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Gestational Diabetes Mellitus and Metabolic Disorder Among the Different Phenotypes of Polycystic Ovary Syndrome

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ABSTRACT

Objectives: Polycystic ovary syndrome (PCOS) is a common endocrine disorder related to several metabolic consequences. However, there remains uncertainty regarding the metabolic features of various phenotypes. The aim of this study was to explore the relationship between the prevalence of gestational diabetes mellitus (GDM) and metabolic disorders among the four different phenotypes of PCOS. ***Methods***: A cross-sectional study was performed in Royan Institute including 208 pregnant women with a history of infertility and PCOS. Using the diagnostic criteria of the American Diabetes Association (ADA), pregnant women with a documented diagnoses of PCOS were further categorized into four different phenotypes (A, B, C, and D) as defined by the Rotterdam criteria. ***Results:*** The prevalence of GDM failed to demonstrate a significant relationship among the four phenotypes of PCOS. The mean levels of fasting blood sugar, plasma glucose concentrations at three hours (following the 100 g oral glucose tolerance test) and triglyceride levels were significantly higher in phenotype B compared to the remaining phenotypes ($p < 0.050$). There was a statistically significant difference between the mean free testosterone level and phenotypes A and C groups (1.8±1.6 vs. 1.1±1.0, $p = 0.003$). ***Conclusions:*** Women with a known diagnosis of PCOS who exhibited oligo/anovulation and hyperandrogenism demonstrated an increase of metabolic disorders. These results suggest that metabolic screening, before conception or in the early stages of pregnancy, can be beneficial particularly in women with PCOS phenotypes A and B. Early screening and identification may justify enhanced maternal fetal surveillance to improve maternal and fetal morbidity among women affected with PCOS.

Polycystic ovary syndrome (PCOS) is a female heterogeneous endocrine disorder affecting approximately 6–18% of all women of reproductive age.[1] Frequent clinical signs and sequels of PCOS include hyperandrogenism, oligomenorrhea, and anovulation.[2] It is well established that PCOS has been associated with an increased risk of gestational diabetes mellitus (GDM).[3] Women with PCOS often develop complex endocrine sequela such as increased levels of free testosterone, androstenedione, dehydroepiandrosterone sulfate (DHEA-S), luteinizing hormone (LH), elevated LH/follicle stimulating hormone (FSH) ratio, increased LH peak pulse frequency as a response to gonadotropin-releasing hormone, and wide variations in LH pulse frequency.[4]

Left unchecked, this syndrome often results in ovulatory dysfunction and increased levels of androgens. While the etiology of PCOS is unknown, there is evidence of a genetic relationship.[5] More concerning is an increased incidence of insulin resistance, obesity, dyslipidemia, in addition to laboratory findings suggestive of systemic inflammation, which over time, contributes to hypertension, cardiovascular disease, and stroke.[4,6,7] There is conflicting evidence surrounding the relationship between PCOS with related metabolic disorders and the various phenotypes of PCOS. A small sample of research suggests that metabolic disorders are more common in women diagnosed with the androgenic or oligomenorrheic phenotypes of PCOS,[8,9] whereas other research indicates there is no relationship between the specific phenotypes

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and increased metabolic risk and increased androgen levels.[10,11]

Zhao et al,[12] established a range of metabolic and biomedical variations among women with different phenotypes of PCOS compared to healthy control group. These findings demonstrated elevated high-density lipoprotein (HDL) level in phenotypes A, B and C groups in comparison with that of women unaffected in the control group. The total cholesterol level also increased considerably between phenotype A and D groups compared to the control group.

