Original Article

Are Lean and Normal Weight Patients with Polycystic Ovarian Syndrome at Risk of Preeclampsia?

Bibi Shahnaz Aali, M.D.[1*], Seyed Adel Mahdi, M.D.[2], Nouzar Makhaee, M.D., M.P.H.[3],
Shiva Soboutipour, M.D.[2], Anahita Mehdizadeh, B.Sc.[4]

1. Physiology Research Center, Kerman University of Medical Sciences, Kerman, Iran
2. Obstetrics and Gynecology Department, Kerman University of Medical Sciences, Kerman, Iran
3. Community Medicine Department, Kerman University of Medical Sciences, Kerman, Iran
4. Neuroscience Research Center, Kerman University of Medical Sciences, Kerman, Iran

Abstract

Background: We examined whether pregnant women with preeclampsia have an increased rate of pre-pregnancy polycystic ovary syndrome (PCOS). This study also evaluated whether the association, if any, was a result of preeclampsia and its relationship to PCOS or dependent upon concurrent obesity.

Materials and Methods: In this study, 75 preeclampsia cases and 225 normotensive pregnant controls, matched for age and gravidity, were enrolled. A confirmation of pre-pregnancy PCOS was ascertained by recording medical history, along with a physical examination directed for signs and symptoms of PCOS, an ultrasound report of polycystic ovaries and laboratory tests which confirmed hyperandrogenism prior to pregnancy. Body mass index (BMI) was calculated for each patient. Participants were classified into two categories: lean/normal and obese according to a BMI <25 or greater than 25.1, respectively. Chi-square, Student t test, Fisher-exact and Mann-Whitney tests were used to assess the differences between the groups in addition to the relationship between preeclampsia and PCOS. P values less than 0.05 were considered significant.

Results: Age, gravidity and parity were not significantly different between cases and controls. However, a significant difference was found in gestational age and BMI between the groups. Additionally, preeclamptic patients more frequently suffered from pre-pregnancy PCOS than controls and a significant relationship was found between preeclampsia and previous PCOS, even amongst lean/normal weight patients.

Conclusion: This study provides convincing evidence that a pre-pregnancy diagnosis of PCOS could predispose the patient to preeclampsia, regardless of a concomitant obesity risk factor.

Keywords: Preeclampsia, Polycystic Ovary Syndrome, Body Mass Index

Introduction

Polycystic ovarian syndrome (PCOS) is a common endocrine disorder associated with characteristic features including hyperandrogenemia, insulin resistance and obesity, which profoundly impact a woman's reproductive life (1, 2). There is increasing evidence of adverse pregnancy outcomes in women with PCOS, including a higher rate of pregnancy induced hypertension and. preeclampsia (3). Whether PCOS by itself or the associated obesity obesity is responsible for the increased risk of preeclampsia is a continuing matter of debate (4). Approximately 50% of PCOS women are overweight or obese (5) and obesity, by itself, is considered to be one of the predisposing factors for developing preeclampsia during pregnancy (6). Moreover, several studies have confirmed a strong association between hyperinsulinemia and PCOS (7, 8) and there is evidence to support the relationship of hyperinsulinemia to hypertensive disorders seen during pregnancy (8, 9). Gjonnaess's study has indicated a high frequency of preeclampsia (12.9%) in a group of PCOS cases who conceived after ovarian electro-cauterization and interestingly, all members of this group were overweight. Therefore they could not find a direct relationship between the condition of PCOS per se and preeclampsia (10). On the other hand, de Vries et al. have reported a significantly higher incidence of preeclampsia in patients with PCOS than in controls. They concluded that this higher incidence could not be explained by body mass index (BMI), endocrine profile prior to pregnancy, induction of ovulation or treatment regimens (11). A recent meta-

analysis of 15 studies on the adverse outcomes of pregnancy and PCOS revealed that women with PCOS demonstrated approximately a 3.5 greater chance of developing preeclampsia, but all studies in which preeclampsia was an endpoint reported a lower parity, higher BMI or more multiple pregnancies among women with PCOS versus controls (2). Therefore, to investigate the impact of PCOS per se on developing preeclampsia, it is mandatory to exclude as many of the confounding factors as possible, thus the present study was carried out with this aim.

