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Association between polycystic ovarian syndrome and adverse pregnancy and neonatal outcomes among women in Oman

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Abstract

Objectives: To examine the association between PCOS and selected metabolic, pregnancy and neonatal outcomes among pregnant women and their newborns.

Methods: Cohort study using electronic hospital records from two tertiary hospitals in Oman. Data were collected from 922 women, contributing 1,939 pregnancies and 1,721 live born infants, in the period from 1 January 2006 to 31 May 2017. Metabolic, pregnancy and neonatal outcomes in the 305 women with a diagnosis of PCOS were compared to outcomes in 617 women without PCOS using multivariable multilevel regression models.

Results: Women with PCOS were more likely to develop adverse metabolic outcomes during pregnancy compared to women without PCOS, including developing gestational diabetes mellitus (odds ratio (OR) 3.79, 95% CI 2.22, 6.48) and pregnancy induced hypertension (OR 2.81, 95% CI 1.26, 6.24). The odds of adverse birth outcomes of miscarriage (OR 4.43, 95% CI 2.92, 6.71) and preterm delivery (OR 3.46, 95% CI 1.94, 6.16) were also higher, as was the risk of undergoing emergency caesarean section (OR 3.51, 95% CI 1.80, 6.86). Infants born to mothers with PCOS were not at increased risk of macrosomia, low weight for gestational age or low APGAR score, but they were more likely to require admission to a neonatal unit (OR 2.41, 95% CI 1.10, 5.27).

Conclusions: Pregnant women in Oman with PCOS are at a significantly increased risk of metabolic disorders during pregnancy and several adverse birth and neonatal outcomes. Close antenatal monitoring will help early detection and control of metabolic disorders and timely intervention.

Key words: pregnancy; polycystic ovary syndrome; metabolic diseases; newborn; Oman

Introduction

Background

Polycystic ovarian syndrome (PCOS) is one of the most prevalent endocrinopathies affecting women of reproductive age. It is characterized by irregular menses, hyper-androgenism and polycystic ovaries(1). There is a wide variation in the clinical and biochemical manifestations of PCOS and as such, worldwide prevalence estimates of PCOS vary considerably depending on the diagnostic criteria used. A worldwide prevalence of 6-12% has been reported using the Rotterdam diagnostic criteria(2).

Although the exact pathogenesis of the disorder is not yet fully understood, many studies have found an association between PCOS and insulin resistance, leading to hyperinsulinemia and subsequently to hyper-androgenemia. This excess androgen leads to features of alopecia, hirsutism, acne and oligo- or anovulation among affected women(1). Population studies show up to 73% of women with PCOS suffer from oligo- or anovulation(3). However, some women succeed in conceiving and carrying a pregnancy either with or without medical assistance. Despite extensive research on PCOS and the reproductive health of affected women, there is still contention as to whether PCOS is associated with an increased risk of adverse pregnancy and birth outcomes in mothers and their newborns. These include metabolic outcomes in women, namely gestational diabetes (GDM), pregnancy-induced hypertension (PIH) and preeclampsia, and adverse birth outcomes including preterm birth, miscarriage, stillbirth and undergoing caesarean section(4-6). Studies conducted to date are non-conclusive with mixed results and have mostly been retrospective with small numbers of cases (<100) and discrepancy in the criteria used to diagnose PCOS(7-9).

Though existing literature supports an association between PCOS and adverse birth outcomes, findings are not consistent (10-12). Many studies have found an increased incidence of miscarriage among pregnant women with PCOS compared to those without the condition, though in many of these studies women conceived with the help of various assisted reproductive techniques (ARTs) (10, 11, 13); it is not clear whether the causative factor might be the entity of PCOS itself or the ART.

Fewer studies have examined neonatal risks for babies born to mothers with PCOS, such as macrosomia (birth weight >=4500g), low APGAR score, need for admission to a neonatal intensive care unit (NICU) and low weight for gestational age (LWGA). Findings have been contradictory. Whilst babies born to mothers with PCOS were more likely to have macrosomia in one large cohort study(14), another found them to be more likely to have

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LWGA instead(15). Similarly, conflicting findings have been reported with regard to APGAR scores and NICU admission (16, 17).

