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Pregnancy complications and glucose intolerance in women with polycystic ovary syndrome

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Abstract. Polycystic ovary syndrome (PCOS) is a common endocrine disorder characterized by insulin resistance and hyperandrogenism. The interaction of these factors might result in increased risks of miscarriage and pregnancy complications such as gestational diabetes mellitus (GDM). To examine the pregnancy risks in women with PCOS, we compared obstetrical outcomes between patients with and without PCOS. We also studied the differences in maternal characteristics, glucose intolerance and pregnancy complications between PCOS patients with and without GDM, with and without obesity, and between successful pregnancies and miscarriages. We observed a high incidence of GDM and prevalence of GDM diagnosis in the first trimester in PCOS. Patients with GDM had higher body mass index (BMI) and lower homeostasis model assessment of β-cell function (HOMA-β) at preconception than those without GDM. Obese pregnant women with PCOS demonstrated a high incidence of GDM with severe insulin resistance, including high fasting insulin, HOMA of insulin resistance (HOMA-IR), and HOMA-β at preconception compared with normal-weight patients. BMI was significantly correlated with HOMA-IR or HOMA-β, and both indices were lower in PCOS patients with than without GDM for the same BMI. There were no significant differences in maternal characteristics (excluding maternal age) between PCOS patients with successful pregnancy and PCOS patients with miscarriages. Our data suggest that pregnant women with PCOS have an increased risk of GDM, especially if they have obesity and/or poorer insulin secretion. Measure of β-cell function, such as HOMA-β, at preconception might be a useful predictor of the risk of GDM in pregnant PCOS patients.

Key words: Polycystic ovary syndrome, Insulin resistance, Pregnancy complication, Gestational diabetes mellitus

POLYCYSTIC OVARY SYNDROME (PCOS) is a common endocrine and metabolic disorder present in 5–15% of women of reproductive age depending on the diagnostic criteria used [1, 2]. The common features of PCOS are hyperandrogenism, irregular menstruation and polycystic ovaries by ultrasonography [3, 4]. In addition, insulin resistance, hyperandrogenism and obesity might play important roles in the pathophysiologic process of PCOS, and the interaction of these factors might result in an increased risk of not only type 2 diabetes mellitus, metabolic syndrome and cardiovascular disease [5–7] but also miscarriage and obstetrical complications such as preeclampsia and gestational diabetes mellitus (GDM) [8].

Because insulin resistance and obesity might affect the course of pregnancy in women with PCOS, we compared the obstetrical outcomes between the patients with PCOS and without PCOS. We also examined the differences in maternal characteristics and perinatal outcomes between PCOS patients with and without GDM and with and without obesity. Furthermore, we examined the differences in maternal characteristics between successful pregnancies and miscarriages to determine the risks of pregnancy loss in women with PCOS.

Materials and Methods

A total of 64 Japanese pregnant women with PCOS (including 49 successful singleton pregnancies and 15 miscarriages) who visited the Okayama University Hospital, Department of Obstetrics and Gynecology (Okayama, Japan) from 2007 to 2014 were included in the present study. In addition, 49 healthy preg-

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nant women matched for age, gestational age, parity and body mass index (BMI) with normal pregnancies who visited our hospital from 2007 to 2014 were included. PCOS was defined according to the criteria of the Japanese Society of Obstetrics and Gynecology including three main features: 1) cycle irregularities, 2) polycystic changes in the ovary by ultrasonography and 3) endocrine anomalies (luteinizing hormone or androgen hypersecretion) [9]. In Japan, the usual clinical presentation of PCOS is slightly different than in Europe or the United States, with less frequently encountered cases of hyperandrogenism; therefore, European or US diagnostic criteria [5] are clinically less useful. Patients with pre-existing renal disorders, diabetes or essential hypertension or disease similar to PCOS, such as Cushing disease and congenital adrenal hyperplasia were excluded.

