The Risk of Adverse Pregnancy, Delivery and Neonatal Outcomes Among Overweight/Obese Women with Polycystic Ovary Syndrome: A Retrospective Study, 2010 - 2015

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Background: Existing retrospective studies comparing the perinatal outcome in women with PCOS versus women without PCOS have proven that pre-pregnancy maternal overweight and obesity have a negative influence on the perinatal outcome of these women.
Objective: To compare the pregnancy, delivery and neonatal outcomes in singleton pregnancies between overweight/obese and normal weight women with Polycystic Ovary Syndrome (PCOS).
Materials and Methods: This is a retrospective cohort study of 185 women with PCOS who had achieved spontaneous pregnancy and delivered between January 2011 and December 2015. All data were retrieved from patient medical charts. Women diagnosed with polycystic ovary syndrome according to the Rotterdam criteria between the ages of 15 and 44 years who had conceived spontaneously were included.
Results: Pregnancy loss occurred more frequently in the obese/overweight group as compared with the normal weight group (RR 1.3, 95% CI 1.0 - 1.8, p 0.04). Gestational hypertension and pre-eclampsia occurred less frequently in the group with normal BMI, although a statistical significance was not demonstrated (RR 1.1, 95% CI 0.6 - 2.3, p=0.37 and RR 1.0, 95% CI 1.5 - 1.9, p 0.49, respectively). The proportion of women who developed GDM was higher among women with increased BMI, however, this was also not statistically significant (RR 1.4, 95% CI 0.9 - 2.2, p=0.07). The prevalence of preterm birth was higher among overweight/obese women although this was also not statistically significant (RR 0.79, 95% CI 0.29 - 2.19, p 0.66). The proportion of women with a poor 1st minute APGAR score was significantly higher in the overweight and obese group as compared to the normal weight group (RR 1.78, 95% CI 1.10 - 2.89, p 0.012).
Conclusion: Overweight and obese women with PCOS with an ongoing singleton pregnancy have an increased risk of pregnancy loss. Furthermore, they also have an increased risk of delivering babies with a poor APGAR score. Thus the importance of lifestyle modification in overweight and obese women with PCOS in order to reduce the risk of adverse perinatal outcomes should be emphasized.

Key words: polycystic ovary syndrome, overweight, obesity

Introduction

Polycystic ovary syndrome (PCOS) is a condition in which there is an imbalance of the female sex hormones. It is a common endocrine disorder in women of reproductive age and is one of the leading causes of female infertility.[1] Elevated levels of testosterone, dehydroepiandrosterone sulphate, androstenedione, prolactin and luteinizing hormone (LH) are noted while estrogen levels may be high, normal or low.

Polycystic ovary syndrome affects 5-10% of women of childbearing age. Common clinical manifestations include menstrual irregularities and signs of androgen excess such as hirsutism, alopecia and acne.[2] PCOS is not a disease, and reflects multiple potential etiologies with variable clinical presentations. The heterogeneity of the disorder makes the pathogenesis and diagnosis difficult.[2] According to the joint meeting of the European Society for Human Reproduction and Embryology and the American Society of Reproductive Medicine in Rotterdam, 2003, the diagnosis of polycystic ovary syndrome is made when 2 out of the 3 following criteria have been met: 1) oligo-ovulation or anovulation, 2) clinical/biochemical hyperandrogenism and 3) finding of polycystic ovaries on ultrasound examination.[2] It is well accepted to exclude also other etiologies of hyperandrogenism such as congenital adrenal hyperplasia, androgen-secreting tumors and Cushing's syndrome prior to the diagnosis of polycystic ovary syndrome.

