

# Obstetric and Neonatal Outcome in PCOS with Gestational Diabetes Mellitus

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Received July 2013; revised and accepted September 2013

## Abstract

**Objective:** There are some metabolic similarities between women with gestational diabetes mellitus (GDM) and polycystic ovary syndrome (PCOS); it is still uncertain, however, to what extent coexistence GDM and PCOS affects pregnancy outcome. The present study was designed to determine the obstetric and neonatal outcome in PCOS with GDM.

**Materials and methods:** A case-control study was conducted involving 261 GDM women. Thirty hundred-one cases had PCOS based on Rotterdam criteria and the other thirty hundred cases (control group) were women without PCOS. The subjects in each group were evaluated regarding obstetric and those women whose documentation's were complete entered the study.

**Results:** In present study, women with PCOS and GDM had more than twofold increased odds of preeclampsia ( $p = 0.003$ , CI = 1.56–5.01, and OR = 2.8) and PIH ( $p = 0.04$ , CI = 1.28–4.5, and OR = 2.4). Maternal PCOS and GDM were also associated with threefold increased odds of neonatal hypoglycemia ( $p = 0.004$ , CI = 1.49–6.58, and OR = 3.13).

**Conclusion:** Our finding emphasized that pregnant PCOS patients should be followed carefully for the occurrence of various pregnancy and neonatal complications including hypertension and hypoglycemia. We suggested that these neonates should be given more care regarding hypoglycemia symptoms.

**Keywords:** Gestational Diabetes Mellitus (GDM), Polycystic Ovarian Syndrome (PCOS), Preeclampsia, Hypoglycemia

## Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age. It is estimated that 5 to 10% of women suffer from the disease (1). The symptoms typically associated with PCOS, including

amenorrhea, oligomenorrhea, hirsutism, obesity, infertility, anovulation and acne (2).

Affected women have an increased risk of glucose intolerance and type 2 diabetes (3). Some, but not all, studies suggest the risk of Gestational diabetes mellitus (GDM) is higher among PCOS versus non-PCOS women (4-8), and several studies note an increased prevalence of polycystic ovarian morphology and symptoms in women with prior GDM (9-11). A majority of obese PCOS patients as well as a significant number of lean ones are also

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hyperinsulinemic (12-13). By prescribing drugs that correct insulin resistance, the levels of plasma androgen and some metabolic changes are relatively corrected, which shows the importance of insulin resistance in the pathogenesis of PCOS (14).

There is an increasing body of evidence indicating that PCOS may have significant implications for pregnancy outcomes and long-term health of a woman and her offspring. Miscarriage rates among women with PCOS are believed to be increased compared with normal fertile women, although supporting evidence is limited (15-17). Pregnant women with PCOS experience a higher incidence of prenatal morbidity from GDM, pregnancy-induced hypertension (PIH), and preeclampsia (18). According to the Barker hypothesis, there is an in utero fetal programming of fetal nutrition and of the endocrine and metabolic environment in which the fetus develops, a fact that explains why PCOS complications might affect the fetus (19). Their babies are at an increased risk of neonatal complications, such as preterm birth and admission at a neonatal intensive care unit (20). Therefore, pre-pregnancy, antenatal, and intrapartum care should be aimed at reducing these risks.

GDM is defined as glucose intolerance that has its onset or is first recognized during pregnancy (21-22). GDM occurs in 2-5% of all pregnancies, although the majority of women with GDM regain normal glucose tolerance postpartum (23). Women with history of GDM are at a substantially increased risk of developing type 2 diabetes later in the life (24); also, they demonstrate abnormalities in both insulin secretion and function which resembles those with type 2 diabetes (25). It shows the most common metabolic complications of pregnancy, and fetal mortality and morbidity. GDM causes significant and often potentially maternal and fetal complications including preeclampsia, polyhydramnios, fetal macrosomia, birth trauma, neonatal metabolic complications and prenatal death. Development of obesity and diabetes in offspring during childhood and later development of diabetes mellitus in the mother are also related with GDM (26).