Studies published to date on PCOS and reproductive health outcomes refer mainly to Western populations, though evidence supports the influence of genetic and environmental factors on the phenotype of PCOS and a higher prevalence of PCOS symptoms among South Asian women compared to Caucasians(18). The majority of existing studies are retrospective case control studies with poor study designs, including discrepancies in the criteria used to diagnose PCOS, small sample sizes (<100) and failure to control for important confounders such as the use of ARTs. This study therefore uses a cohort design to examine the risk of adverse metabolic, pregnancy and neonatal outcomes during pregnancy among a representative sample of pregnant women with PCOS in Oman.

Material and Methods

Data Source and study population

In Oman pregnant women normally have a total of five antenatal appointments at a local primary health centre and are referred to a tertiary hospital at 30 weeks of gestation for late pregnancy follow up and delivery. Electronic hospital records from two tertiary hospitals in the Omani capital city Muscat were used to identify all hospital births in the period from 1st January 2006 to 31st May 2017. Inclusion criteria were: women of Omani origin; aged 15-49 at the time of delivery; no diagnosis of diabetes mellitus or hypertension before pregnancy; and no other medical conditions that clearly affect pregnant mothers or their pregnancy outcome such as endocrine, haematological, oncological, obstetrics or gynaecological health problems. Women were eligible for inclusion regardless of spontaneous or assisted conception, and regardless of singleton or multiple gestation.

Rotterdam criteria were used to identify women with a diagnosis of PCOS based on information recorded in their electronic medical record. Thus, PCOS was diagnosed in women recorded as having at least two of the three following clinical presentations: 1) endoscopic or ultrasound identification of enlarged ovaries with fluid filled cysts; 2) clinical or biochemical presentation of hypergonadism; 3) oligo- or anovulation(19). All women identified as having PCOS and meeting the eligibility criteria were included as exposed cases in the study population. Women without PCOS (the unexposed control group) were randomly selected from all eligible women identified as not having PCOS in a ratio of 2 unexposed: 1 exposed (see details of sample size calculation below).

Study outcomes

Three metabolic disorders were identified as outcomes of interest: a diagnosis of GDM based on a 2 hour 75gm Oral Glucose Tolerance Test (OGTT) of >=8.5 mmol/L (>=153mg/dl) after 20 weeks of gestation(20); PIH defined as a blood pressure reading >=140/90 mmHg after 20 weeks of gestation; preeclampsia defined as high blood pressure(>=140/90 mmHg) along with proteinuria. Adverse pregnancy-related outcomes were: miscarriage (loss of the embryo before 23 weeks of gestation); preterm delivery (delivery before 37 weeks of gestation); stillbirth (defined according to clinical practice in Oman as intrauterine foetal death after 22 weeks of gestation); and undergoing emergency caesarean section. Neonatal outcomes were: macrosomia (birth weight >= 4kg); LWGA (birth weight below the 10th percentile for the gestational age); low APGAR score (score of <7 out of a maximum 10 five minutes after delivery); admission to a NICU.

Statistical analysis

Data management and analyses were undertaken using STATA SE v14.0 (StataCorp, College Station, TX). Characteristics of women, pregnancies and newborns were described. Data were hierarchical in nature – some pregnancies were of multiple gestation and some women delivered more than once during the study period. Therefore, we used multivariable multi-level logistic regression modelling to assess the association between PCOS and outcomes measured at the level of the pregnancy and child, adjusting for the effect of clustering at each level (study hospital, woman and pregnancy) and to control for confounders. Given multiple hypothesis testing we have presented full odds ratios, confidence intervals and p-values to allow the reader to judge the full weight of evidence.

Pregnancy and birth-related outcomes

In a subset of all pregnancies which were delivered at or after 20 completed weeks of gestation (the gestation when metabolic outcomes are first identified) we calculated unadjusted and adjusted odds ratios for the association between PCOS and occurrence of GDM, PIH, preeclampsia, preterm delivery and emergency caesarean section. In all pregnancies regardless of gestation at the end of pregnancy we calculated unadjusted and adjusted odds ratios for the association between PCOS and miscarriage and stillbirth. Analyses were adjusted for: age (<25, 25-24, 35+); area of residence (urban or rural); education (college or university or higher, secondary, primary or less); employment (employed or unemployed); gravidity (1, 2+); mode of conception (unassisted or assisted); multiple gestation (singleton or multiple). Missing data for confounders were coded as separate categories. For pregnancy and birth related outcomes two levels of clustering were accounted for - hospital of delivery and woman.

