Pregnancy outcomes after laparoscopic ovarian drilling in women with polycystic ovarian syndrome

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ABSTRACT

Objectives: To study whether there is an increased risk of glucose intolerance and hypertensive complications during pregnancy in women with polycystic ovarian syndrome (PCOS) who conceived after laparoscopic ovarian drilling and to investigate if there is an adverse pregnancy outcome.

Methods: This prospective study took place at Salmaniya Medical Complex in Bahrain, between June 1996 and June 2003. We compared the pregnancy and neonatal outcomes of 134 patients with PCOS who were treated with laparoscopic ovarian drilling with 479 pregnant women without PCOS (controls). We used the multiple logistic regression analysis to assess the risk of PCOS on impaired glucose tolerance (IGT), gestational diabetes mellitus (GDM), hypertensive disorders in pregnancy (HDP) and premature delivery.

Results: Subjects with PCOS had a significantly greater prepregnancy body mass index, prevalence of obesity and nulliparity as compared with controls. The incidence of IGT (p=0.007), GDM (p=0.01) and HDP (p=0.001) were significantly higher in pregnant PCOS compared with the control group. There were no significant differences in the neonatal outcomes and prevalence of premature delivery between the 2 study groups. When non-obese PCOS patients were compared with non-obese controls, the incidence of GDM (p=0.04) and HDP (p=0.004) were still significantly higher in the former. The prevalence of pregnancy complications were not significantly different when obese PCOS were compared with obese control patients. The PCOS was demonstrated as a risk factor for IGT (p=0.05), GDM (p=0.03) and HDP (p=0.03), but not for premature delivery.

Conclusion: Women with PCOS who conceived after the drilling were at higher risk of IGT, GDM and HDP, and this risk seemed to be independent of maternal obesity.

Saudi Med J 2006; Vol. 27 (4): 519-525

Polycystic ovarian syndrome (PCOS) is the most common endocrine disorder in women, characterized by hyperandrogenism and chronic anovulation.[1] It is often associated with significant insulin resistance (IR) as well as with ß-cell dysfunction.[2] Thus, patients with PCOS may be at risk of developing glucose intolerance or frank diabetes. Pregnancy itself induces IR.[3] Therefore, this condition may constitute in PCOS an additional risk for impaired carbohydrate metabolism, which might affect the pregnancy outcome. However, some published data are conflicting. Some investigators have reported an increase in the prevalence of gestational diabetes mellitus (GDM) in PCOS subjects compared with controls, while others have not.[4-11] Furthermore, there is an evidence that IR is associated with hypertensive disorders in pregnancy (HDP).[12] Thus, women with PCOS may also be at risk

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Received 26th September 2005. Accepted for publication in final form 18th February 2006.

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for HDP. It has been demonstrated that PCOS patients have a higher incidence of HDP or preeclampsia (PE) than the controls.[4,5,9,13-15] In contrast, other reports did not show such increased risk.[6,8,10,11]

Conflicting results regarding these associations led us to undertake this study, to investigate whether our PCOS subjects who had become pregnant after laparoscopic ovarian drilling had a greater incidence of impaired glucose tolerance (IGT), GDM and HDP compared to non-PCOS control women. Furthermore, due to the close link between PCOS and obesity and the association of obesity with adverse pregnancy outcomes,[16,17] it is important to distinguish the possible confounding effect of body mass index (BMI) from the effect of PCOS. Therefore, as a second goal of our study, we examined the impact of body weight on these pregnancy complications, if they occurred, in both PCOS subjects and controls, and investigated the differences between the groups in terms of pregnancy complications and pregnancy outcomes.