Fasting insulin and glucose levels at preconception were determined by fluorescence enzyme immunoassay (Tosoh Corp., Tokyo, Japan) and the glucose oxidase method (Shino-Test Corp. Tokyo, Japan), respectively. Insulin resistance was measured using the homeostasis model assessment (HOMA) of insulin resistance index (HOMA-IR) = fasting glucose level (mg/dL) × fasting insulin level (μU/mL) / 405 [10] and the quantitative insulin sensitivity check index (QUICKI) = 1 / [log fasting insulin level (μU/mL) + log fasting glucose level (mg/dL)] [11]. Insulin secretion was indicated by the HOMA of β-cell function (HOMA-β) (%) = 360 × fasting insulin level (μU/mL) / [fasting glucose level (mg/dL) − 63] [10]. The patients were sub-divided into two groups, overweight or obese women (overweight group; BMI ≥25 kg/m^2) and normal-weight women (normal-weight group; BMI >18.5 kg/m^2 but <25 kg/m^2). Gestational diabetes mellitus (GDM) was defined abnormal glucose values at one time point in the 75-g oral glucose challenge test (OGTT) after the universal screening using an untimed random plasma glucose level. The cutoff of glucose values for fasting was ≥92 mg/dL, 1 h after fasting was ≥180 mg/dL, and 2 h after fasting ≥153 mg/dL [12] for all cases in this study retrospectively, although the criteria for GDM was changed on July, 2010. Almost all GDM patients in PCOS and non PCOS had the dietary counseling and monitoring with or without insulin therapy under glucose level monitoring, but two GDM patients with PCOS, who was diagnosed before 2010 due to abnormal glucose values at one time point, had only dietary intervention without glucose level monitoring. Pregnancy induced hypertension (PIH) was defined as patients with persistent blood pressure elevation to a systolic level of 140 mmHg or a diastolic level of 90 mmHg on two occasions, several hours apart, with or without proteinuria of > 300 mg in a 24-h urine collection according to the definition of PIH by the Japan Society of Obstetrics and Gynecology [13]. Fetal growth restriction (FGR) was a fetal estimated weight that is below the -1.5SD for the standard deviation of estimated weight from Japanese standard fetal weight [14]. Clinical records were carefully reviewed and women who did not meet the above criteria were eliminated from the study. This study was approved by the Institutional Ethical Review Board of Okayama University Hospital and all subjects gave informed consent.

All values are expressed as mean ± SD. The Kruskal-Wallis test and Scheffe's test were used for inter-group comparisons of clinical parameters. The associations of BMI with HOMA-IR or HOMA-β were analyzed using Spearman's rank correlation. Statistical analysis was performed using StatView software (Abacus Concepts, Berkeley, CA, USA). A level of $p<0.05$ was considered to be statistically significant.

Results

Obstetric characteristics in successful pregnancies with PCOS are summarized in Table 1. There was the significantly high incidence of GDM (24.5%) and prevalence of GDM diagnosis in the first trimester in pregnancies with PCOS compared with normal pregnancies without PCOS, but no other significant differences of perinatal outcomes. And the prevalence of treatment before pregnancy using ovulation-inducing agents was significantly higher in PCOS compared with non PCOS. Comparing maternal and neonatal characteristics in the GDM and non-GDM groups, the BMI at preconception was significantly higher in the GDM group than the non-GMD group ($p<0.01$) in both PCOS and non PCOS. Furthermore, HOMA-β at preconception was lower in the GDM group than the non-GDM group. No significant differences were observed in maternal age, fasting glucose, fasting insulin, HOMA-IR, QUICKI, and testosterone at preconception, and gestational weeks at delivery, birth weights and the prevalence of treatment before pregnancy using ovulation-inducing agents between the GDM and non-GDM group (Table 2). Overweight and obese pregnant women with PCOS (BMI at preconception ≥25 kg/m^2) demonstrated

Table 1 Obstetric characteristics in pregnancies with PCOS

	PCOS	non PCOS	*p*-value
Case number	49	49	
Primigravida (%)	35 (71.4%)	35 (71.4%)	n.s.
Age (y)	31.7±4.5	31.9±4.3	n.s.
BMI at preconception	24.4±5.2	24.2±4.9	n.s.
Gestational weeks at delivery	38.1±2.6	38.5±1.9	n.s.
Birth weight (g)	2844±637	2825±514	n.s.
Cesarean section (%)	16 (34.7%)	14 (28.6%)	n.s.
Obstetrical complications (%)			
GDM	12 (24.5%)	5 (10.2%)	$p<0.01$
Diagnosis in the first trimester	3/12 (25.0%)	0/5 (0%)	$p<0.01$
Maternal weight gain at GDM diagnosis (kg)	4.5±2.4	6.2±3.6	n.s.
PIH	2 (4.1%)	3 (6.1%)	n.s.
FGR	3 (6.1%)	4 (8.2%)	n.s.
Preterm delivery	6 (12.2%)	5 (10.2%)	n.s.
Preterm PROM	3 (6.1%)	3 (6.1%)	n.s.
Treatment (Ovulation induction)	20 (40.8%)	6 (12.2%)	$p<0.01$

n.s., not significant; PCOS, polycystic ovary syndrome; GDM, gestational diabetes mellitus; PIH, pregnancy induced pregnancy; FGR, fetal growth restriction; PROM, premature rupture of membrane

