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Prevalence of Diabetes Mellitus among different phenotypes of Polycystic Ovary Syndrome in Egypt

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Abstract: Objective: To study the prevelance of Diabetes Mellitus in different phenotypes of polycystic ovary syndrome (PCOS) among attendants to Obstetric and Gynecology Clinic at Mansoura University Hospital (MUH) in Egypt utilizing OGTT and HBA1C. **Design:** Observational Prospective study. **Setting:** MUH (Tertiary Hospital), Obstetric and Gynecology Clinic. Dakahlia, Egypt. **Population:** A total of 140 women, among attendants to Obstetric and Gynecology Clinic at MUH which were diagnosed as PCOS based on the 2003 Rotterdam criteria. **Methods:** PCOS patients were divided into four subgroups: (i) Classic type: oligoand/oranovulation (O), hyperandrogenism (H), and polycysticovay morphology (P); (ii) Non classic type: O + H; (iii) Ovulatory type: H + P; and (iv) Normoandrogenic type: O + P., Then screening for DM using OGTT and HBA1C. **Results:** No significant difference between the 4 different phenotypes of PCOS regarding fasting blood sugar and the most significant type is classic type (phenotype A) regarding OGTT and HbA1C. The high sensitivity of 2-Hour postprandial blood glucose in detecting diabetic cases. The high specificity of HbA1C specially in detecting prediabetic cases**. Conclusions:** Classic PCOS phenotype has the highest risk of impaired glucose tolerance. Hyperandrogenism is associated with increasing risk of DM. High sensitivity of 2-Hour postprandial blood glucose in detecting diabetic cases and high specificity of HbA1C specially in detecting prediabetic cases.
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1. Introduction:

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder affecting women in childbearing age **(1).** According to the 2003 Rotterdam European Society of Human Reproduction and Embryology/American Society for Reproductive Medicine (ESHRE/ASRM) consensus workshop, PCOS was diagnosed by the presence of at least2of 3cardinal features: chronic oligoanovulation, hyperandrogenism, and polycysticovary morphology (POM), after exclusion of other identifiable endocrine disorders **(2)** Clinically, the specific phenotypes of PCOS women include a classic phenotype, which presents all three polycystic ovarian morphologies in addition to hyperandrogenism and ovulatory dysfunction (PCO+HA+OD); a phenotype with ovulation in addition to POM and hyperandrogenism (PCO+HA); a phenotype without POM but with androgen and ovulatory dysfunction (HA+OD); and a phenotype without hyperandrogenism but with POM and ovulatory dysfunction (PCO+OD **(3).** PCOS is promoted by insulin resistance and hyperandrogenism **(4).** Insulin resistance and subsequent compensatory hyperinsulinemia can be exacerbated by the coexistence of obesity which affects approximately 50% of PCOS women **(5)** A state of impaired glucose tolerance (IGT) precedes the onset of DM and usually remains asymptomatic. So it is important for a clinician to identify these 'at risk' cases at the adequate time and any intervention is justified to prevent the long-term complications of insulin resistance and glucose intolerance **(6).** Previous study was done in China showed that the non hyperandrogenic PCOS phenotype, was associated with lower risk of DM compared with the other phenotypes **(7)** Other recent study done in Brazil revealed that there is no significant difference in the prevelance of impaired glucose tolerance among different phenotypes of PCOS**. (8)**

As there are significant Deomographic, ethnic and racial variations in the clinical presentation of PCOS, the frequency of hirsutism, acne, polycystic appearing ovaries and obesity, the prevelance of insulin resistance in PCOS differs from area to other., So in this study we look for obtaining preliminary data about the prevalence of IGT and DM in the different phenotypes of PCOS and to assess the ability of OGTT and HBA1c as screening tests to predict these abnormalities within this population.

Subjects and methods

Subjects: Women with PCOS were recruited from Obstetrics and Gynecology clinics,

predominantly at the Mansoura University Hospital, Dakahlia., Egypt. Women were considered affected if they had at least 2 of 3 cardinal features: hyperandrogenism, chronic oligoanovulation, and POM, after exclusion of secondary causes **(2).** Different PCOS phenotypes, subsequently named classic (charactrized by hyperandrogenism and oligoanovulation, with PCO morphology, non classic (hyperandrogenism and oligoanovulation without POM, ovulatory (hyperandrogenism and PCO), and normoandrogenic (oligoanovulation and PCO**) (3).** A diagnosis of hyperandrogenism required clinical and /or biochemical evidence **(6).** Other potential endocrine and neoplastic causes of hyperandrogenemia were excluded. This diagnosis is consistent with the Rotterdam consensus criteria. Subjects were divided into four PCOS subgroups based on the criteria outlined in the Rotterdam PCOS consensus workshop. The groupings included (i) O (fewer than nine menstrual periods per year) + H (elevated Ferriman-Gallwey (F_G) score or androgen level) + P (at least one ovary >10 ml or at least 12 follicles 2–9 mm in diameter); (ii) O + H without polycystic ovaries; (iii) H + P with regularmenstrual cycles of 21–35 days; and (iv) O + P with no hyperandrogenemia. None of these 140 women were taking medication that could confound the clinical and endocrine presentation None of these 140 women were taking medication that could confound the clinical and endocrine presentation. All the women who participated in this study were informed regarding the procedure and consent was taken.