Since there are similarities in between women with GDM and PCOS about metabolic condition, it has been hypothesized that some shared etiopathological factors may be present. There are previous studies on association between GDM and PCOS and also pregnancy complications of the PCOS; nevertheless the simultaneously effects of

existence the PCOS and GDM on pregnancy and fetal have not been studied. So the relatively high prevalence of PCOS (27), multiple and serious complications attributed to these diseases were main factors to us for evaluation of Iranian women with PCOS. To investigate the association between PCOS and GDM, we arranged this study to determine the obstetric and neonatal outcome in PCOS with GDM. It's seemed this might help to add to the existing knowledge about accurate screening and early diagnosis of this condition and allow timely intervention in order to make certain a satisfactory pregnancy outcome and perhaps improve health in women with PCOS.

## Materials and methods

This research is a case-control study that all women who were diagnosed with GDM and delivered at the Shahbikhani Hospital (Kashan, Iran) during 2012 were included and then divided into two groups (PCOS and control). The diagnosis of GDM previously has been demonstrated based on the blood glucose levels and oral glucose challenge test (GCT) and glucose tolerance test (OGTT) during pregnancy. The diagnosis of PCOS was made with and the Rotterdam criteria by gynecologist pre pregnancy and the patient divided to control (without PCOS) and case (PCOS) group.

The sample size was determined based on findings of Haakova et al study (4) using following formula:

$$N = (Z_{(1-\alpha/2)} + Z_{(1-\beta)})^2 [P_1(1-P_1) + P_2(1-P_2)] / (P_1 - P_2)^2$$

With  $\alpha=0.05$ ,  $\beta =0.2$ ,  $P_1=3\%$ ,  $P_2=12\%$ . The calculated sample size was at least 130 per group.

Inclusion criteria were having GDM, maternal age  $\leq 36$  years and Iranian race. Exclusion criteria were maternal age greater than 36 years, a history of diabetes mellitus in a first-degree relative (e.g., parent, brother, or sister), pre pregnancy mother's weight greater than 90 kg, parity greater than 4, GDM in previous pregnancy, a previous abortion, a history of preterm labor or delivery, a history of stillbirth, a history of recurrent abortion, a history of maternal smoking, a history of a neonate with a congenital malformation, a history of neonatal death, and a history of maternal disease (according to their health documentations and hormonal and sonography evidences), including congenital adrenal hyperplasia, malignant ovarian tumors, Cushing's syndrome, hypothyroidism, and hyperprolactinemia.

From their medical records, information was obtained including maternal age, parity, gestational age, height, weight, having preeclampsia and PIH, preterm labor, Cesarean or NVD delivery, Shoulder dystocia, neonatal apgar score, Neonatal weight, Polyhydroamnious, neonatal icter, Polycythemia, hypocalcemia, hypoglycemia, Respiratory distress syndrome and Intrauterine fetal death.

### Statistical Analysis

Demographic data of the groups were expressed as mean  $\pm$ SD or case (percentage) and comparison of these data was performed by t-test. The normality of the distributions was tested using the Kolmogrov-Smirnov test. Multivariable logistic regression was specified to evaluate obstetric and neonatal outcome in patients between two groups. The statistical program for Social Sciences (SPSS, version 11.5; SPSS, Chicago, IL). P values were set as 0.05 for all analyses.

### Results

During the study period, a total 261 patients were included. Patient characteristics were presented in table 1. There were no statistically significant differences between the two groups according to age, BMI, gestational age, parity and Cesarean delivery.

Pregnancy complications were shown in table 2. There was no significant difference between the two groups with respect to preterm labor, shoulder dystocia, polyhydroamnios and oligohydroamnios. In

two groups, the incidence preeclampsia was 36.2% and 16.8%, respectively ( $p < 0.001$ ). Moreover, the incidence of PIH in patients with and without PCOS was 27.7% and 13.7%, respectively ( $p = 0.005$ ).

Neonatal characteristics were presented in table 3. In two groups, there isn't any polycythemia, hypocalcaemia and intrauterine fetal death. There were no significant differences between the two groups with respect to neonatal Apgar scores, neonatal weight, macrosomia, neonatal icter, respiratory distress syndrome. The patients with a history of PCOS have statistically different ( $p = 0.002$ ) in the neonatal hypoglycemia incidence versus to not PCOS group.