Table 2 Comparison between GDM and non-GDM groups in pregnancies with PCOS

	PCOS			non PCOS		
	GDM	non GDM	*p*-value	GDM	non GDM	*p*-value
Number (%)	12 (24.5%)	37 (75.5%)		5 (10.2%)	44 (89.8%)	
Age (year)	32.9±5.3	31.1±3.8	n.s.	32.7±3.8	31.5±4.2	n.s.
At preconception						
BMI	27.1±6.0	23.4±3.7	$p<0.01$	26.9±4.5	23.9±3.9	$p<0.01$
Fasting glucose (mg/dL)	96.1±15	92.8±6.2	n.s.			
Fasting insulin (μU/mL)	8.4±6.6	9.8±7.4	n.s.			
HOMA-IR	2.3±2.2	2.1±1.8	n.s.			
QUICKI	0.36±0.03	0.4±0.04	n.s.			
HOMA-β (%)	85.4±42	121.1±78	$p<0.05$			
Testosterone (ng/dL)	65.2±23.0	58.5±17.4	n.s.			
Gestational weeks at delivery	37.5±2.1	38.9±1.2	n.s.	38.6±2.2	38.5±1.6	n.s.
Birth weight (g)	2907±485	2822±404	n.s.	2915±485	2815±404	n.s.
Treatment (Ovulation induction)	6 (50.0%)	14 (37.9%)	n.s.	1 (20.0%)	5 (11.4%)	n.s.

n.s., not significant; PCOS, polycystic ovary syndrome; GDM, gestational diabetes mellitus; HOMA, homeostasis model assessment; QUICKI, quantitative insulin sensitivity check index

severe insulin resistance, including high fasting insulin, high HOMA-IR and low QUICKI, but good insulin secretion (indicated by high HOMA-β) and a high incidence of GDM at preconception ($p<0.01$). There were no significant differences in maternal age, fasting glucose and testosterone at preconception, gestational weeks at delivery, birth weights and treatment before pregnancy using ovulation-inducing agents between obese and normal weight group (Table 3). There were similar results of gestational weeks at delivery, birth weight and treatment before pregnancy using ovulation-inducing agents between GDM and non GDM and obese and non obese in both PCOS and non PCOS.

We also examined whether BMI correlated with HOMA-IR and HOMA-β at preconception in GDM and non-GDM patients with PCOS. There were significant correlations of BMI with HOMA-IR ($r=0.61$, $p<0.01$, Fig. 1A) or HOMA-β ($r=0.44$, $p<0.01$, Fig. 1B). In addition, both indices in almost all PCOS patients with GDM were located under the regression line, in comparison with PCOS patients without GDM with the same BMI (Fig. 1A, B). Moreover, the differences in maternal characteristics between successful pregnancies and miscarriages in women with PCOS were

Table 3 Comparison between the obese and non-obese group in pregnancies with PCOS

	PCOS			non PCOS		
	Obese (BMI≥25)	Non-obese (25>BMI)	*p*-value	Obese (BMI≥25)	Non-obese (25>BMI)	*p*-value
Number (%)	16 (32.7%)	33 (67.3 %)		15 (30.6%)	34 (69.4 %)	
Age (year)	31.3±4.6	31.6±4.0	n.s.	32.2±4.3	31.8±4.8	n.s.
At preconception						
Fasting glucose (mg/dL)	97.1±12	91.6±5.6	n.s.			
Fasting insulin (μU/mL)	16.8±9.6	6.3±3.2	$p<0.01$			
HOMA-IR	4.06±2.5	1.5±0.7	$p<0.01$			
QUICKI	0.31±0.02	0.41±0.03	$p<0.01$			
HOMA-β (%)	198±146	82.2±51	$p<0.01$			
Testosterone (ng/dL)	59.1±16	59.4±18	n.s.			
GDM	6 (37.5%)	6 (18.2%)	$p<0.01$	2 (13.3%)	3 (8.8%)	n.s.
Gestational weeks at delivery	38.1±3.6	38.3±2.9	n.s.	38.5±2.1	38.6±2.4	n.s.
Birth weight (g)	2945±763	2730±571	n.s.	2917±463	2784±431	n.s.
Treatment (Ovulation induction)	8 (50.0%)	12 (36.4%)	n.s.	2 (13.3%)	4 (11.8%)	n.s.