Methods. All the 181 PCOS women who underwent laparoscopic ovarian drilling[18,19] in our department at Salmaniya Medical Complex (SMC) between June 1996 and June 2000 have been followed for up to 3 years; 153 of them conceived during this period. The diagnosis of PCOS was based, as described previously,[19] on the presence of at least 3 of the following criteria: 1) menstrual irregularities and anovulation, 2) clinical or biochemical evidence of hyperandrogenemia, 3) presence of characteristic appearances of PCOS on ultrasound examination, and 4) elevated luteinizing hormone (LH) concentration or LH: follicle stimulating hormone ratio >2. Cushing's syndrome, congenital adrenal hyperplasia and thyroid disease were excluded by appropriate tests. Most of the PCOS subjects who had become pregnant after laparoscopic ovarian drilling were consecutively enrolled in the current pregnancy follow-up study, and were prospectively followed at our institution throughout their pregnancies under direct supervision. Since 100% of our studied patients with PCOS conceived after drilling, we did not have access to a second potentially informative control group, example; women with PCOS who conceived without drilling. Therefore, to obtain a representative sample of the background population, all normal pregnant women not known to have PCOS were used as controls. The control patients had a history of normal menstruation, had no clinical signs of hyperandrogenism, and were not receiving any drug therapy. These women were identified as they attended routine booking clinic at our department during the same time period. Both study and control groups were interviewed personally to obtain the relevant information about their medical and family history. On interview, prepregnancy weight, family history of diabetes and parity were documented; and height, current weight, maternal age and arterial blood pressure were measured. The prepregnancy BMI was calculated and those who had a BMI of ≥30 kg/m^2 were considered to be obese. In the family history, we considered first and second-degree relatives, namely; parents, siblings and grandparents. A family history of diabetes mellitus (insulin dependent or non-insulin dependent) was considered positive if one or more of first or second-degree relatives had onset of disease before the age of 45 years. Cases and controls with medical disease, multiple pregnancy, previous history of pregnancy-induced hypertension (PIH), PE and GDM, and whose index pregnancies did not continue beyond 22 weeks of gestation were excluded from the study.

The remaining study and control subjects were followed in our institution. Duration of gestation, maternal weight and blood pressure were recorded at each visit. Between the 24th and 28th gestational week, all women were screened for GDM with a 50 g oral glucose challenge test (GCT). Chilled glucose syrup with 50 g of glucose as syrup with orange flavor (manufactured by Bahrain Danish Dairy Company) was given orally and a blood sample was collected after one hour in a fluoride oxalate tube. The chilled and orange-flavored glucose syrup was preferred to reduce vomiting tendency among the pregnant subjects. If the screening plasma glucose value was ≥7.8 mmol/l (140 mg/dl), the patient underwent a standard 3-hour oral glucose tolerance test (OGTT). The women were advised to follow a carbohydrate diet for 3 days before testing, followed by an overnight fast for 8-14 hours before visiting the laboratory for OGTT on the day of appointment. Blood samples were collected every hour for 3 hours in fluoride oxalate tubes. The samples were assayed for plasma glucose by the hexokinase method (Roche Diagnostics Mannheim, Germany). Patients were classified as gestationally diabetic if 2 or more of 4 plasma glucose concentrations equaled or exceeded the following values: fasting blood sugar 5.3 mmol/l (95 mg/dl); 1-hour level 10 mmol/l (180 mg/dl); 2-hour level 8.6 mmol/l (155 mg/dl); and 3-hour level 7.8 mmol/l (140 mg/dl).[20,21] Impaired glucose tolerance (IGT) was defined as one abnormal glucose value during OGTT. All the subjects with IGT were treated with diet regulation only.

Both PIH and PE are components of HDP and were considered in this study. The PIH was defined as gestational hypertension (blood pressure ≥140/90

mm Hg without proteinuria occurring after 20 weeks' gestation on 2 or more occasions at least 6 hours apart), and PE was diagnosed when PIH was accompanied by proteinuria (2 urinary dipstick readings of ≥1+ or ≥300 mg protein in a 24-hour urine collection). Premature delivery was considered as delivery at <37 weeks of gestational age. Total pregnancy weight gain was based on prepregnancy weight and the last weight measured within a week before delivery. Gestational age at birth was determined by menstrual history in combination with early ultrasound examination before 20 weeks of gestation when available.

