Pregnancy, childbirth and neonatal outcomes in women with different phenotypes of polycystic ovary syndrome and healthy women: a prospective cohort study

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Abstract

Aims: The aim of this study was to compare the complications of pregnancy, childbirth and neonatal in women with different forms of polycystic ovary syndrome (PCOS) with healthy women.

Methods: A prospective study from the beginning to the end of pregnancy for 41 pregnant women with PCOS (case) and 49 healthy pregnant women (control) was completed. Based on the presence or absence of menstrual dysfunction (M), hyperandrogenism (HA) and polycystic ovaries (PCO) on ultrasound, the PCOS (case) group were divided into three phenotypes (HA + PCO (n=22), M + PCO (n=9), HA + M + PCO (n=10).

Result: Pre-eclampsia, gestational diabetes and lower birth weight among newborns were significantly higher in the PCOS case group compared to the control group especially in the phenotype HA + M + PCO ($P<0.05$). High BMI ($\beta=2.40$; $P=0.03$) was the strongest predictor of pre-eclampsia in patients with PCOS. High androgen levels (free androgen index) ($\beta=13.71$, 3.02; $P<0.05$), was the strongest predictor of developing diabetes during pregnancy and reduced birth weight baby, respectively.

Conclusion: The results of the present study suggest that PCOS is a risk factor for adverse pregnancy and neonatal outcomes including gestational diabetes, pre-eclampsia and reduced weight babies.

Keywords: polycystic ovary syndrome, pregnancy complications, neonatal complications, phenotype.

Introduction

Polycystic ovary syndrome (PCOS) is a common and complex endocrine disorder that affects women of reproductive age (1). The Rotterdam criteria suggest that are three detectable phenotypes in women presenting with PCOS symptoms: anovulation/menstrual irregularities with polycystic ovary with ultrasound (M + PCO), hyperandrogenism with polycystic ovary with ultrasound (HA + PCO) and hyperandrogenism with anovulation/menstrual irregularities and polycystic ovary (M + HA + PCO). The prevalence of PCOS in the studies was estimated 2.2-26% in developed countries (2-5). Complications associated with polycystic ovary syndrome can occur across the life span for women (6). In this study, we considered complications and outcomes associated with pregnancy, childbirth and neonatal period. Prospective and retrospective studies have been reported PCOS as a risk factor for increased incidence of pregnancy complications (7-9). Pregnancy complications in the first trimester in women with PCOS include hyperemesis gravidarum, abortion and fetal abnormalities (10-12).

Pregnant women with PCOS are at increased risk of gestational diabetes as pregnancy is one of the predisposing factors to increased insulin resistance that may result in gestational diabetes during pregnancy. In addition, insulin resistance is higher in women with PCOS who are overweight (25-70% of women with PCOS has insulin resistance). Further potential risks include gestational diabetes, preeclampsia, gestational hypertension, premature birth, mortality and an increased risk of hospitalization in the intensive care unit for newborns in pregnant patients with PCOS (13). In the only study to assess pregnancy and neonatal outcomes in women with PCOS with different phenotypes (n=97) compared to healthy pregnant women (n=73), Palomba et al. reported significant differences in the prevalence of abortion, gestational hypertension,

gestational diabetes, pre-delivery bleeding between the phenotypes of PCOS and control groups, respectively. In Palomba et al.(14) study, there were no significant differences between groups in terms of incidence of fetal malformations, placental abruption and Apgar score. And in a meta-analysis, Qin et al.(15), suggested that the effects of pregnancy and neonatal outcomes among phenotypes of PCOS are unknown and requires further studies in this regard.

Given the prevalence of PCOS in Iran (1.7-6.14%) and the lack of adequate information on pregnancy and neonatal outcomes in women with different phenotypes of PCOS, this study aimed to evaluate the results of pregnancy, childbirth and neonatal outcomes in women with different PCOS phenotypes compared to healthy pregnant women.

Methods

Design and data collection

The present study is a prospective cohort study using convenience sampling. In this study exposure was having PCOS and not exposure was no PCOS for investigate how adverse obstetric outcomes vary. Therefore, the exposure group included women with PCOS referred to an infertility clinic in Shahid Beheshti hospital in Kashan, Isfahan, Iran from April 2014 to April 2016. This is the only referral clinic in Kashan. The non exposure group comprised healthy women who had been referred to this clinic because of male factor infertility. After presenting the purpose of the study to suitable participants who met the inclusion criteria, a written consent was obtained from each volunteer who were asked to complete the three measures.