New-born-level outcomes

In a subset of all pregnancies, which resulted in one or more live born infants we calculated unadjusted and adjusted odds ratios for the association between PCOS and macrosomia, LWGA, low APGAR score, and NICU admission. Adjustment for confounders was as described above. For child-level related outcomes, three levels of clustering were accounted for - hospital of delivery, woman and pregnancy.

Power calculation

Prior to data collection commencing, it was estimated that data would be available for at least 500 pregnant women with PCOS across the two centres. Therefore, the minimum prevalence of each outcome detectable in women with PCOS was computed compared to controls based on a sample size of 1000 (equal groups), a two-sided significance level of 5% and power of 80%. However, fewer than 500 women with PCOS were identified and so controls were recruited in a ratio of 2:1. Additionally, in practice there was likely to be significant clustering of outcomes within the data and it was not possible to estimate the impact of these effects prior to data collection without knowing the intracluster correlation for each outcome. Therefore, a post-hoc power analysis was carried out post data collection. The minimum detectable odds ratio was computed at 80% power and 5% significance accounting for the observed intraclass correlation, estimated for a 2 unexposed: 1 exposed population structure and using the observed prevalence of each outcome among the unexposed group. The obtained effective sample size for each outcome was greater than the target of 1000 used as the basis for the original power calculation. However, for 4 outcomes (stillbirth, macrosomia, LWGS and low APGAR score) the observed odds ratio was smaller than the critical ratio from the post-hoc power analysis, and so there is a greater than 20% chance that a study of this size would miss a significant effect of the observed size if it were truly present in the population.

Ethical approval

The study was conducted in accord with prevailing ethical principles and was approved by the University of Nottingham's School of Medicine Research Ethics Committee (Reference number OVS 14112016), plus the relevant approval bodies for the two study hospitals: Sultan Qaboos University Medical Ethics Committee (for Sultan Qaboos University Hospital) (Reference number SQU-EC/193/16) and the Ministry of Health Research and Ethical Review and Approve Committee, Directorate General for Planning and Studies (for the Royal Hospital) (Reference number MOH/DGPS/CSR/PROPOSAL_APPROVED/45/2016) .

Results

We identified a total of 922 eligible women during the study period, yielding a total of 1,939 pregnancies and 1,721 liveborn infants. Of these, 305 women (contributing 529 pregnancies and 413 live births) had PCOS and 617 women (contributing 1,410 pregnancies and 1,308 live births) did not have PCOS. Sociodemographic characteristics of women are shown in Table 1. The two groups were similar with respect to their hospital of delivery, place of residence and level of education. However, more women with PCOS were employed compared to women without PCOS.

Table 1. Sociodemographic characteristics of women

Women's characteristics	All women
(n=922)	Women with PCOS (n=305)
(n=617)	p-value for difference between groups
Hospital of delivery (n, %)	
SQUH	263 (28.5)
RH	659 (71.5)
Residence (n, %)	
Urban	639 (69.3)
Rural	279 (30.3)
Missing	4 (0.4)
Educational level (n, %)	
Primary or less	79 (8.6)
Secondary	351 (38.1)
College/university or higher	316 (34.3)
Missing	176 (19.1)

Table 2 describes characteristics of the 1,939 pregnancies included in the study. Pregnancies where the mother had PCOS were generally conceived at an older age, were more likely to have been conceived with additional support (clomifene citrate (Clomid) being the most commonly used method), had lower parity and gravidity and were more likely to be of multiple gestation compared to pregnancies where the mother did not have PCOS. In addition, pregnancies where the mother had PCOS were more likely to result in a non-live outcome, less likely to reach term, and more likely to result in a birth requiring intervention.