Immediately after delivery, a physical examination of the newborn was performed. Birth weight and Apgar scores at 1 and 5 minutes were recorded. Low birth weight was defined as birth weight <2500 g, and macrosomia as birth weight ≥4000 g at ≥37 weeks' gestation. Apgar score of <7 at 5 minutes after birth was considered as the criterion for assessment of the morbidity of neonate.[22] Perinatal death rate was defined as the total number of stillbirths delivered after 22 completed weeks of gestation and the total number of first week neonatal deaths expressed as a percentage of all deliveries.

Cases and controls who delivered elsewhere or who did not continue their antenatal care in our hospital were also excluded from this study. After exclusion of the above subjects, the remaining women were included in the final analysis. The 2 groups were compared for the prevalence of family history of diabetes mellitus (DM), prepregnancy BMI, total pregnancy weight gain, gestational age at birth, obstetric complications such as premature delivery, IGT, GDM, PIH, and PE. We also compared the 2 groups for the infants' birth weight, Apgar score at 5 minutes and perinatal mortality.

Data were analyzed using the Statistical Package for Social Sciences computer program. Comparisons of continuous variables were made using independent samples T-test when normally distributed and the Mann-Whitney U-test when not normally distributed. Chi-square tests were used to compare discrete variables. Multiple logistic regression analysis was preformed with IGT, GDM, HDP and premature delivery as dependent variables. Significance was taken as $p<0.05$.

Results. Between June 1996 and June 2003, there were 182 pregnancies in 153 PCOS patients who were treated with laparoscopic ovarian drilling, and 608 pregnancies in 550 women who were used as the controls. However, after strict application of inclusion and exclusion criteria, the study sample consisted of 134 pregnancies in the study group and 479 in the control group. Patients' characteristics of both groups are shown in **Table 1**. The mean prepregnancy BMI ($p=0.001$), prevalence of obesity ($p=0.007$), and nulliparity ($p=0.000$) were significantly higher in the PCOS than in the control women. However, there were no significant differences between the 2 groups in their age, proportion of women ≥30 years of age, prevalence of primigravidity or family history of DM.

The pregnancy outcomes of the subjects are presented in **Table 2**. A significantly shorter length of gestation was found in the PCOS women compared with the controls ($p=0.006$), whereas the total gestational weight gain was not significantly different between the 2 group. Eighty-nine (66.4%) of PCOS patients and 188 (39.3%) of the controls with elevated values after 50 g GCT were received an OGTT. Of these, 60 PCOS women (44.8%) and 154 controls (32.2%) had IGT ($p=0.007$); and 29 (21.6%) PCOS patients and 61 (12.7%) controls were diagnosed as GDM ($p=0.01$) as per criteria mentioned above. After analysis with logistic regression, obesity ($p=0.000$) emerged as the most important predictor for IGT, but the effect of family history of DM ($p=0.02$) and PCOS ($p=0.05$) also remained statistically significant. However, PCOS appeared to be the only significant risk factor for GDM ($p=0.03$), while family history of DM, age, obesity and nulliparity had no predictive value.

Prevalence of PIH was significantly higher in the PCOS than in the control group ($p=0.002$). The PE seemed more common among the PCOS women (6/134) than among controls (10/479), but the difference did not reach statistical significance ($p=0.13$). If PIH and PE subjects were pooled, the rate of HDP was significantly higher in the PCOS patients compared with the controls ($p=0.001$). Using multiple logistic regression analysis, GDM ($p=0.008$), obesity ($p=0.02$) and PCOS ($p=0.03$) were independent risk factors for HDP. However, after excluding the PE subjects, the greatest predictor for PIH remained GDM ($p=0.02$) and nulliparity had a marginal effect ($p=0.05$), whereas obesity and PCOS had no predictive value. Although the incidence of prematurity was 11.2% in PCOS patients and 6.9% in controls, this difference was not statistically significant ($p=0.1$). Using logistic regression, HDP was the only significant independent risk factor for premature delivery.

Pregnancy outcomes were evaluated, comparing obese and nonobese subjects in the 2 study group separately (**Table 3**). Gestational age at birth, total weight gain and the prevalence of IGT, GDM, HDP, PIH, PE and premature delivery were not significantly

Table 1 - Demographic characteristics of polycystic ovarian syndrome women and controls.

