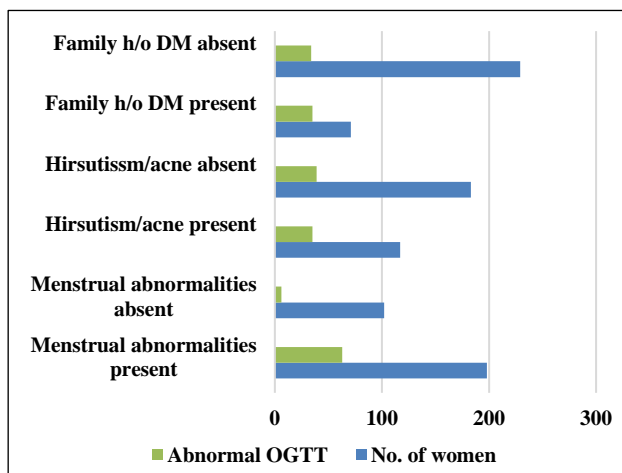| Clinical feature	No. of persons with the clinical feature Yes/No	No. of women with abnormal OGTT	Percentage of patients with abnormality (column 3/column 2x100)
Menstrual abnormality	Yes, n=198	63	31.81%
	No, n=102	6	5.88%
Hirsutism/acne	Yes, n=117	30	25.64%
	No, n=183	39	21.31%
Family h/o DM	Yes, n=71	35	49.29%
	No, n=229	34	14.84%

Figure 2: clinical features and abnormal OGTT.

Fasting blood glucose vs OGTT

Among 300 women OGTT was normal in 231 (77%) women and abnormal in 69 (23%) women, among 69

women with abnormal OGTT values, impaired glucose tolerance was seen in 65 (21.66%) and diabetes in 4 (1.33%) women. Among 300 women FBG values were normal in 227 (75.66%) women and abnormal in 53 (17.66%), among 53 women with abnormal FBG values, impaired fasting glucose was seen in 50 (16.66%) women and diabetes was seen in 3 (1%) women.

Among 231 subjects with normal OGTT, FBG values were also normal in 227 subjects but abnormal in 4 subjects. Among 69 subjects with abnormal OGTT, FBG values were abnormal only in 49 subjects and in remaining 20 subjects FBG values were normal (Table 3 and Figure 3).

The sensitivity of FBG in assessing glucose abnormalities was lower 71.01% (95% CI 58.84% to 81.31%) and the specificity was 98.27% (95% CI 95.63% TO 99.53%). The positive predictive value was 92.45% (95% CI 82.09% to 97.04%). The negative predictive value was 91.90% (95% CI 88.69% to 94.26%). The overall diagnostic accuracy was 92.00% (95%CI 88.33% to 94.81%) (Table 4).

Table 3: Fasting blood glucose test with standard OGTT.

OGTT (No.)		FBG (No.)	
		Normal	Abnormal
Normal	231	227 (true negative)	4 (false positive)
abnormal	69	20 (false negative)	49 (true positive)
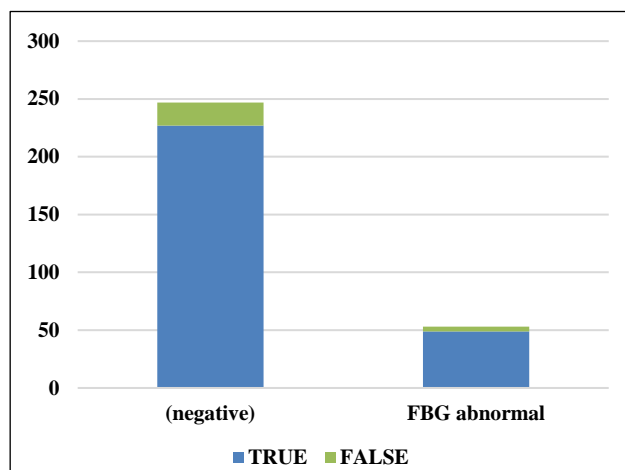
Figure 3: FBG test evaluation.

Table 4: Efficacy of fasting blood glucose test.

Statistical measures	Value	95% CI
Sensitivity	71.01%	58.84% to 81.31%
Specificity	98.27%	95.63% to 99.53%
Positive predictive value	92.45%	82.09% to 97.04%
Negative predictive value	91.90%	88.69% to 94.26%
Accuracy	92.00%	88.33% to 94.81%

DISCUSSION

PCOS is a common chronic condition with implications for morbidities, both in short term (subfertility and pregnancy related complications) and long-term complications (type 2 diabetes, cardiovascular disease, depression, poor quality of life and overall morbidity).