Insulin resistance with subsequent hyperinsulinemia seems to be the unifying factor in the pathophysiology of pregnancy loss in polycystic ovary syndrome. Insulin resistance also has an important influence on the development of diabetes type 2 and hypertension.[3] Hypertension is thought to be associated with androgen excess and a subsequent increased stimulation of sympathetic nerve activity.[4,5] Abdominal overweight and obesity-also important components of polycystic ovary syndrome that affect ~30-70% of the PCOS population[6,7] - are associated with insulin resistance and increased testosterone production.[6]

Polycystic ovary syndrome in itself has a negative influence on the perinatal outcome for these women. In women with polycystic ovary syndrome, pregnancy is often complicated by pregnancy-induced hypertension, pre-eclampsia, gestational diabetes mellitus (GDM), preterm delivery or a risk of delivery by cesarean section is raised.[8,9,10,11] The newborn babies stay more frequently in a neonatal intensive care unit and perinatal mortality also occurs more frequently.[8,11] Since it has been proven that pre-pregnancy maternal overweight and obesity have a negative influence on the perinatal outcome[12,13,14,15] existing retrospective studies comparing the perinatal outcome in women with PCOS versus women without PCOS have matched the samples for BMI or have adjusted the analyses for BMI. As such, Turhan, et al. (2003)[16], looking into the pregnancy, delivery and neonatal outcome in women with polycystic ovary syndrome, concluded that pre-pregnancy overweight (BMI 25 kg/m^2) is an important predictor of GDM. A study by Han, et al. (2011)[17] of Asian women looked into the influence of overweight (BMI 25 kg/m^2) on the pregnancy outcome in women with polycystic ovary syndrome, using a case-control design of overweight versus non-overweight women, and showed that the prevalence of GDM and fetal macrosomia was significantly higher in overweight versus normal weight women with PCOS.

To date, these studies are rather scarce and literature review will reveal that most have mainly included women undergoing assisted reproductive technology. Thus, this study aimed to answer the question: Do obese and overweight women with polycystic ovary syndrome (PCOS) have a higher risk of perinatal complications than normal weight women with PCOS at a tertiary hospital?

The study aimed to compare the pregnancy, delivery and neonatal outcomes in singleton pregnancies among obese, overweight and normal weight women with polycystic ovary syndrome.

Materials and Methods

Study Design

This is a retrospective cohort study involving a review of hospital records of subjects diagnosed with polycystic ovary syndrome seen at the Department of Obstetrics-Gynecology at the De La Salle - University Medical Center from January 2010 to December 2014. Their pregnancy, delivery and neonatal outcomes from January 2011 until December 2015 were followed up by retrieving their medical charts at the medical records, consultants' clinics and outpatient department.

Setting

The study was conducted at De La Salle University Medical Center, a tertiary hospital in Dasmarinas, Cavite from April 2016 to August 2016.

Participants

Inclusion Criteria

The study population included all women diagnosed with polycystic ovary syndrome according to the Rotterdam criteria between the ages of 15 and 44 years who had history of pregnancy, whether pregnancy loss or live birth, conceived spontaneously. All pregnancies were taken into account.

Exclusion Criteria

Medical charts of women with the following conditions were excluded:

1. Multiple gestation
2. Ultrasonography-documented uterine anatomical anomalies
3. Pregnancies complicated by medical conditions such as hypothyroidism, diabetes mellitus, hypertension prior to pregnancy
4. Confirmed cases of immunoreproductive disorder
5. Patients who received metformin, progesterone or any tocolytics during pregnancy
6. Pregnancies achieved through fertility workup

Data Collection

All parameters and pregnancy outcomes were collected from the medical records retrospectively. A patient with polycystic ovarian morphology was diagnosed by means of transvaginal ultrasound showing the presence of >12 follicles with a diameter of 2-9 mm and/or an increased volume of >10 cm^3. Patient was described as having an oligo/ anovulatory cycle if she had a mean cycle length of >35 days [oligomenorrhea] or >180 days [amenorrhea].[18] Hyperandrogenism was diagnosed using the modified Ferriman-Galleway scoring system. A patient's data sheet was the primary mode of data gathering.