Reduced insulin sensitivity and impaired β-cell function during pregnancy predispose women with PCOS to glucose intolerance increasing the risk of GDM.[3] Previous research has established that the incidence of GDM is higher among women diagnosed with PCOS than those without.[3,13]

Several elements of diagnostic criteria have been suggested to confirm a diagnosis of PCOS. The original definition of PCOS, proposed by the European Society for Human Reproductive and Embryology and the American Society for Reproductive Medicine, required at least two of three following criteria; oligo or anovulation, increased androgen causing hirsutism, and multiple immature adnexal follicles ultrasound examination.[14] According to 2003 Rotterdam phenotypes, there are four different phenotypes of the syndrome identified; (a) hyperandrogenism, oligo/anovulation, and polycystic ovaries (HA+AO+PCO); (b) oligo/anovulation and hyperandrogenism (AO+HA); (c) hyperandrogenism and polycystic ovaries (HA+PCO); (d) oligo/anovulation and polycystic ovaries with normoandrogenic (AO+PCO).[14] Systematic changes that occur during PCOS cause pathological alterations within metabolic response as well as the changes in ovarian function.[15] However, there is no clear evidence whether these phenotypes have common features of metabolic disorder markers.[14] Determination of GDM prevalence, along with metabolic and endocrine disorders among different PCOS phenotypes is critical as it can employ early screening and identification in high-risk groups.

Despite a limited demonstration of the relationship between GDM and specific phenotyping of PCOS, this cross-sectional study was conducted to explore the potential relationship between the prevalence of GDM and metabolic disorders among the four phenotypes of PCOS.

METHODS

This cross-sectional quantitative study was performed in a reproductive research center between September 2012 to February 2013. The study received IRB approval from the Institution Review Board and Ethics Committee of Royan Institute. The study evaluated 208 pregnant women with a history of infertility and PCOS and no other known etiology of infertility. The sample size was determined based on a formula with a significance level of 0.050 and a power level of 0.540 with an anticipated appropriate size (difference of means/standard deviation) of 2.5.

A diagnosis of PCOS was established based on the presence of at least two Rotterdam criteria.[14] These include oligomenorrhea/amenorrhea, HA causing hirsutism, acne or androgenic alopecia, and PCO on ultrasound. Informed consent was obtained at the initial visit with additional permission attained to use results anonymously in future studies. Exclusion criteria included; maternal age ≥ 40, body mass index (BMI) 35 kg/m^2, family history of diabetes in first-degree relative, pre-pregnancy type II diabetes mellitus, history of gestational diabetes, history of stillbirth, recurrent miscarriage and birth weight baby ≥ 4.5 kg (macrosomia), parity > 4, diagnosis of Cushing syndrome, congenital adrenal hyperplasia, untreated hypothyroidism, and hyperprolactinemia. Fasting plasma glucose measurements were collected in all participants during the first trimester of pregnancy. According to American Diabetes Association (ADA) criteria (2005), the presence of GDM was made based on evaluating plasma glucose level using 50 g oral glucose challenge test (OGCT) at 24–28 weeks gestation. Women classified as high-risk (glucose ≥ 7.8 mmol/L or 140 mg/dL) were followed-up with a 100 g 3-hour oral glucose tolerance test (OGTT). When two or more of the 100 g OGTT glucose levels exceeded the ADA cut-off values (fasting ≥ 5.3 mmol/L (≥ 95 mg/dL); 1-hour ≥ 10 mmol/L (≥ 180 mg/dL); 2-hour ≥ 8.6 mmol/L (≥ 155 mg/dL); 3-hour ≥ 7.8 mmol/L (≥ 140 mg/dL)), a diagnosis of GDM was made. Additional evaluation of homeostasis model assessment of insulin resistance (HOMA-IR) index, HOMA of β-cell (HOMA-B) index, and Quantitative Insulin Sensitivity Check (QUICK) index were completed using the following formulas (GO and IO referred to the fasting levels of glucose [mg/dL] and insulin [mg/dL], respectively).