n.s., not significant, PCOS, polycystic ovary syndrome; GDM, gestational diabetes mellitus; HOMA, homeostasis model assessment; QUICKI, quantitative insulin sensitivity check index

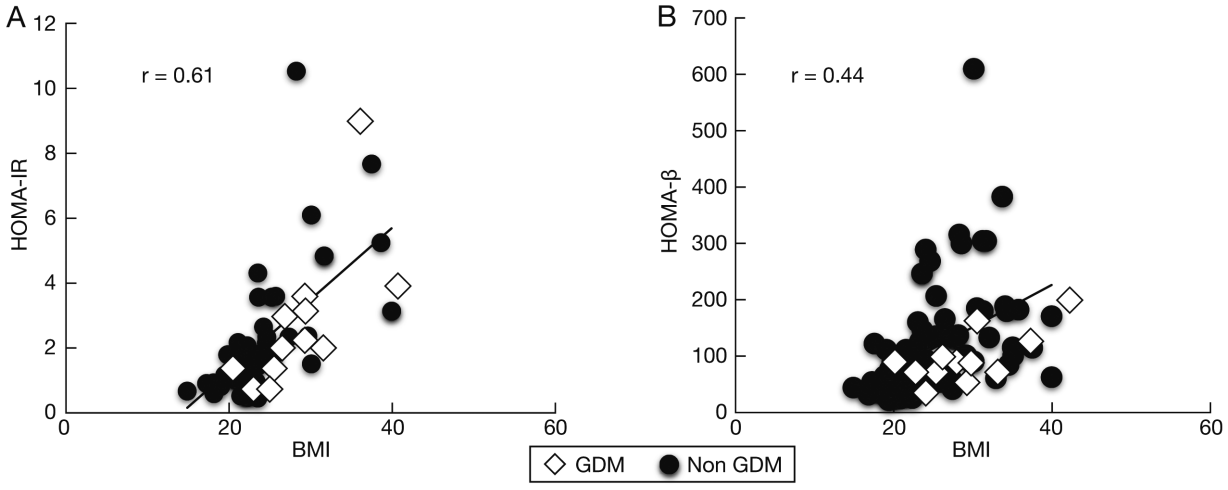

Fig. 1 The significant correlations of BMI with HOMA-IR (A) and HOMA-β (B) in pregnant women with PCOS

Table 4 Comparison between the successful pregnancy and miscarriage group

	Successful	Miscarriage	*p*-value
Number	49	15	
Age (year)	31.7±4.0	35.1±3.3	$p<0.01$
At preconception			
BMI	24.4±5.3	24.3±4.6	n.s.
Fasting glucose (mg/dL)	93.4±9.1	90.0±6.2	n.s.
Fasting insulin (μU/mL)	9.1±7.7	8.1±6.1	n.s.
HOMA-IR	2.1±1.8	1.86±1.4	n.s.
QUICKI	0.4±0.04	0.37±0.04	n.s.
HOMA-β (%)	112±104	104±76	n.s.
Testosterone (ng/dL)	67.1±23.2	60.0±21.2	n.s.
Treatment (Ovulation induction)	20 (40.8%)	6 (40.0%)	n.s.

n.s., not significant; HOMA, homeostasis model assessment; QUICKI, quantitative insulin sensitivity check index

investigated. Maternal age was significantly higher in the miscarriage group than the successful pregnancy group ($p<0.01$). However, no significant differences were observed in BMI, fasting glucose level, fasting insulin level, HOMA-IR, QUICKI, HOMA-β, testosterone level at preconception and treatment before pregnancy with ovulation induction between the successful pregnancy and miscarriage groups (Table 4).

Discussion

In this study, we observed a high prevalence of GDM and prevalence of GDM diagnosis in the first trimester in pregnancies with PCOS compared with nor-

mal pregnancies without PCOS. Patients with GDM demonstrated significantly higher BMI and lower HOMA-β at preconception compared with those without GDM. Compared with normal-weight pregnant women with PCOS, overweight and obese pregnant women with PCOS demonstrated severe insulin resistance before pregnancy, including high fasting insulin, high HOMA-IR and low QUICKI, but good insulin secretion indicated by high HOMA-β and a high prevalence of GDM. There were significant correlations of BMI with HOMA-IR and HOMA-β at preconception, and both indices in almost all PCOS patients with GDM were lower than in PCOS patients without GDM with the same BMI. In addition, there were no significant differences in maternal characteristics (excluding maternal age) between successful pregnancies and miscarriage in PCOS patients.