Inclusion criteria were Desire to participate in the study, being 15–40 years of age, Married, Absence of non-classic adrenal hyperplasia, thyroid dysfunction, hyperprolactinemia, Non-smoking, No problems in speaking or listening, Iranian, First pregnancy, Spontaneous pregnancy, Not having uterus malformations, Not having chronic diseases, Having two of the following Rotterdam diagnostic criteria:

1) Polycystic ovaries visualized on ultrasound scan (presence of 12 follicles or more in one or both ovaries and/or increased ovarian volume i.e., >10 ml),

2) clinical signs of hyperandrogenism (hirsutism score based on hirsutism score greater than 7 or obvious acne) ,

3) having an interval between menstrual periods >35 days and/or amenorrhea, defined as the absence of vaginal bleeding for at least 6 months (i.e. 199 days).

According to Palomba et al.(14), P1:46.2%, P2:85.5%, α=0.05 and β=0.20, sample size was estimated at 40 couples per group.

Hormonal profiles were sought in both groups before pregnancy. The participants were followed from 7 weeks (6-10 weeks) of pregnancy until after delivery. The pregnancy visit intervals were according to Iran Ministry of Health guideline.

Measures

1. Menstrual history: women were asked about the interval of two menstrual cycles in the last 12 months; their menstrual cycles were classified as following: <21 days, 21-34-34-60, >199 days and irregular.
2. BMI: this variable was estimated by dividing each patient's weight by height^2 (Kg/m^2).
3. Hirsutism: hirsutism scoring was based on the Gallway scale (1961). Hutch et al.(16) modified this scoring system and limited it to 9 androgen sensitive areas each area based on the growth of terminal hair scored from 0-4 (17). A score of 7 or more indicated hirsutism .
4. Acne: Global Acne Grading Scale (GAGS) was assessed to measure acne. This scale considers six areas of the face, chest and upper back to measure the level of involvement, distribution, density and pilosebaceous units. Each of the six areas scores from 0-4 with the most severe lesion in each area determining the score of that area; the score of each region is multiplied by the factor score. The factor score is calculated according to the area involved: forehead: 2; left

and right cheek: 2; nose: 1; chin: 1; chest and upper back: 3. The total score is obtained by multiplying the factor score by total score of involved area (18).

5. Evaluation of cervical incompetence: transvaginal ultrasound from 16-24 weeks' gestation was performed by a gynecologist. The mean cervical length from 16-24 weeks of pregnancy is 25 mm. Cervical length < 25 mm does not indicate cervical incompetence but it is a risk factor for adverse pregnancy outcomes. Cervical incompetence indicates preterm delivery due to passive dilation of the uterine cervix. Cervical length < 25 mm is an indication for cerclage placement in a population of pregnant women with a history of preterm delivery. In this study we considered

6. cervical length <25 mm as cervical incompetence and cervical length >25 mm as not having cervical incompetence (19).

7. Pregnancy-Unique Quantification of Emesis/Nausea (PUQE) Index: The three PUQE questions each have a rating from 1–5, thus the composite sum ranged from 3–15. A score between 3–6 points was defined as mild, 7–12 points as moderate and scores ≥13 points was classified as severe nausea and vomiting. Reliability and validity of the questionnaire is approved (20).

Laboratory measure

An overnight 8-12 hours fasting venous blood sample was obtained from each patient. Serum total testosterone (TT), sex hormone-binding globulin (SHBG), follicle-stimulating hormone (FSH), and luteinizing hormone (LH), thyroid stimulating hormone (TSH) and prolactin (PRL) were concomitantly assessed in all participants by ELISA (DRG Instruments GmbH, Marburg, Germany). TT and SHBG were used to calculate the free androgen index (FAI). FAI was estimated as TT (nmol/l)/SHBG (nmol/l) ×100. Except for amenorrhoeic women, all laboratory determinations were performed in the early follicular phase (3-day menstruation) of the cycle. In

amenorrhoeic women, after roll out of pregnancy the all laboratory determinations were performed.

What does this mean? Because amenorrhea may be related to pregnancy that the hormonal profile will be different with non pregnancy.