$$\text{HOMA-IR index} = \frac{(IO \times GO)}{405}$$

$$\text{HOMA-B index} = \frac{(360 \times IO)}{(GO-63)}$$

$$\text{QUICK index} = \frac{1}{[\log(IO) + \log(GO)]}$$

Glucose, triglycerides (TG), low-density lipoprotein (LDL) and HDL were measured by the enzymatic colorimetric method. Insulin was measured using the immunoenzymometric assay. Measurement of FSH, LH, prolactin, and testosterone was performed by chemiluminescence immunization. We determined the serum levels of thyroid-stimulating hormone (TSH), 17-hydroxyprogesterone (17-OH), DHEA-S, alkaline phosphatase (ALP), serum glutamic pyruvic transaminase (SGPT), and serum glutamic oxaloacetic transaminase (SGOT). A transvaginal ultrasound was used to detect PCO defined with 12 or more follicles with a diameter of 2–9 mm in one or both ovaries or ovarian volume higher than 10 cm.[14] Maternal hirsutism was defined using the Ferriman and Gallwey tool, with a score of seven or greater reported.[16]

The data was statistically analyzed using IBM SPSS Statistics for Windows, version 21 (IBM Corp., Armonk, N.Y., USA). Normality of analyzed variables was determined with Kolmogorov–Smirnov test. Comparisons among groups were made by one-way analysis of variance (ANOVA) or Kruskal–Wallis tests for non-normal variables (FBS, GTT). To compare two independent groups, the *t*-test for independent samples or the Mann-Whitney U test for non-normal variables was used. Tukey's test was applied for normal variables and Dunnett's T3 test for non-normal (free testosterone, TSH) variables to compare means among groups. Chi-square was used to compare nominal variables between groups. The significant level was set at $p \leq 0.050$.

RESULTS

We evaluated 208 PCOS pregnant patients who conceived with assisted reproductive technology (ART). The presence of GDM, along with endocrine and metabolic disorders, was compared among different phenotypes of PCOS. The results indicated that phenotype A (n = 113) was the most common phenotype (54.3%). The prevalence of the other three phenotypes was lower, B (n = 5; 2.4%), C (n = 74; 35.6%), and D (n = 16; 7.7%). The prevalence of GDM was most common in phenotype A (54.7%), followed by C (32.6%), D (7.4%), and B (5.3%). None of the four PCOS phenotypes showed a statistically significant relationship that influenced the prevalence of GDM ($p = 0.095$).

The study population characteristics among different PCOS phenotypes are illustrated in Table 1. The results did not identify significant differences in maternal age, ethnicity, education level, employment status, prepregnancy BMI, systolic and diastolic blood pressure, primary/secondary infertility, parity, age at menarche, or type of infertility treatment among the four different PCOS phenotypes ($p > 0.050$).

There was no statistically significant difference among various phenotypes regarding prepregnancy laboratory test; cholesterol, LDL-C, HDL-C, SGOT, SGPT, ALP, fasting insulin, LH, FSH, LH/FSH, TSH, 17-OH progesterone, DHEA-S ($p > 0.050$). The mean FBS was higher in phenotype B in comparison to that of the PCOS phenotypes A, C, or D (100.0±4.84, $p < 0.001$). The Man-Whitney U test results showed a statistical difference in the mean level of FBS when compared between groups (phenotypes A and B ($p = 0.002$), phenotypes A and D ($p = 0.015$), phenotypes B and C ($p < 0.001$)). The results of Man-Whitney test showed that the mean plasma glucose concentrations at 3-hour OGTT was significantly higher in phenotype B in comparison to phenotype A and C groups ($p = 0.002$ and $p = 0.008$, respectively).

According to the results of Dunnett's T3 test, there was a statistically significant difference in the mean level of free testosterone between phenotype A and C groups (1.8±1.6 vs. 1.1±1.0, $p = 0.003$). Results of Tucky-test revealed that there was a significant difference in the mean level of TG between phenotypes A and B ($p = 0.004$) as well as phenotypes B and C ($p = 0.004$), phenotypes B and D groups ($p = 0.040$). There was no statistically significant difference in four phenotypes regarding HOMA-IR, HOMA-B, and QUICK indexes. Ultrasound examination showed that there was no

Table 1: Comparison of the study population characteristics among different PCOS phenotypes groups.