Parameter	PCOS (n=134)	Controls (n=479)	*P*-value
Age (years)	29.4 ± 5.5	28.3 ± 5.4	NS
Age ≥30 years	57 (42.5)	171 (35.7)	NS
Prepregnancy BMI (kg/m^2)	30.9 ± 6.7	29.4 ± 3.6	0.001
BMI ≥30 kg/m^2	80 (59.7)	223 (46.6)	0.007
Primigravidity	63 (47)	182 (38)	NS
Nulliparity	102 (76.1)	260 (54.3)	0.000
Family history of DM	54 (40.3)	155 (32.4)	NS

Data expressed as number (%) and mean ± SD.
PCOS - polycystic ovarian syndrome, BMI - body mass index, DM - diabetes mellitus, NS - not significant

Table 2 - Pregnancy outcomes in polycystic ovarian syndrome and control patients.

Parameter	PCOS (n=134)	Controls (n=479)	*P*-value
Total weight gain (kg)	14.8 ± 3.5	14.3 ± 3.1	NS
GA at birth (weeks)	37.6 ± 2.1	38 ± 1.9	0.006
IGT	60 (44.8)	154 (32.2)	0.007
GDM	29 (21.6)	61 (12.7)	0.01
HDP	26 (19.4)	42 (8.8)	0.001
PIH	20 (14.9)	32 (6.7)	0.002
Preeclampsia	6 (4.5)	10 (2.1)	NS
Premature delivery	15 (11.2)	33 (6.9)	NS

Data expressed as number (%) and mean ± SD.
PCOS - polycystic ovarian syndrome, GA - gestational age, IGT - impaired glucose tolerance, GDM - gestational diabetes mellitus, HDP - hypertensive disorders in pregnancy, PIH - pregnancy induced hypertension, NS - not significant

Table 3 - Comparison of pregnancy outcomes between obese and nonobese subjects in each group separately.

Parameter	PCOS group		*P*-value	Control group		*P*-value
	Obese (n=80)	Non-obese (n=54)		Obese (n=223)	Non-obese (n=256)	
Total weight gain (kg)	14.6 ± 3	15.1 ± 4.1	NS	14.1 ± 2.4	14.5 ± 3.5	NS
GA at birth (weeks)	37.8 ± 1.7	37.3 ± 2.6	NS	37.9 ± 1.8	38.1 ± 2	NS
IGT	41 (51.3)	19 (35.2)	NS	89 (39.9)	65 (25.4)	0.001
GDM	18 (22.5)	11 (20.4)	NS	35 (15.7)	26 (10.2)	NS
HDP	17 (21.3)	9 (16.7)	NS	28 (12.6)	14 (5.5)	0.006
PIH	13 (16.3)	7 (13)	NS	21 (9.4)	11 (4.3)	0.03
Preeclampsia	4 (5)	2 (3.7)	NS	7 (3.1)	3 (1.2)	NS
Premature delivery	10 (12.5)	5 (9.3)	NS	18 (8.1)	15 (5.9)	NS

Data expressed as number (%) and mean ± SD.
PCOS - polycystic ovarian syndrome, GA - gestational age, IGT - impaired glucose tolerance, GDM - gestational diabetes mellitus, HDP - hypertensive disorders in pregnancy, PIH - pregnancy induced hypertension, NS - not significant

Table 4 - Comparison of pregnancy outcomes in obese (PCOS versus controls) and nonobese (PCOS versus controls).

Parameter	Obese		*P*-value	Non-obese		*P*-value
	PCOS (n=80)	Controls (n=223)		PCOS (n=54)	Controls (n=256)	
Total weight gain (kg)	14.6 ± 3	14.1 ± 2.4	NS	15.1 ± 4.1	14.5 ± 3.5	NS
GA at birth (weeks)	37.8 ± 1.7	37.9 ± 1.8	NS	37.3 ± 2.6	38.1 ± 2	0.007
IGT	41 (51.3)	89 (39.9)	NS	19 (35.2)	65 (25.4)	NS
GDM	18 (22.5)	35 (15.7)	NS	11 (20.4)	26 (10.2)	0.04
HDP	17 (21.3)	28 (12.6)	NS	9 (16.7)	14 (5.5)	0.004
PIH	13 (16.3)	21 (9.4)	NS	7 (13)	11 (4.3)	0.01
Preeclampsia	4 (5)	7 (3.1)	NS	2 (3.7)	3 (1.2)	NS
Premature delivery	10 (12.5)	18 (8.1)	NS	5 (9.3)	15 (5.9)	NS