Sample Size

Using OpenEpi, Version 3 software[19], a minimum sample size of 57 patients per group was required for this study based on a level of significance of 5%, with a power of 80%. The values used for the sample size computation was noted from the reference article by Sunita J. and Ramanand, et al.[20]

Statistical Method

The number of pregnancy loss, hypertension during pregnancy, presence of gestational diabetes mellitus, mode of delivery, gestational age at delivery, birthweight were compared between overweight/obese and normal weight women and statistically significant difference was determined using the appropriate test.

The level of significance was set at 0.05 threshold for significance. Missing variables were not replaced or estimated during the analysis. All data analysis were performed in STATA 12.

Descriptive statistics was used to summarize the clinical characteristics of the patients. Frequency and proportion was used for nominal variables, and mean and SD for interval/ratio variables. Chi-square test and independent samples t-test were used to determine the difference of mean and frequency between the overweight/ obese and normal weight women with PCOS, respectively. All valid data were included in the analysis. Null hypotheses were rejected at 0.05?-level of significance. STATA 12.0 was used for data analysis.

Consent

A letter addressed to the custodian of the Records Section of the De La Salle - University Medical Center, as well as the Medical Director, for access to medical records was submitted. This is with the assurance that confidentiality in the

perusal of records of patients was maintained throughout the conduct of the study.

Ethical Considerations

The study was conducted in accordance to the ethical principles based on the Declaration of Helsinki and the National Guidelines for Biomedical Research of the National Ethics Committee (NEC) of the Philippines. The research protocol was submitted for approval to the Independent Ethics Committee (IEC) of De La Salle University Medical Center prior to its conduct. The results and patient information was kept strictly confidential by the primary investigator. A unique alphanumeric code was assigned to each research subject and the subjects' names did not appear on any of the data collection tools. Only the primary investigator had access to the patients' names and other pertinent information, to ensure patient confidentiality at all times. The data was stored in the primary investigator's database, password-protected, and the projected duration of storage is at least 10 years.

Results

The study consisted of 185 pregnant women with PCOS of whom 26/185 (14%) had classic PCOS (hyperandrogenism, anovulation and polycystic ovarian morphology), 37/185 (20%) suffered from oligo- or anovulation and hyperandrogenism, 76/185 (41%) had PCOM and oligo- or anovulation, and 60/185 (32.4%) suffered from hyperandrogenism and PCOM.

There were 69 normal weight, 57 overweight, and 59 obese pregnant women included. The mean BMI in the overweight/obese and normal weight women was 26.4 and 20.9 kg/m^2, respectively. Weight groups were comparable in terms of age, parity, polycystic ovarian morphology (PCOM), presence of menstrual irregularities, and hirsutism at baseline. Majority of women were in their early 30s. Per weight category, more than half were primiparous mothers; likewise, more than half possessed a PCOM. Irregular menstrual periods and hirsutism were each found in at least a third of women per group (Table 1).

Complications of pregnancy differ between the two categories of patients. Pregnancy loss occurred more frequently in the obese and overweight group as compared with the normal weight group (RR 1.3, 95% CI 1.0 - 1.8, p=0.04). Gestational hypertension and pre-eclampsia occurred less frequently in the group with normal BMI, although a statistical significance was not demonstrated (RR 1.1, 95% CI 0.6 - 2.3, p=0.37 and RR 1.0, 95% CI 1.5 - 1.9, p=0.49, respectively).

Table 1. Demographic and clinical characteristics of 185 obese + overweight and normal BMI pregnant women with PCOS.