Characteristics	Phonotypical group				*p*-value
	A HA+AO+PCO (n = 113)	B AO+HA (n = 5)	C HA+PCO (n = 74)	D AO+PCO (n = 16)	
Age, years	**29.5 ± 3.8**	**28.6 ± 5.4**	**29.90± 4.2**	**28.3 ± 2.8**	**0.383**
Parity	**1.4 ± 0.7**	**1.0 ± 0.0**	**1.4 ± 0.7**	**1.4 ± 0.6**	**0.658**
Age of first menarche, years	**13.2 ± 1.5**	**13.4 ± 1.5**	**13.4 ± 1.7**	**13.8 ± 1.3**	**0.560**
Prepregnancy BMI, kg/m²	**26.1 ± 3.1**	**27.7± 3.2**	**25.94± 4.1**	**25.9 ± 2.1**	**0.756**
Levothyroxine treatment	**36 (31.9)**	**2 (40.0)**	**19 (25.7)**	**5 (31.3)**	**0.724**
Blood pressure > 130/80	**14 (12.4)**	**1 (20.0)**	**6 (8.1)**	**2 (13.0)**	**0.543**
GDM	**52 (46.0)**	**5 (100.0)**	**31 (41.9)**	**7 (43.8)**	**0.095**
Ethnicity					
Persian	66 (58.4)	4 (80.0)	44 (59.5)	9 (56.3)	0.372
Turkish	30 (26.5)	0 (0.0)	17 (22.90)	2 (12.5)	
Kurdish	6 (5.3)	1 (20.0)	5 (6.7)	2 (12.5)	
Gilak	11 (9.7)	0 (0.0)	8 (10.8)	3 (18.7)	
Education level					
Elementary	40 (35.4)	0 (0.0)	29 (39.2)	4 (25.0)	0.786
Secondary	42 (37.2)	4 (80.0)	27 (36.5)	8 (80.0)	
University	31 (27.4)	1 (20.0)	18 (24.3)	4 (25.0)	
Type of infertility					
Primary	83 (73.5)	5 (100.0)	50 (67.6)	11 (68.7)	0.493
Secondary	30 (26.5)	0 (0.0)	24 (32.4)	5 (31.3)	
Occupation					
Homeworker	95 (84.0)	5 (100.0)	61 (82.4)	14 (87.5)	0.964
Employed	18 (15.9)	0 (0.0)	13 (17.6)	2 (12.5)	

AO: oligo/anovulation; BMI: body mass index; GDM: gestational diabetes mellitus; PCOS: polycystic ovary syndrome; HA: hyperandrogenism; PCO: polycystic ovaries. Statistically significant p-values are in bold; the quantitative and qualitative variables are presented as mean (standard deviation) and number (percentage), respectively.

significant difference between right and left ovarian volume, right and left numbers of adnexal follicle count among the four phenotypes [Table 2].

DISCUSSION

This study concurs with previous research that suggests phenotype A is the most prevalent PCOS phenotype compared to types B, C, and D.[17–19] Our findings also suggest that women diagnosed with PCOS phenotype A demonstrated higher circulating free testosterone than women with PCOS phenotype C. These findings align with findings of Panidis et al,[19] who determined that circulating androgens were higher in normal weight PCOS women with phenotype A than women with phenotype B. Of the literature we identified, some previous studies have not detected differences in circulating androgens between four phenotypes.[17,18,20] One study reported that serum testosterone concentrations and insulin resistance were highest in PCOS women with phenotype A and B, intermediate in cases with phenotype C, and lowest in cases with phenotype D.[21]

Neves et al,[22] examined the correlation between phenotypes of PCOS and metabolic syndrome. Their results showed metabolic syndrome prevalence in patients with PCOS was 21% and was observed in phenotypes A and B which rose to 71% in phenotype B and 67.4% in phenotype A contaminate with an increase in BMI.

Moreover, previous studies showed that the prevalence of metabolic disorder was highest in phenotype B among all PCOS phenotypes.[23–25] A common hypothesis that has been proposed is that various PCOS phenotypes may exhibit differing levels of insulin resistance.[26] If this hypothesis is confirmed, PCOS patients should be screened and

Table 2: Comparison of the study population laboratory tests and ultrasound examination among different polycystic ovary syndrome phenotypes groups.