Table 2. Sociodemographic characteristics of women

Pregnancy characteristics	All pregnancies (n=1,939)	Pregnancies in women with PCOS (n=529)	Pregnancies in women without PCOS (n=1,410)	p-value for difference between groups
Maternal age (n, %)				
15-19	43 (2.2)	3 (0.6)	40 (2.8)	<0.001
20-24	347 (17.9)	77 (14.6)	270 (19.2)	
25-29	741 (38.2)	212 (40.1)	529 (37.5)	
30-34	515 (26.6)	164 (31.0)	351 (24.9)	
35-39	238 (12.3)	66 (12.5)	172 (12.2)	
40+	55 (2.8)	7 (1.3)	48 (3.4)	
Support to conceive (n, %)				
None	1,723 (88.9)	326 (61.6)	1,397 (99.1)	<0.001
Metformin	5 (0.3)	5 (1.0)	0 (0.0)	
Clomid	108 (5.6)	100 (18.9)	8 (0.6)	
IUI	35 (1.8)	33 (6.2)	2 (0.1)	
IVF	66 (3.4)	63 (11.9)	3 (0.2)	
Missing	2 (0.1)	2 (0.4)	0 (0.0)	
Gravidity (n, %)				
1	536 (27.6)	193 (36.5)	343 (24.3)	<0.001
2	500 (25.8)	141 (26.7)	359 (25.5)	
3	320 (16.5)	76 (14.4)	244 (17.3)	
>=4	583 (30.1)	119 (22.5)	464 (32.9)	
Parity (n, %)				
0	707 (36.5)	313 (59.2)	394 (27.9)	<0.001
1	511 (26.4)	121 (22.9)	390 (27.7)	
2	312 (16.1)	50 (9.5)	262 (18.6)	
3	194 (10.0)	23 (4.4)	171 (12.1)	
>=4	215 (11.1)	22 (4.2)	193 (13.7)	
Number of foetuses in current pregnancy (n, %)				
1	1,886 (97.3)	493 (93.2)	1,393 (98.8)	<0.001
2	46 (2.4)	29 (5.5)	16 (1.2)	
>=3	7 (0.4)	7 (1.3)	0 (0.0)	
Pregnancy outcome (n, %)				
Live birth	1,669 (86.1)	377 (71.3)	1,292 (91.6)	<0.001
Miscarriage	216 (11.1)	124 (23.4)	92 (6.5)	
Ectopic pregnancy	30 (1.6)	22 (4.2)	8 (0.6)	
Stillbirth	21 (1.1)	4 (0.8)	17 (1.2)	
Livebirth and stillbirth	3 (0.2)	2 (0.4)	1 (0.1)	
Pregnancy lasting at least 20 weeks (n, %)				
Yes	1,700 (87.7)	388 (73.4)	1,312 (93.1)	<0.001
No	238 (12.3)	141 (26.7)	97 (6.9)	
Missing	1 (0.1)	0 (0.0)	1 (0.1)	
Pre-term delivery <37 weeks of gestation^ (n, %)				
Yes	169 (9.9)	78 (20.1)	91 (6.9)	<0.001
No	1,531 (90.1)	310 (79.9)	1,221 (93.1)	
Mode of delivery^ (n, %)				
Spontaneous	1,233 (72.5)	223 (57.5)	1,010 (77.0)	<0.001
Assisted	58 (3.4)	10 (2.6)	48 (3.7)	
Elective c-section	110 (6.5)	30 (7.7)	80 (6.1)	
Emergency c-section	287 (16.9)	118 (30.4)	169 (12.9)	
Missing	12 (0.7)	7 (1.8)	5 (0.4)	

In the multivariable multilevel regression model women with PCOS were found to be 3.79 times more likely to develop GDM (95% CI 2.22, 6.48) and 2.81 times more likely to develop PIH (95% CI 1.26, 6.24) compared to women without PCOS (Table 3). However, there was no difference in the risk of preeclampsia between the two groups (OR 2.11, 95% CI 0.59, 7.62). When adverse birth related outcomes were examined, women with PCOS were found to be 3.46 times at increased risk of delivering preterm (95% CI 1.94, 6.16) and 3.51 times more likely to undergo emergency caesarean section (95% CI 1.80, 6.86). The odds of miscarriage among women with PCOS was 4.43 times higher than women without PCOS (95% CI 2.92, 6.71). However, there was no evidence of an increased odds of stillbirth (OR 0.75, 95% CI 0.21, 2.64).