Data analysis

In the present study, we used descriptive and analytic statistics using SPSS 21. Data are presented as mean (standard deviation) for quantitative variable and n (%) for qualitative variable. The normality of the distributions was tested using the Kolmogrov-Smirnov test. In order to make comparison between groups, a *t*- test was used for quantitative and Mann-Whitney test for ordinal variables. For comparison between phenotypes of PCOS, the ANOVA test was used for quantitative and Kruskal-Wallis test for ordinal variables. Linear regression (for neonate weight) and logistic regression (for preeclampsia and diabetes) were used to determine the most important predictors.

Univariate and stepwise multiple logistic regression analysis were used to evaluated risk factors associated with above outcomes (significant differences related to these outcome between different phenotypes of PCOS). The analysis of risk factors was concluded in two steps. All the socioeconomic and characteristics of patients presented in Table 1 were tested one by one in separate, univariate analysis. Secondly, all statistically significant variables in the univariate analysis were tested using multivariable logistic regression analysis. Significant variable were entered in a stepwise manner. Results from the final model are presented as odd ratio with 95% confidence interval. The information entered to the regression models was limited to women

with PCOS (significant differences related to these outcomes between different phenotypes of PCOS). A significance level of 0.05 was acceptable.

Ethics

The ethics committee of Kashan University of Medical Sciences approved the present study. All women gave written inform consent.

Findings

1. Baseline characterize of participant

Demographic and reproductive characteristics of participants are presented in **Table 1**. The results show that significant differences between PCOS and control groups in terms of acne score (3.62±4.80 vs. 1.82±4.08; P=0.05), hirsutism score (3.18±4.25 vs. 1±2.31; P=0.003), irregularities menses (P<0.001), testosterone levels (1.02±0.52 vs. 0.65±0.43; P=0.05), SHBG (146.66±2.29 vs. 120.50±3.24; P=0.05), FAI (10.21±34.45 vs. 4.71±1.70; P=0.02) were observed.

2. Obstetric and neonatal status between PCOS and control patients

Table 2 compares pregnancy, delivery and neonatal outcomes between the two groups. Results show that significant differences between the two groups in the incidence of pre-eclampsia (P=0.05), gestational diabetes (P=0.05) and birth weight (P=0.05) were observed. It should be noted that there are any IUGR and LGA in two groups.

3. Obstetric and neonatal outcome between different phenotypes of PCOS

Results of **Table 3** show the comparison of pregnancy, delivery and neonatal outcomes among women with different PCOS phenotypes. Significant differences related to pre-eclampsia (P=0.05), gestational diabetes (P=0.05) and birth weight (P=0.05) between the three PCOS phenotype were observed. HA + M + PCO phenotype have a higher frequency of pre-eclampsia and gestational diabetes and lower birth weight of neonates than other phenotypes respectively. It should be noted that there are any IUGR, LGA and PROM in any of the three groups.

4. Predictive factors of obstetric and neonatal outcome

The regression results showed that high BMI (β=2.40; CI=1.02-1.58) and increased FAI (β=13.71; CI=13.71-76.07) were the strongest predictors of pre-eclampsia and diabetes in patients with PCOS (Data not shown). Moreover, the regression results show that the increase in FAI (β=3.02; CI=- 20.86, -66.91) was the strongest predictor of weight babies were born to mothers with PCOS.

Discussion

This study aimed to assess the pregnancy, delivery and neonatal outcomes in women with PCOS compared to controls. Results of the study show a higher incidence of pre-eclampsia and diabetes, and lower weight infants in women with PCOS compared to the control group. Similar to our findings, in a study conducted by Bjercke et al.(9), the results showed that the prevalence of pre-eclampsia was higher significantly in women with PCOS (13.5%) compared with the control group (7%). The prevalence of gestational diabetes in women with PCOS (7.7%) was higher compared with control (0.6%). The results from Roos et al.(21) also show significantly increased prevalence of gestational diabetes and pre-eclampsia in women with PCOS compared

with the control group. Although the study of Palomba et al.(14), the prevalence of gestational diabetes in PCOS lower than the control group and M + PCO phenotype of PCOS had the highest prevalence. Roos et al. and Bjercke et al. not cited in literature review or background: this was cited in background as whole.