Variables	Phenotypical group				*p*-value
	A HA+AO+PCO (n=113)	B AO+HA (n = 5)	C HA+PCO (n = 74)	D AO+PCO (n = 16)	
LH, IU/L	7.3 ± 4.5	6.4 ± 4.0	7.9 ± 6.8	5.9 ± 2.9	0.553
FSH, IU/L	6.2 ± 2.7	6.1 ± 1.4	6.4 ± 3.0	5.16 ± 2.0	0.511
TSH, mIU/L	2.6 ± 2.1	7.7 ± 14.1	2.2 ± 1.8	2.0 ± 1.4	0.370
TG, mg/dL	124.2 ± 66.7	237.4 ± 144.6	123.1 ± 64.3	140.3 ± 104.4	0.006*
Cholesterol, mg/dL	176.5 ± 33.8	180.6 ± 45.8	174.3 ± 36.3	182.7 ± 33.1	0.802
LDL, mg/dL	106.0 ± 28.2	87.4 ± 40.5	104.9 ± 30.2	111.8 ± 31.5	0.492
HDL, mg/dL	47.7 ± 14.7	39.0 ± 6.4	47.59 ± 14.7	46.0 ± 17.4	0.614
SGOT, mg/dL	21.3 ± 9.7	25.6 ± 7.1	21.1 ± 10.6	19.0 ± 7.3	0.636
SGPT, mg/dL	21.8 ± 13.5	30.4 ± 12.5	19.2 ± 8.7	18.7 ± 8.5	0.114
Free testosterone, ng/dL	1.8 ± 1.6	2.5 ± 3.3	1.1 ± 1.0	1.8 ± 1.5	0.010*
17-OH progesterone, ng/dL	1.4 ± 1.0	1.2 ± 0.5	1.2 ± 1.2	1.1 ± 0.8	0.664
DHEA-S, ng/dL	106.9 ± 120.3	187.7 ± 370.2	82.9 ± 110.9	99.9 ± 133.1	0.313
ALP, IU/L	157.2 ± 51.5	183.6 ± 72.5	164.7 ± 52.0	172.3 ± 63.6	0.681
Prolactin	119.2 ± 163.3	99.2 ± 117.0	151.7 ± 187.2	167.1 ± 189.8	0.502
Fasting insulin, mg/dL	13.9 ± 12.7	19.4 ± 8.3	15.8 ± 17.2	20.6 ± 24.2	0.415
FBS, mg/dL	86.4 ± 8.9	100.0 ± 4.8	87.1 ± 8.6	93.6 ± 10.3	0.000*
HOMA-IR	3.0 ± 2.8	4.8 ± 2.0	3.46 ± 3.8	4.5 ±5 .1	0.297
HOMA-B	254.8 ± 278.0	194.9 ± 94.0	253.2 ± 310.5	311.6 ± 402.6	0.879
QUICK	0.3 ± 0.1	0.3 ± 0.0	0.3 ± 0.0	0.3 ± 0.0	0.190
Right ovary volume	8.2 ± 3.3	7.1 ± 5.0	9.1 ± 6.0	9.2 ± 4.7	0.915
Left ovary volume	8.1 ± 4.0	4.7 ± 2.9	8.6 ± 5.6	7.4 ± 4.4	0.594
Right antral follicle count	15.8 ± 4.8	11.6 ± 7.0	15.3 ± 4.7	15.3 ± 7.3	0.337
Left antral follicle count	15.3 ± 5.5	11.4 ± 7.2	15.4 ± 5.0	14.2 ± 6.3	0.384
3-hours OGTT	102.5 ± 19.1	127.4 ± 16.5	102.5 ± 24.8	113.4 ± 26.0	0.031*
FSH/LH ratio	1.3 ± 0.8	1.0 ± 0.6	1.4 ± 1.2	1.6 ± 1.9	0.501