	Normal BMI (N=69)	Overweight + Obese (N=116)	t value	Df	p value	
	Mean + SD; Median (Range); Frequency (%)					
Age, years	31.1 + 5.3	30.1 + 4.6	1.3	183	0.191$^{\infty}$	NS
Height, cm	173 (152 - 200)	159 (122 - 188)	7.5	183	<0.00001$^{\infty}$	S
Weight, kg	61 (45 - 88.5)	65 (36 - 93)	-3.6	183	<0.0005$^{\infty}$	S
BMI, kg/m^2	20.99 (18.59 - 22.89)	25.22 (22.91 - 38.87)	-13.2	183	<0.00001$^{\infty}$	S
Parity						NS
Nulli	13 (18.8)	36 (31)	-	-	-	
Primi	43 (62.3)	69 (59.5)	-	-	-	
Multi	13 (18.8)	11 (9.5)	-	-	-	
PCOM	67 (97.1)	107 (92.2)	-	-	0.176$^{\Omega}$	NS
Irregular menses	49 (71.0)	94 (81.0)	-	-	0.115$^{\Omega}$	NS
Hirsutism	43 (62.3)	66 (56.9)	-	-	0.467$^{\Omega}$	NS

PCOM, Polycystic Ovarian Morphology
Statistical tests used were as follows: ∞ - Independent samples t-test; Ω - Chi-squared test
NS - not significant, S - significant

The proportion of women who developed GDM was higher among women with increased BMI, however, this was also not statistically significant (RR 1.4, 95% CI 0.9 - 2.2, p=0.07) (Table 2).

There was insufficient evidence to demonstrate a statistical difference in the delivery outcomes of women. The prevalence of preterm birth was higher in the overweight/obese women although this was not statistically significant (RR 0.79, 95% CI 0.29 - 2.19, p=0.66). For both groups, the median completed gestational age was more than 37 weeks and the prevalence of preterm births was less than nine per cent. With regard to the mode of delivery, there was marginal evidence of a difference in the prevalence of Caesarean sections between groups (RR 0.99, 95% CI 0.63 - 1.56, p=0.97). About 3 in 10 delivered by cesarean section for both groups. Reasons for delivery through cesarean section were fetal distress, malpresentation, cephalopelvic disproportion and dystocia.

There were 5 infants with low birth weight. Macrosomia was most frequently seen among the overweight and obese women (5.2%) (RR 1.78, 95% CI 0.37 - 8.60, p=0.5). The proportion of women with a poor 1st minute APGAR score was significantly higher in the overweight and obese group as compared to the normal weight group (RR 1.78, 95% CI 1.10 - 2.89, p=0.012).

Table 2. Pregnancy outcomes in different weight categories of pregnant women with PCOS.

	Normal BMI (N = 69)	Overweight + Obese (N = 116)	RR (95% CI)	p value	
		Frequency (%)			
Loss of pregnancy	31 (44.9)	68 (59.0)	1.3 (1.0 - 1.8)	0.04	S
Pre-eclampsia	12 (17.4)	20 (17.2)	1.0 (1.5 - 1.9)	0.49	NS
Gestational hypertension	19 (27.5)	10 (8.6)	1.1 (0.6 - 2.3)	0.37	NS
Gestational diabetes	44 (63.8)	19 (16.4)	1.4 (0.9-2.2)	0.07	NS

Statistical test used was Chi-squared test NS - not significant, S - significant

Table 3. Delivery outcomes in different weight categories of pregnant women with PCOS.

	Normal BMI (N = 69)	Overweight + Obese (N = 116)	RR (95% CI)	p value	
		Frequency (%)			
Preterm birth	6 (8.7)	8 (6.9)	0.79 (0.29 - 2.19)	0.66	NS
Vaginal spontaneous delivery	35 (50.7)	49 (42.2)	0.83 (0.61 - 1.14)	0.27	NS
Cesarean section	21 (30.4)	35 (30.2)	0.99 (0.63 - 1.56)	0.97	NS

Statistical test used was Chi-squared test NS - not significant, S - significant

Table 4. Neonatal outcomes in different weight categories of pregnant women with PCOS.