Materials and Methods

In this case-control study, there were 75 preeclamptic patients admitted to the Maternity Center at Afzalipour Hospital, main University Hospital, in Kerman, southeastern Iran, who were selected as cases. The control group consisted of 225 women with uneventful pregnancies, matched for age and gravidity. Preeclampsia was defined as having hypertension of 140/90 or greater and a 24 hour proteinuria level of ≥ 300 mg after 20 weeks of gestation. Patients with a history of endocrine disorders such as hyperprolactinemia and thyroid disease, multifetal pregnancy, renal disease, chronic hypertension, overt and gestational diabetes mellitus, rheumatologic disorders, adrenal disease and current or previous use of corticosteroids were excluded from the study. The project was approved by the Ethics Committee of the Research Council at Kerman Medical University and written informed consent was obtained from the study population. A history of PCOS was investigated in both groups based on the symptoms of oligomenorrhea/amenorrhea prior to pregnancy, along with an ultrasound report of polycystic ovaries and clinical features of hyperandrogenism (hirsutism and acne) or laboratory records of hyperandrogenemia. BMI was calculated in both groups based on the formula BMI = weight(Kg)/height²(m²), using the weight records of patients prior to 10 weeks of pregnancy as the weight reference [weight does not change remarkably before 10th week of pregnancy (12)]. The groups were divided into lean/normal weight and obese categories based on a BMI calculation of ≤ 25 and >25.1. Data on demographics and obstetrics history were reported. The groups were compared with the Chi-square, Student t, Fisher-exact and Mann-Whitney tests. P values<0.05 were considered significant.

Results

Demographic and obstetric characteristics of the groups are shown in table 1.

Table 1: Comparison of obstetric characteristics and BMI between the groups

Group characteristic	Preeclampsia (mean±SD)	Control	P value
Age (year)	26.9 (6.5)	26.0 (5.1)	0.3
Gravidity (number)	1.7 (1.3)	1.9 (1.2)	0.1
Parity (number)	1.5 (1)	1.8 (1.1)	0.06
Gestational age (weeks)	33.2 (3.8)	37.9 (2.2)	0.00*
BMI	25.3 (5.4)	22.6 (4.0)	0.03*

Significant

As demonstrated, gestational age was significantly lower in the case group. Moreover, preeclamptic patients had a significantly higher mean BMI in comparison to the controls (25.3 versus 22.6). Table 2 reveals a significant relationship between preeclampsia and PCOS. As seen, 17.3% of the preeclamptic patients had a history of PCOS while only 8.3% of the control group were diagnosed with PCOS (p=0.04).

Table 2: Frequency of previous PCOS in the groups

Group Previous condition	Preeclampsia	Control	P value
PCOS	13 (17.3%)	17 (8.1%)	0.04*
Non-PCOS	62 (82.7%)	193 (91.9%)	

Significant

Interestingly, a similar relationship was found in women with low and normal BMI, i.e., there was a significantly higher number of PCOS cases seen in lean and normal weight women with preeclampsia when compared to the matched subgroup of uneventful pregnancies (Table 3).

Table 3: Frequency of previous PCOS in the lean/normal weight category of the groups

Group Previous condition	Preeclampsia	Control	P value
PCOS	7 (18.4%)	12 (7.3%)	0.04*
Non-PCOS	31 (81.6%)	152 (92.7%)	

Significant

Discussion

Preeclampsia is a major cause of maternal and neonatal morbidity and mortality that occurs in 5% of pregnancies worldwide (12). Although the etiology is still unclear, there are known risk

factors such as nulliparity, chronic renal disease, obesity, molar and multifetal pregnancy (6, 12). Based on several studies, PCOS is also regarded as a predisposing factor of preeclampsia (1, 2-4, 8). Our study also showed a positive relationship between preeclampsia and PCOS, as a higher number of preeclamptic patients suffered from previous PCOS. More importantly, we confirmed this relationship after the effects of known confounding factors were excluded. By matching the groups for age and gravidity in the first step and then by excluding multiple pregnancies and performing an analysis on the subgroup of lean/ normal weight cases, we provided evidence that PCOS was related to developing preeclampsia during pregnancy, regardless of concomitant obesity. In Boomsma's meta-analysis, women with PCOS demonstrated a significantly higher chance of developing pregnancy-induced hypertension (OR 3.67) and preeclampsia (OR 3.47). Although their study showed that the higher risk of developing pregnancy-induced hypertension remained after excluding all studies in which there were confounding factors, unfortunately no subgroup analysis on the relationship between preeclampsia and PCOS was possible due to the higher rate of obesity, lower parity and multiple pregnancies in PCOS patients versus controls. Conversely, De Vries et al.'s study provided evidence that favored an association between preeclampsia and PCOS in the absence of obesity (11) which was in line with our findings. We also found a significantly higher BMI in preeclamptic patients that supported the association of obesity and preeclampsia as previously demonstrated in other studies (8, 10, 13).