AO: oligo/anovulation; LH: luteinizing hormone; FSH: follicle stimulating hormone; TSH: thyroid stimulating hormone; TG: triglyceride; LDL: low-density lipoprotein; HDL: high-density lipoprotein; SGOT: serum glutamic oxaloacetic transaminase; SGPT: serum glutamic pyruvic transaminase; DHEA-S: dehydroepiandrosterone sulfate; FBS: fasting blood sugar; ALP: alkaline phosphatase; HA: hyperandrogenism; PCO: polycystic ovaries; OGTT: oral glucose tolerance test.
**statistically significant p-values < 0.050; the quantitative variables are presented as mean±standard deviation.*

treated differently according to their unique type of PCOS phenotype for the metabolic dysfunction.[27]

Insulin resistance is a common sequela of PCOS.[28] Several studies detected that while insulin resistance was a common feature of PCOS, there was no difference between PCOS phenotypes and degree of insulin resistance.[4,19,29] The HOMA calculation, used as an index of insulin sensitivity, showed that there was no difference between PCOS phenotypes in terms of insulin sensitivity. However, Zhang et al,[21] detected that the three phenotypes with higher levels of testosterone (A, B, and C) demonstrated higher insulin resistance in comparison to phenotype D and that of the control group. Another study suggested that only phenotype B (AO+HO) demonstrated higher insulin resistance.[30] In contrast to our findings, Ghuszak et al,[4] showed that the highest HOMA-B level was found in the phenotypes B and D compared to phenotypes A and C. These results might be associated with the obesity prevalence in this population. The difference detected here between our studies, and previous studies may be related to environmental factors and genetic variation among various ethnic populations investigated in different studies.[30]

Our results indicated no significant differences in total cholesterol, LDL, and HDL cholesterol among the four PCOS phenotypes. However, TG levels

were significantly higher in women with PCOS phenotype B. Therefore, cardiovascular disease and metabolic disorder may be increased in PCOS phenotype B compared to the other groups.[17,31,32] Zhang et al,[21] identified that levels of TGs and LDL were significantly higher between PCOS phenotype B and the control group. Yilmaz et al,[33] showed that serum cholesterol and LDL concentrations were the highest in women with phenotype A. Furthermore, they found that TG concentrations were significantly higher in phenotypes A and B than in the control group. Chae et al,[34] reported no significant difference among PCOS subgroups in terms of serum cholesterol and HDL concentrations. According to our study the LH/FSH ratio was similar in all phenotypes; in contrast to Zhang et al,[21] reported this ratio highest in women diagnosed with PCOS phenotype D. Zhao et al,[12] showed that the incidence of adverse biochemical and metabolic changes were higher in PCOS phenotype A than other phenotypes. In addition, LH level and LH/FSH ratio was much higher in PCOS phenotype A compared to other phenotypes.

There are several limitations noted in this study. The inclusion criteria only compared the prevalence of GDM and metabolic disorder between different PCOS phenotypes in women with matched BMI. Additionally, this research addressed only the prevalence of GDM and metabolic disorders among PCOS women without the comparison of a control group. To address this, future studies to compare the prevalence of these disorders among PCOS phenotypes A, B, C, and D compared to unaffected women as a control group will be necessary. This is the first study of this type that has been conducted in Iran to date. Therefore, it provides valuable information that can be used as a foundation for future and reproductive investigations.

CONCLUSIONS

Iranian women with PCOS phenotype A and B have higher risk for metabolic disorders compared to those women with PCOS that demonstrate other phenotypes. Performing endocrine and metabolic screening and diagnostic tests for pregnant women with PCOS, particularly phenotype A and B, before or within the first trimester of pregnancy, could identify complications earlier. This enhanced maternal fetal surveillance may improve maternal and fetal morbidity among pregnant women affected with PCOS. In addition, the identification of these women can guide future initiatives in primary care that may decrease the likelihood of long-term complications of PCOS such as metabolic syndrome, hypertension, and cardiovascular disease. Patient education efforts, related to diet, lifestyle management and primary health care screenings can positively impact the long-term health of this generation of mothers.

Disclosure

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