In the present study, we found that women with PCOS and GDM had a more than twofold increased odds of preeclampsia and PIH. Maternal PCOS and GDM were also associated with threefold increased odds of neonatal hypoglycemia (table 4).

### Discussion

Although, several studies have addressed relationship between GDM and PCOS, it is still uncertain, however, to what extent coexistence GDM and PCOS affects pregnancy outcome. We found that pregnant women with diagnosed PCOS and GDM have a more than twofold increased odds of preeclampsia and PIH compared with women without PCOS. The meta-analysis Boomsma et al (2008) have been shown 5.3 times higher risk of preeclampsia and 75.1 for preterm birth in pregnant women with PCOS(20). In

**Table 1:** Clinical features of the case (PCOS) and control groups

	PCOS (n=130)	Control (n=131)	p value
Age (year) *	28.83 $\pm$ 4.94	29.30 $\pm$ 4.86	0.40
BMI (kg/m <sup>2</sup> ) *	28.01 $\pm$ 3.8	27.67 $\pm$ 3.2	0.07
Gestational age (week) *	37.42 $\pm$ 1.4	37.74 $\pm$ 1.6	0.10
Parity*	2.17 $\pm$ 0.99	2.16 $\pm$ 1.07	0.23
Cesarean delivery**	103(79.2%)	91(69.5%)	0.07

\*Mean  $\pm$ SD

\*\* n (%)

**Table 2:** Outcome of pregnancy in case (PCOS) and control groups

	PCOS n (%)	Control n (%)	p value
Preeclampsia	47(36.2%)	22(16.8%)	<0.001
Preterm labor	15(11.5%)	20(15.3%)	0.37
Shoulder dystocia	5(3.8%)	2(1.5%)	0.28
Polyhydroamnios	0(0)	4(3.1%)	0.12
Oligohydroamnios	1(0.8%)	10(7.6%)	0.60
PIH	36(27.7%)	18(13.7%)	0.005
Total	130 (100)	131 (100)	

**Table 3: Neonatal outcome in PCOS and control groups**

	PCOS (n=130)	Control (n=131)	p value
Neonatal weight*	3404.23±504.1	3421.37±473.69	0.70
Macrosomia**	21(16%)	16(12.2%)	0.37
Neonatal apgar score*	8.85±0.467	8.85±0.466	0.92
Neonatal icter**	28(21.5%)	23(17.6%)	0.41
Respiratory distress syndrome**	22(16.7%)	18(13.7%)	0.49
Hypoglycemia**	29(22.3%)	11(8.4%)	0.002

\*Mean ±SD  
\*\* n (%)

**Table 4: The result of logistic regression test**

	p value	SE	Odds ratio	95% CI	
				Lower	Upper
Preeclampsia	0.003	0.48	2.8	1.56	5.01
PIH	0.04	0.34	2.4	1.28	4.5
Hypoglycemia	0.004	0.38	3.13	1.49	6.58

Hosmer and Lemeshow test p = 0.67

contrast, Mikola and Hiilesmaa (2001) followed obstetric outcome of women with PCOS and reported that PCOS slightly increased the risk for GDM but didn't have an important effect on preeclampsia (7). Juff and Esterlitz (1998) investigated relationship between abnormal glucose tolerance and hypertensive disorders of pregnancy in healthy nulliparous women. They observed that level plasma glucose 1 hour after a 50g glucose challenge was positively correlated with the likelihood of preeclampsia and thus women with GDM were at increased risk for hypertensive disorders during pregnancy (28).

The incidence of PIH in the PCOS groups was 36(27.7%) versus 18(13.7%) that was statistically significant. Pregnant women with GDM and PCO are 2.4 times higher at risk for developing PIH versus pregnant women with GDM alone. Moreover, the rate of preeclampsia was 36.2% in PCOS and 16.8 % in control group, which was a significant difference. This indicates the coexistence of PCOS and GDM increases the risk of preeclampsia and high blood pressure in pregnant women. As it is emphasized before, hyperinsulinemia is one of the various metabolic abnormalities commonly found in conjunction with PCOS relatively independent of obesity. Insulin is a hormone with hemodynamic actions. Insulin resistance and hyperinsulinemia have been proposed as permissive factors in the development of future serious vascular disease. There is evidence to suggest that insulin is a vasodilator of skeletal muscle vasculature with this effect impaired in states of insulin resistance such as obesity and non-insulin dependent diabetes mellitus.