2. Methods:

Clinical assessment:

Personal medical history was obtained from every woman according to a customised prepared questionnaire. Menstrual cycle history was carefully documented since menarche and a detailed recall of the last 2 to 3 year interval. Ovulatory dysfunction was defined as less than eight cycles per year **(9).,** and regular menstrual cycle as 21–35days in length. Physical examination was performed in each woman. BMI is calculated as weight (kg) divided by height squared (m^2).

Laboratory tests:

In cases with oligomenorrhoea measurement of serum Prolactin, TSH, and17-hydroxyprogesterone levels was performed to exclude other causes of menstrual disorders. Hirsutism was defined by a modified Ferriman-Gallwey score >6.14 and Hyperandrogenism was defined when serum total testosterone was 0.6 ng/ml or higher, free testosterone was2.5pg/ml or greater **(10,11)**

Blood samples were taken from patients to evaluate:

1-OGTT>Fasting blood sugar and 2h postprandial blood glucose.

2-Haemoglobin A1C**.**

After overnight fasting for at least 12 hours, venous blood samples had been drawn twice, the first one at 8–10 AM and the second one at 2-hour post glucose loading to measure glucose and 2 hours following oral 75 g glucose loading**.** Abnormal OGTT is classified as follows:

(1) impaired fasting glucose (IFG), that is, fasting glucose (FG) ≥100 and<126 mg/dL. (2) impaired glucose tolerance test (IGT), that is, 2 hr glucose ≥140 and <200 mg/dL. (3) type 2 Diabetes mellitus (DM), that is, fasting blood glucose ≥126 mg/dL and/or 2 hr glucose ≥200 mg/dL **(12).**

-Special Kits were used for HBA1C measurement and classified as: (1) Normal<5.7%(< 39mmol/mol). (2) Prediabetic 5.7-6.4 %(39-46 mmol/mol). (3) Diabetis 6.5% or greater (48 mmol/mol or greater**) (13)**. People with diseases affecting haemoglobin, such as anemia,. Kidney disease and liver disease may affect the test., So these things had been excluded **(3)**.

Statistical Analysis:

Data analysis was performed using statistical software program (SPSS for Windows, version 21, USA). Normal distribution of variables was tested with the Shapiro Wilks test. The data were normally distributed in the four groups, so the results of numerical data were expressed as Mean ± Standard deviation. However, the results were expressed as number (percentages) for categorical variables.

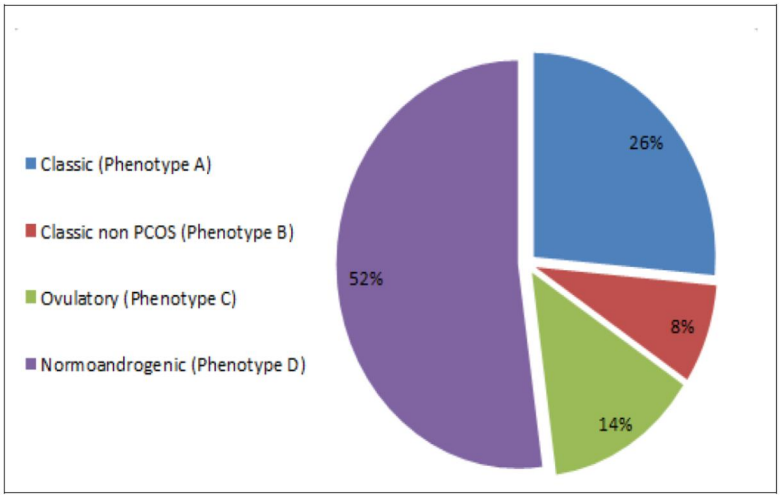
3. Results:

Of the total number of PCOS patients who met the diagnosis criteria of ESHRE/ASRM 2003 at least 2 of 3**)**: Oligomenorrhea Hyperandrogenism and PCO; 37 (26.43 %) fulfilled the criteria for Classic, 11 (7.86%) for Non Classic PCOS, 19 (13.57%) for ovulatoy, and 73(52.14) for Normoandrogenic (Table 1). Subjects in each subset differed slightly in age **(Table2)**. BMI was increased in women with classic and non classic PCOS compared with those with ovulatory and normoandrogenic type. A Ferriman Gallwey score (F-G) score with the higher score related to the classic non PCOS (phenotype B) group and the lower score to ovulatory (phenotype C) group. According to screening tests, No significant difference between the 4 different phenotypes regarding fasting blood sugar and The most significant type is classic type (phenotype A) regarding OGTT and HbA1C (Table 3). The high sensitivity of 2-Hour postprandial blood glucose in detecting diabetic cases. The high specificity of HbA1C specially in detecting prediabetic cases (Table 4).