Despite the high prevalence of gestational diabetes mellitus in patients with PCOS compared to control in the study, the fetal macrosomia was expected. But, the birth weight in PCOS was less than the control group especially phenotype HA + M + PCO. This finding may be due to the incompetence of the placenta in these women who tend to have a high incidence of pre-eclampsia. In a recent review, Qin et al.(15) have proposed there is no definite risk factor for adverse pregnancy complications in women with PCOS identified as yet. But, Veltman-Verhulst et al.(22) found that low level of SHBG predicts GDM in women with PCOS. It has been suggested that FAI is a better and more accurate indicator to measure abnormal androgen level (23). In the present study, testosterone and SHBG levels were evaluated to assess the FAI. The results showed that the FAI level was the strongest predictor of gestational diabetes and weight loss of babies in patients with PCOS.

Previous studies have shown that insulin resistance in PCOS could play a role in the pathogenesis of pre-eclampsia (9). Although in the current study, the level of insulin resistance was not measured, the relationship between insulin resistance and androgen levels in non-pregnant women with PCOS has already been demonstrated (24). Introducing higher BMI as the strongest predictor of pre-eclampsia in the present study and increased levels of androgens in fatty status is approved this finding. Moreover, in regard to the high incidence of the above outcomes in HA+M+PCO phenotypes of PCOS, it should be noted that previous studies have

shown that androgen levels in this phenotype of PCOS women was higher than other phenotypes and more prone to metabolic complications. In other words, biochemical hyperandrogenism plays an essential role in metabolic changes and non-androgenic phenotypes of PCOS are at a reduced risk of metabolic adverse effects than other phenotypes (25-26).

This study is not without limitations. Participants were selected using a simple sampling method. The present study is limited to the women recruited from the only referral hospital for infertility on Kashan, Isfahan, Iran; this may limit the generalizability of our findings. However, it should be noted that the women in previous studies were also undergoing infertility treatments that had different endocrine characteristics and pregnancy outcomes. The merit of the present study is that all women had a spontaneous pregnancy. Moreover, PCOS diagnosis was confirmed by a physician experienced in the clinic. All women were first gravidity.

Conclusions

The results of the present study suggest that PCOS is a risk factor for adverse outcomes in pregnancy and neonatal including GDM, pre-eclampsia and weight of newborn. These results were significantly higher in phenotype HA + M + PCO than other phenotypes. Further prospective studies with bigger sample and different Iranian population are needed to confirm the findings.

Competing interests

The authors declare no conflict of interest.

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Table 1. Demographic and clinical characterizes in participants

Variable		PCOS (n=43)			Non PCOS (n=47)	P value§
		HA+PCO (n=22)	M+PCO (n=9)	M+HA+PCO (n=10)		
Age **		24.30±6.25	24.41±3.49	25.03±9.31	25.53±4.14	0.56
Education **		12.69±3.05	11.63±4.11	11.04±4.92	13.19±3.04	0.60
Acne score**		6.93±1.38	6.58±2.30	6.83±1.10	1.82±4.08	0.05£¥
Hirsutism score**		11.03±0.31	11.17±0.01	9.40±0.18	1±2.21	0.003£¥
BMI (kg/m^2)**		25.80±6.53	23.43±7.11	24.42±2.34	24.34±3.99	0.09
Menstruation *	<21 day	2(3.77)	5(7.57)	4(7.01)	1(2.1)	<0.001£¥
	21-35 day	22(41.50)	28(42.42)	30(52.63)	44 (93.6)	
	35-60 day	15(28.30)	18(27.27)	9(15.78)	2 (4.3)	
	190 day	6(11.32)	8(12.12)	9(15.78)	-	
	Variable	8(15.09)	7(10.60)	5(8.77)	-	
Systolic blood pressure in 6-10 weeks of pregnancy**		117.16±10.67	116.71±20.78	116.16±10.67	115.42±12.71	0.76
Diastolic blood pressure in 6-10 weeks of pregnancy**		76.39±8.33	71.24±8.74	73.37±8.43	75.42±8.58	0.25
FBS in 6-10 weeks of pregnancy**		86.52±8.12	87.62±9.11	88.12±7.21	87.40±7.61	0.93
Hb in 6-10 weeks of pregnancy**		12.31± 0.59	12.03± 0.98	12.59± 0.89	12.68±0.99	0.66
HCT in 6-10 weeks of pregnancy**		36.22±2.92	35.12±3.76	36.82±3.33	37.78±2.91	0.17
Testosterone (nmol/L)**		1.43±0.12	1.0±0.12	1.02±0.52	0.65±0.45	0.05£¥
SHBG (nmol/L)**		153.61±2.12	134.61±2.1	126.66±2.2	120.50±3.34	0.05£¥