Insulin resistance appears to be the central pathophysiological mechanism responsible for various complications of PCOS and it is present in both lean and obese women. Insulin resistance may eventually lead to the development of hyperglycemia and Type 2 diabetes.[10]

Several mechanisms have been postulated to account for the predisposition to the glucose abnormalities among women with PCOS. Dunaif A et al, demonstrated that women with PCOS are insulin resistant, independent of obesity.[11] 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 adipocyte and impaired release of a D- chiro - inositol mediator have all been implicated.[12-15] Furthermore, many women with PCOS exhibit beta cell dysfunction rendering insulin response to a glucose load insufficient for the degree of insulin resistance in PCOS.[16] Approximately 30-40% of women with PCOS have impaired glucose tolerance and 7.5 to 10% have type 2 diabetes. In a study on 168 PCOS adolescent girls in India, 36% had impaired glucose tolerance and 9% had diabetes.[17] In one meta-analysis, an increased risk of metabolic syndrome was found in PCOS women as compared to BMI matched controls, and this increased risk is persisted in lean women.[18] The risk of impaired glucose tolerance and Type 2 diabetes is increased 5 to 7 fold in PCOS. In this study, the prevalence of glucose abnormalities was 23%. In a study by Legro RS et al, normal glucose tolerance was seen in 61.4%, IGT in 31.1% and diabetes in 7.5%. Consistently diabetes was 4 times higher in a recent Danish registry and was diagnosed 4 years earlier.[19,20]

Whilst guidelines consistently recommend screening for glucose abnormalities in PCOS, whether to target subgroups, which test to use and optimal frequency vary between guidelines and remain controversial.[21] Some recommend screening all women with PCOS where as others consider additional risk factors including ethnicity, BMI, previous history of gestational diabetes, family history of type 2 diabetes.[22] In high risk, South Asians PCOS significantly impacts incidence of type 2 diabetes.[23] Regardless of age the prevalence of gestational diabetes, IGT and type 2 diabetes are significantly increased in PCOS with risk independent of yet exacerbated by obesity. Therefore, effective methods of screening and early detection of glucose abnormalities is imperative in the management of women with PCOS. In this study, the mean age of women with glucose abnormalities is higher (27.99±4.3) than the women with normal glucose values (24.7±3.2), the difference seems to be statistically significant (p <0.01). Similarly, the mean BMI of women with glucose abnormalities is higher (27.42±0.88) than the women with normal glucose values (23.36±0.7), this difference also statistically significant (p <0.01). Legro R et al, also showed that an increased risk of IGT in women with advanced age, increased BMI, which are identical risk factors for the general population in developing IGT. In a cross-sectional study of 91 women with PCOS by 24. Trolle B et al, women who were older and had a higher BMI were more likely to have elevated fasting glucose values.[24] In this study, a positive correlation was found between menstrual irregularities, family history and hirsutism/acne. Ehrmann DA et al, found that those diagnosed with type 2 diabetes were 2.6 times more likely to have a first degree relative with diabetes than women with normal glucose tolerance.[25] Ehramnn DA et al, in a separate study evaluating a population of 408 premenopausal women with PCOS, also found a family history of type 2 diabetes in a first degree relative to be associated with a significantly higher risk for IGT and Type 2 diabetes in

women with PCOS. Burghan GA et al, found a positive correlation of hyperandrogenism with hyperinsulinism.[26]

Several studies have documented the prevalence of IGT and type 2 diabetes in women with PCOS. It is estimated that IGT is present in 31-35% of women with PCOS. In addition, type 2 diabetes classified according to WHO criteria is present in 7.5%-10% of women with PCOS. In Indian populations, women with PCOS appear to have worse glucose intolerance than Caucasian populations.[27] The enhanced rate of deterioration in glucose tolerance was corroborated by Legro R et al, who assessed the changes in glucose tolerance over time in U.S. women with PCOS and 23 control women who had baseline normal glucose tolerance.[35]

In this study, glucose abnormalities were found in 69 (23%) women with 2 hours OGTT but only in 49 (16%) women with FBG values alone. The sensitivity of FBG in assessing glucose abnormalities in PCOS women was lower 71.01%, (95% CI 58.84% to 81.31%) and the specificity is 98.27% (95% CI 95.63% to 99.53%). Presently, the only screening method of identifying individuals with IGT is by an OGTT.[28] A position statement of the Androgen Excess Society concluded that all patients with PCOS be screened for IGT with a 2 hours oral glucose tolerance test. It is more sensitive and moderately more specific in diagnosing glucose abnormalities compared with FBG.[29] In addition to providing information on both beta cell secretion and peripheral insulin action, the OGTT provides a better assessment of IGT than homeostatic techniques such as fasting glucose to insulin ratio, fasting insulin and homeostatic model assessment.[30] FBG has been classified as an insufficient screening tool in a recent systematic review on previous small studies in PCOS women by Tomlinson J et al.[31] A study by Legro R et al, found that FBG values are poor predictors of diabetes and found that FBG criteria recommended for diabetes screening by ADA is not applicable to PCOS women as it missed 58% of diabetes women in their study.[3] David CWL, in a study showed that FBG has 79% sensitivity in detecting glucose abnormalities in PCOS women.[32] In this study, also around one third of women with glucose abnormalities would be missed using FBG alone. Though OGTT has higher cost and greater inconvenience yet can define IGT and influence practice around lifestyle intervention and pharmacological treatment with clear evidence of type 2 diabetes prevention, not yet demonstrated based on FBG or HbA1c criteria.[33,34]

CONCLUSION

Women with PCOS are at an increased risk of developing impaired glucose tolerance and type 2 diabetes. Therefore, screening and detecting these glucose abnormalities is imperative in the management of PCOS women. The prevalence of glucose abnormalities was 23% with OGTT in this study population. The sensitivity of FBG in detecting glucose abnormalities is low

compared to OGTT. Increasing age, higher BMI, menstrual abnormalities, hirsutism/acne, family history of diabetes have positive linear correlation with glucose abnormalities in women with PCOS.

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