Table 1: Classification of patients with PCOS into 4 types:

Type	Number (%)
Classic (Phenotype A)	37 (26.43 %)
Classic non PCOS (Phenotype B)	11 (7.86 %)
Ovulatory (Phenotype C)	19 (13.57 %)
Normoandrogenic (Phenotype D)	73 (52.14)
	Total 140 (100 %)

*The most frequent PCOS phenotype is the group with normoandrogenic type (phenotype D).



Distribution of phenotypes of patients with PCOS

Table 2: Comparison of demographics and clinical features in women with polycystic ovary syndrome (PCOS):

	Phenotype (A) Classic	Phenotype (B) Nonclassic PCOS	Phenotype (C) Ovulatory	Phenotype (D) Normo-androgenic
Age	26 ± 4.9	25±5.1	27±3.7	26±4.5
BMI	33.36 ± 3.15**	33.03 ± 3.47**	30.68 ± 5.06	29.17 ± 3.30
F-G score	8.4 ± 4.1	11.2 ± 6.7**	3.2 ± 1.8	4.9 ± 2.2
Family history of DM	14 (37.8%)	3(27.3%)	6(31.6%)	28 (38.4%)

BMI was increased in women with non classic PCOS (phenotype B) and classic (phenotype A). Ferriman Gallwey score (F-G) score with the higher score related to the classic non PCOS (phenotype B) group and the lower score to ovulatory (phenotype C) group.

Table 3: Comparison between the 4 phenotypes regarding blood glucose level

	Phenotype (A) Classic (n=37) Mean ± SD	Phenotype (B) Classic non Pcos (n=11) Mean ± SD	Phenotype (C) Ovulatory (n=19) Mean ± SD	Phenotype (D) Normo androgenic (n=73) Mean ± SD	F-value	P-value
Fasting blood sugar						
Normal	93.5±6.1	92.63 ± 12.07	89.18 ± 13.03	91.74 ± 8.22		
IFG	118.20±4.08	117.50 ± 3.54	120 ± 2.8	117.32 ± 6.25		
DM	139± 15.55	128 ± 0.0	-	133.50 ± 2.12	1.614	0.189*
OGTT						
Normal	122.9±8.2	122.67 ± 8.72	118.65 ± 9.10	123.02 ± 7.82		
IGT	170.4±13.53	183 ± 0.0	181 ± 11.31	166.13±13.46		
DM	240.14±27.8	240 ± 0.0	-	286 ± 5.66 **	3.144	0.0273*
HbA1C						
Normal	5.3±0.1			5.20 ± 0.23		
Prediabetes	6.12±0.17	5.21 ± 0.29	5.15 ± 0.30	6.33 ± 0.09		
DM	7.71±0.928	6.20 ± 0.20-	6.28 ± 0.13-	8 ± 0.14	5.025	0.00247**

*No significant difference between the 4 different phenotypes regarding fasting blood sugar.
*The most significant type is classic type (phenotype A) regarding OGTT and HbA1C.

Table 4: Comparison between the 3 applied screening tests regarding sensitivity of the results:

Screening test	Diabetic		Prediabetic		Normal		Sensitivity	Specificity	Likelihood ratio
	N	%	N	%	N	%			
Fasting blood sugar	5	3.6%	17	12.1%	118	84.3%	0.4	0.8592593	2.842106
2-Hour postprandial blood glucose	10	7.2%	16	11.4%	114	81.4%	0.8888889	0.8778626	7.277778
HbA1C	9	6.4%	24	17.1%	107	76.4%	0.7272727	0.8992248	7.216783

*The low sensitivity of FBS in detecting diabetic cases.*The high sensitivity of 2-Hour postprandial blood glucose in detecting diabetic cases.*The high specificity of HbA1C specially in detecting prediabetic cases