	Normal BMI (N = 69)	Overweight + Obese (N = 116)	RR (95% CI)	p value	
		Frequency (%)			
Low birth weight (<2500 g)	3 (4.3)	2 (1.7)	0.40 (0.07 - 2.31)	0.34	NS
Macrosomia (> 4000g)	2 (2.9)	6 (5.2)	1.78 (0.37 - 8.60)	0.50	NS
Poor APGAR score (<7 at the 1st minute)	16 (23.2)	48 (41.4)	1.78 (1.10 - 2.89)	0.012	S

Statistical test used was Chi-squared test NS - not significant, S - significant

Discussion

Polycystic ovary syndrome (PCOS) is considered to have significant implications for pregnancy outcomes. In a large meta-analysis involving 15 studies with 720 PCOS patients and 4505 weight-matched controls, it was demonstrated that women with PCOS have a significantly higher risk of developing gestational diabetes, pregnancy-induced hypertension and preeclampsia.[8] Furthermore, these women have an increased risk of neonatal complications, such as preterm birth, neonatal intensive care and mortality.[8] However, it remains unclear whether PCOS itself is responsible for the increased pregnancy risks or if the associations could be explained by obesity. Furthermore, it is not known how PCOS and obesity in combination influence pregnancy outcomes.

Present findings confirm the existing evidence that an increased BMI has an influence on the prevalence of gestational diabetes. Since insulin resistance is a common feature of PCOS, it would be expected that women with PCOS run an increased risk of developing gestational diabetes mellitus. In a retrospective case-control study, it was demonstrated that women with a history of gestational diabetes indeed showed a higher prevalence of PCOS compared with women with uncomplicated pregnancies.[21] Conversely, several studies have demonstrated an increased risk of gestational diabetes in women with PCOS.[22-23] There are studies suggesting that the higher incidence of gestational diabetes in women with PCOS could be explained by a higher occurrence of obesity in these women. However, a meta-analysis has demonstrated that the increased risk of developing gestational diabetes in women with PCOS compared with controls remained after exclusion of studies in which a higher BMI among women with PCOS was reported.[8] On the other hand, obesity appears to constitute an additional risk for gestational diabetes in women with PCOS.

Gestational hypertension and preeclampsia appeared to have occurred more frequently with an increased BMI. Gestational hypertension and preeclampsia also appear to be associated with PCOS according to a meta-analysis of eight studies.[8] The underlying mechanisms for this association have not been elucidated. However, they may be related to metabolic disorders in women with PCOS since insulin resistance in early pregnancy is associated with an increased risk of preeclampsia.[24] Higher risk of gestational hypertension and preeclampsia suggest that women with PCOS may run an increased risk of placental insufficiency, which in turn could lead to neonatal complications.

Concerning the rate of pregnancy loss, our results are similar to those in the retrospective cohort study by Fedorscak, et al.[25] investigating the influence of obesity on the prevalence of early pregnancy loss in a sample of infertile women who received IVF or intra-cytoplasmic sperm injection (ICSI). They conclude that obesity was an independent risk factor for early pregnancy loss before 12 weeks of gestation. A cohort study by Wang, et al.[26] found evidence that a pre-pregnancy BMI of 30-34.9 kg/m^2 has a significant negative and independent influence on the prevalence of pregnancy loss before 20 weeks of gestation in women with PCOS.[16,23]

The results of the study do not support the hypothesis that pre-pregnancy overweight and obesity in women with PCOS has a negative influence on the prevalence of preterm birth and the birth weight of singletons. A similar result was found in the case-control study by Han, et al.[17] who found no significant influence of an increased BMI (BMI>25 kg/m^2) in women with PCOS on the prevalence of preterm birth. In contrast, results found by Cnattingius, et al.[14] studied the association between maternal obesity and the risk of preterm delivery in Swedish women using a retrospective design. The authors observed that obesity (BMI>30 kg/m^2) had a significant influence on the prevalence of preterm birth and this negative influence was highest in extremely preterm births. Preterm birth may partly explain the higher incidence of admission to a neonatal intensive care unit and perinatal mortality in the children born to women with PCOS.

