GYNECOLOGY

Postpartum complications increased in women with polycystic ovary syndrome

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BACKGROUND: Women with polycystic ovary syndrome are at a higher risk of cardiometabolic and psychiatric comorbidities and preconception and antepartum complications, but the impact of polycystic ovary syndrome during the postpartum period is unknown.

OBJECTIVE: This study aimed to investigate the risk of postpartum cardiovascular disease complications and perinatal and postpartum depression.

STUDY DESIGN: This was a retrospective cohort study conducted using a United States insurance claims database. Women with and without polycystic ovary syndrome aged 18 to 50 years enrolled continuously in a single health plan during the preconception, antepartum, and postpartum periods between 2000 and 2016 were included. The primary outcome was postpartum cardiovascular disease and depression (perinatal and postpartum). Multivariable logistic regression was used to adjust for covariates including age, geographic location, preterm delivery, assisted reproductive technology use, multiple births, prepregnancy depression, prepregnancy diabetes, prepregnancy hypertension, gestational diabetes, gestational hypertension, obesity, history of hyperlipidemia, smoking, and race.

RESULTS: We identified 42,391 unique women with polycystic ovary syndrome and 795,480 women without polycystic ovary syndrome. In multivariable models, women with polycystic ovary syndrome had significantly higher odds of cardiovascular disease complications, including postpartum preeclampsia (adjusted odds ratio, 1.30; 95% confidence interval, 1.17−1.45), eclampsia (adjusted odds ratio, 1.45; 95% confidence interval, 1.14−1.86) cardiomyopathy (adjusted odds ratio, 1.26; 95% confidence interval, 1.03−1.54), hypertensive heart disease (adjusted odds ratio, 1.32: 95% confidence interval, 1.07−1.64), thrombotic disease (adjusted odds ratio, 1.50; 95% confidence interval, 1.20−1.87), congestive heart failure (adjusted odds ratio, 1.35; 95% confidence interval, 1.13−1.61), and cerebrovascular accidents (adjusted odds ratio, 1.21; 95% confidence interval, 1.14−1.29), than those without polycystic ovary syndrome, as well as both perinatal (adjusted odds ratio, 1.27; 95% confidence interval, 1.22−1.33) and postpartum depression (adjusted odds ratio, 1.46; 95% confidence interval, 1.36−1.57). Nonobese women with polycystic ovary syndrome had higher odds of postpartum eclampsia (adjusted odds ratio 1.72; 95% confidence interval, 1.31−2.26), peripartum cardiomyopathy (adjusted odds ratio, 1.43; 95% confidence interval, 1.14−1.79), and cerebrovascular accidents (adjusted odds ratio, 1.28; 95% confidence interval, 1.19−1.38) than nonobese women without polycystic ovary syndrome. In the group of women without prepregnancy depression, the odds of perinatal depression (adjusted odds ratio, 1.32; 95% confidence interval, 1.26−1.39) and postpartum depression (adjusted odds ratio, 1.50; 95% confidence interval, 1.39−1.62) were higher in women with polycystic ovary syndrome than those without polycystic ovary syndrome.

CONCLUSION: In a large United States cohort, our study found that women with polycystic ovary syndrome are at increased risk of both cardiovascular and psychiatric complications during the postpartum period. Polycystic ovary syndrome should be recognized as an at-risk condition; our findings underscore the need for routine screening and early interventions for these major comorbidities.

Key words: cardiomyopathy, cardiovascular, claims database, depression, fourth trimester, hypertension, Optum, PCOS, postpartum, preeclampsia

Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder affecting women of reproductive age.[1] It is characterized by the presence of 2 of 3 diagnostic criteria: irregular menses, clinical or biochemical hyperandrogenism, and polycystic-appearing ovaries.[2,3] The worldwide prevalence of PCOS is 5% to 7% but can be as high as 8% to 13% depending on the definition used.[4,5] The association between PCOS and several cardiovascular disease (CVD) risk factors such as type 2 diabetes,[6] obesity, and lipid abnormalities[7] is well recognized.[8] In addition, there is growing evidence for increased risk of psychiatric disorders and pregnancy-related complications in PCOS.[9,10] Metaanalyses show abnormal depression scores (odds ratio [OR], 3.78; 95% confidence interval [CI], 3.03−4.72) and anxiety symptoms (OR, 5.62; 95% CI, 3.22−9.80),[10] whereas large registries show increased prevalence of psychiatric morbidities.[11,12] Obstetrical complications including gestational diabetes (OR, 3.43; 95% CI, 2.49−4.74), pregnancy-induced hypertension (PIH) (OR, 3.07; 95% CI, 1.81−5.18), and preeclampsia (PE) (OR, 3.28; 95% CI, 2.06−5.22) are also increased in women with PCOS,[13] further contributing to long-term cardiometabolic risk in this population.