Data expressed as number (%) and mean ± SD.
PCOS - polycystic ovarian syndrome, GA - gestational age, IGT - impaired glucose tolerance, GDM - gestational diabetes mellitus, HDP - hypertensive disorders in pregnancy, PIH - pregnancy induced hypertension, NS - not significant

Table 5 - Neonatal characteristics in PCOS and control women.

Parameter	Neonates		*P*-value
	PCOS (n=134)	Controls (n=479)	
Birth weight (grams)	3215 ± 621	3226 ± 534	NS
Low Birth weight	23 (17.2)	56 (11.7)	NS
Macrosomia	14 (10.4)	39 (8.1)	NS
Apgar Score <7 at 5 min	3 (2.2)	10 (2.1)	NS
Perinatal death	2 (1.5)	6 (1.3)	NS

Data expressed as number (%) and mean ± SD.
PCOS - polycystic ovarian syndrome, NS - not significant

different when obese and nonobese PCOS patients were compared with each other. In the control group, however, the prevalence of IGT (p=0.001) and HDP (p=0.006) were significantly higher in obese subjects. This difference remained after excluding the PE patients from the statistical calculations (p=0.03). When obese (PCOS versus controls) and nonobese (PCOS versus controls) were compared (**Table 4**), the gestational age at birth was significantly lower (p=0.007) and the incidence of GDM (p=0.04), HDP (p=0.004) and PIH (p=0.01) were significantly greater in the nonobese PCOS than in the nonobese control patients. However, the gestational age at birth, total weight gain and the prevalence of IGT, GDM, HDP, PIH, PE and premature delivery were not significantly different when obese PCOS women were compared to obese controls.

Neonatal characteristics are shown in **Table 5**. There were no significant differences between the 2 study groups in their mean birth weight and prevalence of low birth weight, macrosomia, Apgar score <7 at 5 minute and perinatal death. Two (1.5%) perinatal deaths occurred in PCOS patients. One was a case of PIH, abruptio placentae and intrauterine demise at 29 weeks' gestation. The other was a case of GDM delivered at 31 weeks of gestation and the baby died of respiratory distress syndrome 4 days after birth.

Discussion. To date, there have been several reports of different designs that have studied the risk of pregnancy complications in women with PCOS with conflicting conclusions. The different results are most likely due to study design, differing diagnostic criteria of PCOS patients and selection of the control populations. In this study, we tried to evaluate the complications and outcomes of pregnancy in PCOS subjects who were treated with laparoscopic ovarian drilling, with careful selection of the clinical material and control group based on the criteria mentioned above. Confirming previous studies, we observed that

the prepregnancy BMI, prevalence of obesity and nulliparity were significantly greater in our PCOS women than in controls.[6,9] Although previously reported that the family history of DM was more frequently found in PCOS patients,[8] this was not the case in our study, whereas, there was no significant difference in its prevalence between the PCOS and the control subjects. Our data are comparable with those previously described, showing a higher incidence of IGT[8] and GDM in pregnant PCOS women than in the controls.[4,6,9] In 1989, Gjonnaess[13] stated that the prevalence of GDM in PCOS subjects who conceived after laparoscopic ovarian drilling was 8.1%, which was greater than that of the general population at that time. Subsequent reports found that the incidence of GDM in PCOS patients was approximately 20%, while it was 2-9% in controls.[4,6,9] By contrast, there were some studies that did not show a significant difference in the frequency of GDM between PCOS and control women.[7,8,10,11] In the study of Turhan et al,[8] although the GDM rate was similar in both groups, IGT was observed in 18.4% of the PCOS subjects versus 5.1% of the controls.