			9		
PRL(IU/l) **	54.11±31.10	55.81±91.11	56.71±26.18	47.93±20.83	0.71
FAI**	10.21±34.45	8.11±61.41	8.22±37.14	4.71±1.70	0.02£¥
TSH(IU/l) **	2.90±0.2	2.37±0.49	2.67±0.92	2.61±1.78	0.29
LH (IU/l) **	74.65± 2.52	77.84± 3.34	78.69± 3.21	73.84±1.63	0.80
FSH (IU/l) **	58.21±26.18	56.71±9.76	53.82±32.12	47.93±20.83	0.34

*N (%), ** Mean±SD

*ANOVA

**kruskal wallis test

§ P<0.05 between PCOS and Non PCOS phenotype;£ P<0.05 between H+PCO and H+PCO+M phenotype; € P<0.05 between H+PCO and M+PCO phenotype;¥ P<0.05 between H+PCO+M and M+PCO phenotype

Table 2. Comparison the pregnancy, childbirth and neonatal outcomes between PCOS and control groups

Variable			PCOS (n=43)	Control (n=47)	P value
Abortion *			1(2.3)	1(2.1)	0.91
Malformation *			1(2.3)	2(4.3)	0.61
PIH*			3(7)	1(2.1)	0.98
Pre-eclampsia *			4(9.3)	1(2.1)	0.05
GDM*			8(18.6)	6(12.8)	0.05
Amniotic fluid in 32-34 weeks of pregnancy*			3(7)	0	0.06
Abruption *			3(7)	3(6.4)	0.83
Preterm labor *			6(14)	7(14.9)	0.97
PROM*			-	2(4.3)	0.18
PUQE in 6-10 weeks of pregnancy *		Moderate	41(95.3)	44(93.6)	0.36
		Severe	2(4.65)	3(6.4)	
PUQE in 16-20 weeks of pregnancy*		Moderate	40(93)	46(97.9)	0.28
		Severe	2(4.65)	-	
Delivery type*	NVD		23(53.5)	18(38.3)	0.09
	C/S		20(46.51)	29(61.70)	
Anthropometric	Weight		3065.50±0.49	3124.13±0.11	0.05
characterize of neonate**	Height		45.96±2.53	48.43±2.11	0.30
	Head circumstance		33.91±1.56	34.54±1.74	0.29
Neonate’s Apgar in 1 minute **			8.97±0.16	8.86±0.34	0.10
Neonate’s Apgar in 5 minute**			10±0	9.95±0.20	0.20

*N (%), ** Mean±SD

Table 3. Comparison the pregnancy, childbirth and neonatal outcomes among different phenotypes of PCOS

Variable		HA+PCO (n=22)	M+PCO (n=9)	M+HA+PCO (n=10)	P value
Abortion *		-	1(11)	-	0.20
Malformation *		-	-	1(10)	0.20
PIH*		1(4)	1(11)	2(20)	
Preeclampsia*		2(9)	1(11)	4(40)	0.05
GDM*		2(9)	1(11)	3(30)	0.05
Abnormal amniotic fluid in 32-34 weeks of pregnancy*		1(4)	1(11)	2(20)	0.16
Abruption *		2(9)	1(11)	-	0.49
Preterm labor *		2(9)	3(33.33)	1(10)	0.85
PUQE in 6-10 weeks of pregnancy *	Moderate	16(70)	6(66.66)	9(90)	0.20
	Severe	-	-	1(10)	
PUQE in 16-20 weeks of pregnancy*	Mild	-	-	9(90)	0.05
	Moderate	16(70)	5(55.55)	1(10)	
Delivery type*	NVD	8(36.36)	4(44.44)	6(60)	0.81
	C/S	14(63.63)	5(55.55)	4(40)	
Anthropometric characterize of neonate**	Weight	2978.66±22.31	2971.87±87.15	2280±0.52	0.05
	Height	48.64±3.34	48.26±1.43	50.61±1.93	0.40
	Head circumstance	33.82±2.05	33.87±1.36	34.11±1.13	0.60
Neonate's Apgar in 1 minute **		9±0	8.93±0.25	9±0	0.49
Neonate's Apgar in 5 minute**		10	10	10	-

*N (%), ** Mean±SD