Despite extensive research in non−pregnancy-related comorbidities and obstetrical complications,[7,14,15] there are no studies in women with PCOS specifically targeting the postpartum period, typically defined as 4 to 6 weeks after delivery. According to the Centers for Disease Control and Prevention (CDC) report, nearly 70% of pregnancy-related deaths in the general population occur at delivery or within the first year

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AJOG at a Glance

Why was this study conducted?

There is a dearth of data on postpartum complications, including perinatal depression, in women with polycystic ovary syndrome (PCOS).

Key findings

In a nationwide retrospective claims study, women with PCOS were at increased risk for postpartum preeclampsia, eclampsia, cardiomyopathy, hypertensive heart disease, thrombotic disease, congestive heart failure, cerebrovascular accidents, and perinatal and postpartum depression compared with those without PCOS. Nonobese women with PCOS were at increased risk of postpartum eclampsia, cardiomyopathy, and cerebrovascular accidents compared with nonobese women without PCOS.

What does this add to what is known?

Women with PCOS are at a higher risk of postpartum complications and antepartum complications, highlighting the need to include these outcomes in pregnancy counseling and risk assessment.

postpartum, with CVD and stroke accounting for over one-third of the causes.[16,17] Women presenting with postpartum PE are at increased risk of postpartum eclampsia and stroke, and 50% of eclamptic episodes occur after delivery.[18] PE and PIH are also risk factors for peripartum cardiomyopathy,[19] which accounts for 23% of maternal cardiovascular-related deaths.[20] Given that CVD is the number 1 killer of women, the American Heart Association (AHA) has partnered with the American College of Obstetrics and Gynecology (ACOG) to identify female-specific CVD risk factors, recently adding hypertensive disease of pregnancy and PCOS.[21,22] Given the high prevalence of cardiometabolic risk factors in young women with PCOS during pregnancy,[6,14] it is imperative that we understand whether similar risks exist during the postpartum period.

Further, perinatal and postpartum depression are common conditions associated with significant adverse infant and maternal outcomes.[23] The prevalence of postpartum depressive symptoms across 27 states in the United States was reported to be as high as 11.5%.[23] A history of depression before pregnancy is a recognized risk factor for perinatal depression, the most common medical problem during pregnancy, occurring in 1 in 7 patients.[23,24] Although suicide is excluded from several definitions assessing maternal mortality rates, there is increasing evidence that maternal suicide is rising, highlighting the importance of identifying risk factors.[25,26] Despite the importance of mental health, no studies have evaluated the risk for perinatal and postpartum depression in women with PCOS.

Most of these associations between PCOS and its comorbidities in the nonpregnant state and during pregnancy are based on small cross-sectional studies, and large-scale studies in the United States are lacking. In addition, there are no data on postpartum cardiovascular or psychiatric complications in this population. The objectives of this study were therefore to evaluate for significant differences in (1) the prevalence of postpartum cardiovascular complications (PE, eclampsia, peripartum cardiomyopathy, hypertensive heart disease, thrombotic disease, congestive heart failure [CHF], cerebrovascular accidents, and ischemic heart disease) and (2) the prevalence of perinatal and postpartum depression in women with PCOS compared with women without PCOS in a large US nationwide cohort.