4. Discussion:

Among the four PCOS phenotypes, which were defined according to NIH (National Institute Of Health) guidelines, The most common group is normandrogenic type (Oligomenorrhea and polycystic ovaries) which represent 52.14% and the least one is non classic PCOS one (phenotype B) which represent 7.86%(Table1). This results are consistent with the results of a Korean study **(7).** Another studies were done in Korea **(14)** and China **(15)** revealed that the classic phenotype, Oligomenorrhea, Hyperandrogenism and PCO was the most common Phenotype. Most of the studies that have been performed around the world have argued that there are also racial differences in the distribution patterns of PCOS phenotypes. However, this was not supported by a case-control study that was performed by Ladson et al which revealed that differences between black and white PCOS women were minimal **(16)**. In our study, the mean (F-G) score of the PCOS group was 5.56 and the highest score was in with non classic PCOS (Table 2). This is different from study done in China in which the highest F-G score related to the classic phenotype **(7).** Thus, it may be due to ethnic difference in the criteria of hirsutism. BMI was increased in women with non classic PCOS (phenotype B) and Classic (phenotype A) compared with those with ovulatory (phenotype C) and normoandrogenic (phenotype D). This is similar to a study done in China **(17)** and in contrast with the study done in Brazil **(8)** in which no significant difference in BMI between the four phenotypes. That difference may be due to ethenic variation and environmental factors. Also sedentary life, exercise, smoking and food habbits may be the cause. Family history of DM was more prominent in classic type (phenotype A) 37.8% and normoandrogenic type (phenotype D) 38.4%. In contrast with, the study done in China **(7)**, in which Family history of DM was more prominent in ovulatory type. This may be related to ethinic and geographic variations. **Table (3) shows** different distribution of impaired glucose tolerance among different phenotypes of PCOS. This observation is not compatible with the results of recent study done in Brazil which revealed that there is no significant difference in the prevelance of impaired glucose tolerance among different phenotypes of PCOS **(8)**. No cases of DM were detected in a study done in China**,** only cases with IGT were detected **(17)**. These different findings are suggestive of the effects of genetic variation among ethnic populations and environmental factors. This may be due to geographic and racial variations between Egypt and other countries. Other factors as obesity, lifestyle modification, weight loss, exercise and widespread use of OCs, improve the hyperandrogenism by increasing sex hormone binding globulin and also decreasing ovarian steroidogenesis by and therefore decreasing the bioactive androgens. According to International Diabetes Fedration (IDF) 2018, the prevelance of diabetes in Egypt was around 15.1% among adults. The prevelance of DM that has been reported in Egypt and in Ethiopia, 2016 was (6.5%) **(18)**. In this study, the prevelance of IGT and DM found 17% for IGT and 7% for DM. In our study the prevalence of both DM and pre-DM was higher in the PCOS women than these studies. This result is low in contrast to that reported in Thai 13.6% **(19)**. The prevelance rates reported in the Mediterreanean region15.7% **(20)**, and Hispanics 22.1% **(21).** These different findings are suggestive of the effects of sedentary life, smoking, Fast food, environmental factors and ethnicity. **Table (4) shows** the sensitivity of applied tests in the screening. Based on the HBA1C value, 17.1% of women had IGT and 6.4% had DM. However, based on the 2 h OGTT value 11.4% of these women had IGT and 7.2 % had DM. By using FBS 3.8% of women had DM. FBS failed to detect 55.5% of those with DM detected by HBA1C and 2h PPS. Previous studies revealed poor sensitivity of FBS to detect IGT or diabetes in women with PCOS **(22)**. In previous study, 111 women with PCOS were screened for glucose abnormalities. Diabetes and IGT were diagnosed by OGTT in 4% and 20% of subjects, respectively. In a study done in Prague, 12.3% of 244 women with PCOS had abnormal FG, and 9.4% were found to have impaired glucose and 1.6% were found to have diabetes by OGTT (**23).** When data from these two studies were merged, the FG was found to have a poor correlation with the 2-hour glucose in women with IGT **(24)**. Our results indicated high sensitivity of 2-Hour postprandial blood glucose in detecting diabetic cases and high specificity of HbA1C specially in detecting prediabetic cases. In agreement

with our results, large study done in Denmark in which the sensitivity and specificity of a Hb A1c value of 6.5% for the diagnosis of diabetes were 35% and 99%, respectively, when the 2-hour glucose determination by OGTT (**25**). In contrast., large study among 671 women with PCOS showed that the use of HbA1c and fasting plasma glucose cannot be recommended as a screening tool for prediabetes among women with PCOS **(26).**

We concluded that Egyptian women with PCOS are at a higher risk of developing impaired glucose tolerance and diabetes than others. Classic PCOS phenotype has the highest risk of impaired glucose tolerance in our locality and subsequently non classic PCOS phenotype. Hyperandrogenism is associated with increasing risk of DM. High sensitivity of 2-Hour postprandial blood glucose in detecting diabetic cases and high specificity of HbA1C specially in detecting prediabetic cases., While fasting blood glucose screening tests may not reliably detect these abnormalities. Women with PCOS should be informed about their long term consequences like cardiovascular disease and type 2DM and they are recommended for lifestyle programs to prevent progression to T2DM. Glycaemic status should be assessed at baseline in all women with PCOS especially in PCOS with hyperandrogenism and with other risk factors of diabetes.

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