Previous meta-analyses indicated that pregnancies with PCOS were often complicated by pre-eclampsia and GDM, and that the risk of a preterm delivery or a delivery by Caesarean section was raised in women with PCOS [3, 8, 15]. Furthermore, newborn babies stayed more frequently in a neonatal intensive care unit and perinatal mortality also occurred more frequently [3, 8]. In this study, we also observed the high incidence of GDM and the high prevalence of GDM diagnosis in the first trimester in pregnancies with PCOS compared with pregnancies without PCOS. However, GDM patients in PCOS diagnosed in the first trimester had good glucose level during pregnancy with the dietary intervention and insulin therapy. Moreover, PCOS women showed higher incidence of GDM than in non PCOS women in both obese and non-obese groups (37.5% *vs* 13.3%, and 18.2% *vs* 8.8%, respectively). Existence of glucose intolerance at preconception in both obese and non-obese PCOS patients might increase the GDM prevalence compared with non PCOS patients. However, there were no data of insulin resistance and secretion in non PCOS patients in this study. Further analysis will be required to clarify the factors that affect the difference of GDM incidence between PCOS and non PCOS in both obese and non obese patients. Next, we examined the differences in maternal characteristics between the GDM and non-GDM group in pregnant women with PCOS. A recent report demonstrated that obesity might play an important role in the development of GDM [16], and we observed significantly higher BMI in GDM patients than non-GDM patients in both PCOS and non PCOS patients. Although glucose intolerance at preconception has been reported to be a risk factor for GDM in PCOS patients [6], both GDM and non-GDM patients in PCOS patients showed obvious glucose intolerance but there were no significant differences in fasting glucose and insulin levels, HOMA-IR and QUICKI between the GDM and non-GDM group in this study. However, GDM patients showed significantly lower HOMA-β at preconception than patients without GDM. These data suggested that pancreatic β-cell function might not be sufficient to overcome the additional insulin resistance created by hormonal change during pregnancy in PCOS patients with mild insulin resistance before pregnancy, which resulted in the development of GDM.

In general, obesity has a negative influence on perinatal outcome [17, 18]. Being overweight in prepregnancy is an important predictor for the risk of perinatal complications in women with PCOS [19, 20]. Another report showed that the prevalence of GDM and fetal macrosomia was significantly higher in overweight *versus* normal-weight women with PCOS [21]. Regarding obesity, we observed a high prevalence of GDM with glucose intolerance and high insulin secretion at preconception in overweight and obese patients with PCOS, but there was no macrosomia (data not shown). There was no significant difference in testosterone levels between the GDM and non-GDM or the obese and non obese groups, indicating that hyperandrogenism might not play a role in the development of GDM. In addition, we observed that both HOMA-IR and HOMA-β in almost all PCOS patients with GDM were lower than in PCOS patients without GDM with the same BMI. This finding suggests that in PCOS patients with the same BMI, those who develop GDM have lower insulin resistance but poorer insulin secretion than those who do not. Poor pancreatic β-cell function as well as obesity might be risk factors for developing GDM.

There is evidence that women with PCOS are at an increased risk of early pregnancy loss and miscarriage [22]. The increased risk of early pregnancy loss has been attributed to treatment with ovulation-inducing agents, raised androgen levels, insulin resistance and obesity [23]. We examined the differences in maternal characteristics between successful pregnancies and miscarriages. There was only a significant difference of maternal age and no differences in other factors, including BMI at preconception, insulin resistance,

insulin secretion, testosterone level and prevalence of treatment before pregnancy with ovulation induction.

Our data suggest that pregnant women with PCOS have an increased risk of GDM and that weight control before pregnancy is important in reducing the risk of GDM in women with PCOS. Furthermore, measurement of β-cell function, such as HOMA-β, at preconception might be a useful predictor of the risk of GDM in pregnant women with PCOS to identify the high risk pregnancy with PCOS to reduce the risk of developing GDM and its adverse consequences under the close monitoring and intervention. The limitations of the study include a small sample size and the observational nature of the study. Recently, prediction models for developing GDM has been demonstrated using family history and fasting insulin, fasting insulin, androstenedione and sex hormone binding protein at preconception [24], we will do large prospective study using BMI, family history and several measurements of insulin resistance and secretion to detect the risk of developing GDM before pregnancy.

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