Table 3. Sociodemographic characteristics of women

Pregnancy outcome	Pregnancies among women with PCOS n (%)	Pregnancies among women without PCOS n (%)	Crude odds ratio (95% CI)	Adjusted* odds ratio (95% CI)
Gestational diabetes (GDM) ^	134/388 (34.5)	218/1,312 (16.6)	3.98 (2.53, 6.25)	3.79 (2.22, 6.48)
Pregnancy induced hypertension (PIH) ^	51/388 (13.1)	73/1,312 (5.6)	3.59 (1.84, 6.98)	2.81 (1.26, 6.24)
Preeclamp-sia^	12/388 (3.1)	22/1,312 (1.7)	1.96 (0.72, 5.38)	2.11 (0.59, 7.62)
Preterm delivery(<37 weeks) ^	78/388 (20.1)	91/1,312 (6.9)	4.54 (2.83, 7.29)	3.46 (1.94, 6.16)
Emergency caesarean section^	118/388 (30.4)	169/1,312 (12.9)	6.67 (3.63, 12.25)	3.51 (1.80, 6.86)
Miscarriage	124/529 (23.4)	92/1,410 (6.5)	5.13 (3.56, 7.40)	4.43 (2.92, 6.71)
Stillbirth	6/529 (1.1)	18/1,410 (1.3)	0.89 (0.34, 2.33)	0.75 (0.21, 2.64)

Table 4 shows the characteristics of liveborn infants. Babies born to mothers with PCOS were more likely to be born preterm (<37 completed weeks of gestation) compared to babies born to mothers without PCOS. A small difference was observed in the average weight of babies born to mothers with PCOS, being on average 0.3 kg lighter than babies born to mothers without PCOS.

Table 4: Characteristics of liveborn infants

Infants' characteristics	All infants (n=1,721)	Infants born to women with PCOS (n=413)	Infants born to women without PCOS (n=1,308)	p-value for difference between groups
Gestation at delivery (completed weeks)				
Median (IQR)	39 (38-40)	38 (37-39)	39 (38-40)	<0.001
Gestation at delivery - grouped (completed weeks) (n, %)				
Extremely preterm (24-27)	11 (0.6)	10 (2.4)	1 (0.1)	<0.001
Very preterm (28-31)	23 (1.3)	16 (3.9)	7 (0.5)	
Late preterm (32-36)	146 (8.5)	67 (16.2)	79 (6.0)	
Term (37+)	1,541 (89.5)	320 (77.5)	1,221 (93.4)	
Birth weight (kg)				
Mean (SD)	3.0 (0.5)	2.8 (0.7)	3.1 (0.5)	<0.001

In the multivariable multilevel regression model there was no difference in the odds of macrosomia, LWGA or low APGAR score for babies born to mothers with PCOS compared to babies born to mothers with PCOS (Table 5). Babies born to mothers with PCOS had an increased odds of requiring a NICU admission (OR 2.41, 95% CI 1.10, 5.27).

Table 5: Crude and adjusted odds ratios for neonatal outcomes

Newborn outcome	Infants born to women with PCOS n (%)	Infants born to women without PCOS n (%)	Crude odds ratio	73/1,312 (5.6)
(95% CI)	Adjusted* odds ratio	73/1,312 (5.6)	73/1,312 (5.6)	73/1,312 (5.6)
(95% CI)	73/1,312 (5.6)	73/1,312 (5.6)	73/1,312 (5.6)	73/1,312 (5.6)
Macrosomia	8/413 (1.9)	34/1,308 (2.6)	0.73 (0.29, 1.86)	0.98 (0.33, 2.87)
LWGA	64/413 (15.5)	176/1,308 (13.5)	1.27 (0.82, 1.98)	1.00 (0.57, 1.76)
Low APGAR score	8/413 (1.9)	4/1,308 (0.3)	8.08 (1.37, 47.67)	1.86 (0.26, 13.20)
NICU admission	71/413 (17.2)	70/1,308 (5.4)	6.07 (3.11, 11.86)	2.41 (1.10, 5.27)

Discussion

This study showed that pregnant women in Oman with PCOS were more likely to develop GDM and PIH during pregnancy compared to women without PCOS. However, there was no difference in the risk of developing preeclampsia. Women with PCOS were more likely to miscarry their pregnancy or deliver prematurely and were also more likely to have undergone emergency caesarean section as a mode of delivery. Infants born to mothers with PCOS were at an increased risk of needing intensive care compared to those born to mothers without PCOS.

Our findings on metabolic outcomes are in line with the majority of studies that have previously established these associations among Western (9, 21, 22) and Eastern (8, 23, 24) populations. An increasing body of evidence suggests that in 50%-70% of women with PCOS insulin resistance is responsible for a state of hyperinsulinemia and thus the risk of glucose intolerance and GDM among these women and is also believed to be associated with the increased risk of PIH(25).