The PCOS has been demonstrated as a predictive factor for either IGT[8] or GDM.[6,9] In this study, however, PCOS was a risk factor for both IGT and GDM. This could be explained partly by the increased IR and hyperinsulinemia in the pregnant PCOS compared with the control patients.[3,23] It is well known that family history of DM is one of the risk factors for GDM,[9,20,21] and it was considered as one of the indications for an OGTT according to the American Diabetic Association's guidelines.[21] Nevertheless, it was not determined as a risk factor in previous reports.[6,8] In our study, it was illustrated as an independent predictive factor for IGT. Some investigators have shown that obesity was a predictor for GDM[6,8] or PE,[24] while others have not.[9] However, in this study, it was indicated as a risk factor for IGT and HDP. It has been found that the incidence of GDM[6,13] and gestational hypertension was increased by BMI.[14] Therefore, since there was a significant difference in the BMI and prevalence of obesity between our PCOS women and the controls, it might be argued that obesity itself is a risk factor for the pregnancy complications. In the present study, although the differences in the incidence of IGT and HDP occurred among the control group when obese and nonobese control patients were compared with each other, the prevalence of IGT, GDM and HDP were not significantly higher in obese PCOS subjects when compared with nonobese PCOS group. In addition, when nonobese PCOS were compared with nonobese control women, the prevalence of both GDM and HDP were significantly greater in the former. Finally, the incidence of all the studied pregnancy complications were not statistically different when obese PCOS patients were compared with obese controls. These findings lead us to deduce that higher incidence of pregnancy complications in PCOS subjects might not be related to their prepregnancy BMI.

There have been studies of the risk of PCOS on HDP.[4,5,9,13,14] Some reports have found a risk of PCOS on PE,[5,13,14] and some on PIH[4,9] or HDP.[9] By contrast, others did not show the risk of PCOS on PE[6,10] or PIH.[11] In concordance with most of these studies, we illustrated a significantly higher incidence of HDP and PIH in PCOS patients compared with the controls. Although the prevalence of PE was observed to be greater in our PCOS than control women, the difference was statistically not significant. The PCOS has been demonstrated as a risk factor for HDP in our study. This can be explained by the existence of IR. It has been advocated that the pregnant subjects who developed HDP had hyperinsulinemia.[23,25] Furthermore, there was a study of an increased risk of HDP in patients with GDM,[26] supporting our findings in this study. More than one decade ago, the medical community documented that nulliparous women are at above-average risk for PE, with a reported incidence of approximately 10% in certain populations.[27] Indeed, nulliparity was considered as the only significant predictor for PE.[6] In the present study, however, it was indicated as a risk factor for PIH with borderline statistical significance.

There was no significant difference in the incidence of the prematurity between PCOS and control subjects in the current study. This result was consistent with that previously described,[4,11] although others showed an increased prevalence of premature delivery among PCOS patients.[9] In agreement with earlier reports, PCOS was not demonstrated as a predictive factor for prematurity.[4,6] It is well recognized that PE is an important risk factor for premature delivery.[28] Therefore, HDP may, in part, be a risk factor that accounts for premature delivery among pregnant PCOS women. On the other hand, a shorter length of gestation observed in the PCOS subjects might be due to a higher number of cesarean sections and inductions of labor in these patients with pregnancy complications.

Urman et al[4] reported that the prevalence of low birth weight was significantly greater in PCOS women than controls, while others found no differences in any parameter of the neonatal outcomes comparing the singleton pregnancies between the 2 groups.[6,8] In this study, neonatal characteristics were similar in both PCOS and control subjects. The analogous birth

weight, Apgar scores and perinatal death rates in the PCOS patients and controls indicate that no markedly increased risk for perinatal morbidity and mortality exists in PCOS pregnancies.

In conclusion, our results demonstrate that higher incidence of IGT, GDM and HDP among PCOS women who conceived after laparoscopic ovarian drilling, might not be related to maternal obesity, and probably does not affect perinatal outcomes. The PCOS is a predictive factor for IGT, GDM and HDP, but not a potential predictor for premature delivery.

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