Insulin-mediated vasodilatation may play a role in the regulation of vascular Tone since a pressor response to systemic norepinephrine infusions is increased leading to hypertension in insulin-resistant subjects. Finally insulin has been shown to interact in an unknown manner with the endothelium to increase nitric oxide synthesis and release. States of insulin resistance may be associated with a defect in insulin's action in modulating the nitric oxide system. Inhibition of the nitric oxide system during pregnancy has been shown to cause hypertension, proteinuria and fetal growth retardation in pregnant rats (18). Therefore, insulin resistance and hyperinsulinism associated with PCOS and GDM may be responsible in part for some of the pregnancy complications such as PIH and preeclampsia. Although, Siasiakos et al. commented that there is a plausible mechanism for PCOS to cause adverse pregnancy outcome relating to the action of insulin, the studies preceding their review had not been rigorous enough to prove it, some new studies since, notably by Palomba et al. add evidence of better quality to the possible but never proven direct (not due to obesity or iatrogenic) link between PCOS and outcomes (29, 30). For example, Palomba et al. concluded that uterine artery Doppler indices such pulsatility index (PI) and bilateral notch at first and mid second trimester are commonly altered in pregnant women with PCOS than in controls showing predictive adverse perinatal outcomes. Moreover, Palomba et al. showed that there is higher relative risk for adverse obstetric or neonatal outcomes in patients with the full-blown and non-PCO phenotypes than in those with the non-

hyperandrogenic and ovulatory phenotypes (30).

We found that 15 (11.5%) of pregnant women with GDM and PCOS and 20(15.3%) of pregnant women with PCO had preterm that there was not any significant difference. As our finding, Mikola and Hiilesmaa reported that PCOS didn't have an important effect on preterm labor (7).

Of the patients with GDM and PCO, there are were 0% polyhydroamnious, 8% oligohydroamnious, 3.8% dystocia, 16% macrosomia, 16/8% fetal respiratory distress that these rates were 1.3%, 7.6%,1.5%,12.2% and 13.7% in control group respectively. Although the incidence of fetal macrosomia, dystocia and fetal respiratory distress were more in pregnant with both diseases but not significantly and this indicates the PCO has no side effects in this complications, and this increase is due only to the GDM.

In our study, 22.3% of the infants born to mothers with GDM and PCO complicated by fetal hypoglycemia that 13.3 times more than newborns born to mothers with GDM. This represents an increase effect of PCOS moreover to GDM on hypoglycemia since it is not mentioned in other studies. Moreover, there is no significant difference between two groups related to neonatal icter. Although, in one study has shown that women with PCOS and GDM significantly require treatment of phototherapy for neonatal hyperbilirubinemia (31).

Our findings have shown that 79.2% of patients with GDM and PCO and 69.5% of patients in control group have Cesarean. Despite high Cesarean rate in the case group, this relationship was not significant. Boomsma et al (2008) have been shown that the women with PCOS has a higher prevalence of Cesarean, but after matching base on age and BMI, there is no significant difference related to Cesarean forceps using that this is in line with our finding(20) , which is in accordance with the present study.

In conclusion, we found that pregnant women with diagnosed PCOS and GDM have a more than twofold increased odds of preeclampsia and PIH compared with women without PCOS or symptoms. Our finding emphasized that pregnant PCOS patients should be followed carefully for the occurrence of various pregnancy complications including hypertension and hypoglycemia using GCT, GTT, and control of BP, edema, proteinuria and weight gain. Due to the complications of neonatal hypoglycemia in pregnant women with GDM and PCOS versus GDM alone, we suggested that these

neonatal should be given more care hypoglycemia symptoms. With regarding to relatively high incidence of PCOS moreover diabetes in Kashan and prenatal morbidity related to coexistence these disease during pregnancy, further study regarding to approaches for prevention and decline of pregnancy complications associated with PCOS are recommended.

## Acknowledgement

There is no conflict of interest in this article.

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