Contrary to existing meta analyses (22, 26), this study did not find an association between PCOS and preeclampsia despite its higher prevalence among women with PCOS (3.1%) compared to controls (1.7%). This finding was in line with those from a study of 226 Swedish women with a PCOS diagnosis (16), but it is likely explained by the small number of women with preeclampsia (n=34) across the two study groups.

Prior evidence points towards an association between PCOS and miscarriage, which our findings support. Although a high proportion of women with PCOS (approximately 50%) conceive with the help of ARTs(27), studies that have compared miscarriage rates in women with PCOS undergoing IVF and those without PCOS undergoing the same treatment to conceive, found higher rates in the former(28, 29). Carrying a multiple pregnancy and having a high BMI(30) are also known risk factors for miscarriage. Although the impact of BMI could not be accounted for in this study, PCOS was found to be an independent risk factor for miscarriage adjusting for use of ARTs and multiple gestation.

Preterm delivery is common among women undergoing ARTs and those carrying multiple gestations, however, a number of studies have reported PCOS to be an additional risk factor for preterm delivery after controlling for these factors (14, 21), results also supported by the findings of this study. Evidence suggests hyperinsulinemia observed in women with PCOS may be responsible for elevated values of plasminogen activator inhibitor-1 (PAI-1) which interferes with fibrin cross-linking and regulation of fibrinolysis, a process vital for placental formation and thus successful pregnancy outcome (31). In addition, several reports suggest high serum

concentrations of luteinising hormone to be responsible for early pregnancy loss among women with PCOS(11). Furthermore, studies demonstrated a role of hyperinsulinemia in the aetiology of inadequate blood flow to the endometrium, leading to endometrial dysfunction and impaired implantation(32). These factors explain both the higher risk of miscarriage and preterm delivery among women with PCOS.

The risk of stillbirth in women with PCOS has been studied less due to its low prevalence. However, similar to our results, those studies that have examined stillbirth as an adverse birth outcome did not find a positive association(14, 33) . In this study we opted to examine the prevalence of emergency caesarean section specifically, given that it is most often unanticipated and as such carries a higher morbidity and mortality rate for both mothers and their newborns compared to elective caesarean section. Several studies have examined any caesarean section as an adverse outcome among women with PCOS and found a positive association(14, 17) .

Similar to our findings, the majority of existing studies have found no association between PCOS and both macrosomia (7, 34) and LWGA (14, 33). Furthermore, despite the finding that infants born to mothers with PCOS were more likely to be delivered prematurely and through emergency caesarean section, they were not at a higher risk of having a low APGAR score, in agreement with findings from other studies (16, 17). This may be because the majority of the infants born prematurely to mothers with PCOS in this cohort were born late preterm which might have prevented the possible perinatal complications. However, they were more likely to be admitted to a NICU compared to controls, findings consistent other studies(26). This was possibly due to the advanced level of medical care offered to them in the highly specialized study hospitals, where they are monitored in the NICU due to their prematurity rather than as a result any other life-threatening conditions.

Limitations

A recent study has suggested that being overweight is more relevant than having PCOS for the effects on insulin sensitivity and impaired glucose metabolism (Feichtinger et al., 2021). Therefore, lack of data on participants' BMI, and thus the inability to adjust for it in the analysis, was a limitation in this study. This study controlled for other important confounders such as educational level, employment status, women's age, women's gravidity and parity and use of ARTs and accounted for clustering effects by the hospital of delivery and woman. Conducting the study in two hospitals in Muscat may limit the representativeness of the participants to the general population and thus limit the generalizability of our findings. However, the selected hospitals are major tertiary centres that receive referrals from almost nationwide. Future studies should analyse BMI more carefully and systematically to decide whether it has a compounding or a mediating effect on these outcomes.

Conclusions

The higher risk that women with PCOS will develop adverse metabolic and birth outcomes during pregnancy requires vigilant antenatal surveillance and continuous monitoring to prevent the long-term consequences of these outcomes. Results from this study provide reassuring evidence that live infants born to mothers with PCOS are not at an increased risk of severe adverse neonatal outcomes. However, the risk of infants being delivered prematurely should be considered by healthcare providers, who should provide appropriate advice and enable early intervention and prevention of further complications.

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