The increased risk of cesarean section among women with polycystic ovary syndrome found in other studies does not correspond with our findings. In a meta - analysis[8], women with polycystic ovary

syndrome showed a significantly higher rate of cesarean section but in a subgroup analysis restricted to studies of higher validity, no significant risk was observed. Obesity has been shown to be an independent risk factor for cesarean delivery.[28] In the present study, however, the overweight/obese group had more frequent cesarean section than the normal weight group although this was not statistically significant.

Our findings do not confirm the existing evidence that overweight has an influence on the prevalence of macrosomia.[16,17,27] Given the higher rate of gestational diabetes in women with PCOS, an increased incidence of macrosomia might be expected. However, in the present analysis, neonates from women with PCOS were shown to have birth weights that are well within normal range. This is in congruence with the findings of the study of Mikola, et al.[27] which demonstrated that although women with PCOS are often obese and have insulin resistance prior to pregnancy as well as a higher rate of gestational diabetes, there is no evidence of an increased incidence of macrosomia in the infants born to these women.

Infants born to mothers with a previous diagnosis of polycystic ovary syndrome were more often given a low APGAR score. This is in agreement with the findings of Roos, et al.[29] who furthered the idea that these infants may be more susceptible to fetal distress during labor. Moreover, neonates born to women with PCOS had a 2-fold increased risk for admission to the NICU and perinatal mortality was evidently higher in women with PCOS according to a large meta-analsysis.[8]

Results of the study suggest that pre-pregnancy overweight and obesity in women with PCOS has, in addition to the influence of the syndrome in itself, has an important negative influence on the prevalence of pregnancy loss. Furthermore, these women are more prone to give birth to a baby with a poor APGAR score at the first minute of life.

This information may be vital in clinical practice for the management of pregnancy in women with PCOS. These women should be given notice of the additional risks their pregnancies may have, stronger surveillance and attention should be provided, as well as screening for these complications during pregnancy and parturition. However, in order to manage pregnancy in women with PCOS more effectively, further investigation into the importance of glucose control, hormonal status regulation, lifestyle modification and medical therapy among overweight and obese women with polycystic ovary syndrome during pregnancy should be done.

The upward trend in the prevalence of overweight and obesity is continuing despite its well-publicized adverse effects on health. From the standpoint of primary prevention, adverse pregnancy outcomes related to overweight and obesity may, at least theoretically, be preventable. Present findings thus provide further justification for the development of effective strategies to reverse the trends toward increasing body weight and a higher prevalence of overweight and obesity.

Conclusion

In conclusion, overweight and obese women with PCOS with an ongoing singleton pregnancy have an increased risk of pregnancy loss. Furthermore, they also have an increased risk of delivering babies with a poor APGAR score. Thus the importance of lifestyle modification in overweight and obese women with PCOS in order to reduce the risk of adverse perinatal outcomes should be emphasized.

Limitation

The results for pregnancy, delivery and neonatal outcomes can only be generalized to singleton pregnancies and that our analysis may also be vulnerable to selection bias due to the restriction to pregnant women who had experienced fertility problems. The restriction, while difficult to avoid, may induce bias as a result of the fact that pregnancy and fertility problems may themselves be influenced by BMI. For this reason, the results may not be applicable to the general PCOS community. The observable nature of the study is another limitation.

Recommendations

A similar study looking into the influence of pre-pregnancy BMI in women with PCOS on the pregnancy, delivery and neonatal outcome in multiple pregnancies may be indicated.

In this study, the focus is on the influence of pre-pregnancy BMI rather than the gestational weight gain on perinatal outcomes. In women without PCOS, gestational weight gain is also found to be an important predictor of perinatal complications[12] and therefore an important factor to keep in mind during the medical supervision of pregnancy, delivery and postpartum. It would be interesting in the future to perform a prospective follow-up study looking into the difference in influence of pre-pregnancy BMI versus gestational weight gain on perinatal outcome in women with PCOS.

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