The mean gestational age in our preeclampsia group was in the preterm range at 33 weeks which makes babies more susceptible to morbidity and mortality. This result provides supporting evidence that preeclampsia accounts for a major part of preterm births and hence neonatal mortality and morbidity (14, 15). Researchers have shown a higher preterm birth rate in patients with PCOS and they speculate that it might reflect more complications encountered by this group of women (2). It is likely that the higher frequency of prematurity in our preeclamptic group is partly related to the larger number of PCOS cases seen in this group of patients.

Conclusion

Our study confirms the association between preeclampsia and pre-pregnancy PCOS and supports that this relationship is independent of coexistent obesity. Whether this relationship arises from hyperinsulinemia and insulin resistance lying in the pathophysiology of PCOS or other factors remains to be elucidated.

References
1. Hart R, Norman R. Polycystic ovarian syndrome--prognosis and outcomes. Best Pract Res Clin Obstet Gynaecol. 2006; 20(5): 751-778.
2. Boomsma CM, Eijkemans MJ, Hughes EG, Visser GH, Fauser BC, Macklon NS. A meta-analysis of pregnancy outcomes in women with polycystic ovary syndrome. Hum Reprod Update. 2006; 12(6): 673-683.
3. Legro RS. Pregnancy considerations in women with polycystic ovary syndrome. Clin Obstet Gynecol. 2007; 50(1): 295-304.
4. Boomsma CM, Fauser BC, Macklon NS. Pregnancy complications in women with polycystic ovary syndrome. Semin Reprod Med. 2008; 26(1): 72-84.
5. Norman RJ, Noakes M, Wu R, Davies MJ, Moran L, Wang JX. Improving reproductive performance in overweight/obese women with effective weight management. Hum Reprod Update. 2004; 10(3): 267-280.
6. Sibai BM, Gordon T, Thom E, Caritis N, Klenoff M, Mc Nellis D, et al. Risk factors for preeclampsia in healthy nulliparous women: a prospective multicenter study. The National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units. Am J Obstet Gynecol. 1995; 172(2 Pt 1): 642-648.
7. Salehpour S, Taherzadeh Broujeni P, Neisani Samani E. Leptin, Ghrelin, Adiponectin, Homocysteine and Insulin Resistance Related to Polycystic Ovary Syndrome. International Journal Fertility & Sterility (IJFS). 2008; 2(3): 101-104.
8. Mikola M, Hiilesmaa V, Halttunen M, Suhonen L, Tiitinen A. Obstetric outcome in women with polycystic ovarian syndrome. Hum Reprod. 2001; 16(2): 226-229.
9. Bjercke S, Dale PO, Tanbo T, Storeng R, Ertzeid G, Abyholm T. Impact of insulin resistance on pregnancy complications and outcome in women with polycystic ovary syndrome. Gynecol Obstet Invest. 2002; 54(2): 94-98.
10. Gjonnaess H. The course and outcome of pregnancy after ovarian electrocautery in women with polycystic ovarian syndrome: the influence of body-weight. Br J Obstet Gynaecol. 1989; 96(6): 714-719.
11. de Vries MJ, Dekker GA, Schoemaker J. Higher risk of preeclampsia in the polycystic ovary syndrome. A case control study. Eur J Obstet Gynecol Reprod

Biol. 1998; 76(1): 91-95.
12. Cunningham FG, Leveno KJ, Bloom SL, Hauth JC, Gilstrap LC, Weastrom KD. Williams Obstetrics. 22nd ed. Philadelphia: McGRAW-HILL; 2005; 127: 765.
13. Roman H, Robillard PY, Hulsey TC, Laffitte A, Kouteich K, Marpeau L, et al. Obstetrical and neonatal outcomes in obese women. West Indian Med J. 2007; 56(5): 421-426.
14. Goldenberg RL, Culhane JF, Iams JD, Romero R.

Epidemiology and causes of preterm birth. Lancet. 2008; 371(9606): 75-84.
15. Menzies J, Magee LA, Li J, Mac Nab YC, Yin R, Stuart H, et al. Instituting surveillance guidelines and adverse outcomes in preeclampsia.Obstet Gynecol. 2007; 110(1): 121-127.