Materials and Methods

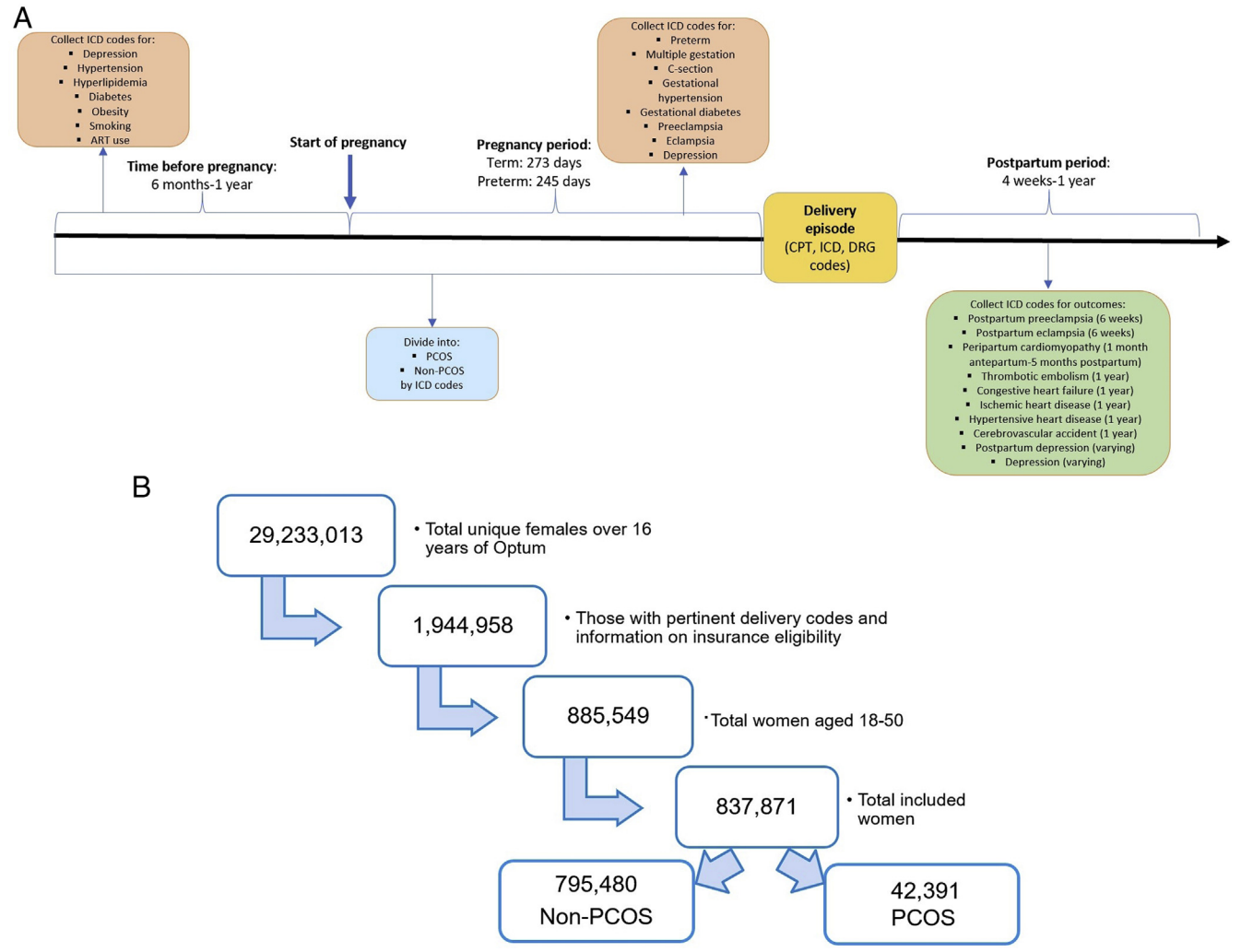
Cohort construction

We conducted a retrospective cohort study using Optum's de-identified Clinformatics Data Mart database containing approximately 13 million unique individuals per year from 2000 to 2016 from all 50 US states. The dataset included outpatient and inpatient services. Subjects were initially identified using International Classification of Diseases (ICD) 9 and ICD 10 codes, Current Procedural Terminology codes, and Diagnosis-Related Group delivery codes (Supplemental Table 1). Date of delivery was defined as the date of filing the first delivery code. To ensure availability of data on comorbidities, we only included women with continuous enrollment in Optum for a minimum of 6 months before conception, throughout pregnancy, and a minimum of 6 weeks postdelivery (Figure 1, A). To keep missing data on comorbidities to a minimum, we also collected data up to 1 year before and after date of delivery when available. For women who had multiple pregnancies with complete data, the first pregnancy was selected. For women with preterm delivery codes, the period of confinement (ie, the pregnancy length) was defined as 245 days, whereas for women without preterm delivery codes, 273 days was used.[27] Women under the age of 18 and over the age of 50 years were excluded. From this eligible cohort, we identified women with PCOS using ICD codes for PCOS (256.4, E282.2). Given that there may be underreporting of PCOS in claims datasets, we also included women who had codes for both hirsutism (704.1, L68.0) and irregular menses (626.1, 626.4, 628.0, N97.0, N91.0−N91.5, N92.5−N92.6). Women who were not identified as PCOS were included in the non-PCOS group.

Covariate identification

Covariates were identified using ICD codes either before pregnancy (depression, type 2 diabetes, hypertension, hyperlipidemia, obesity, assisted reproductive technology [ART] use) or during pregnancy (multiple gestation, gestational hypertension, and gestational diabetes). Information on age; geographic division; smoking; and socioeconomic status including race, education, and net worth were also obtained.

FIGURE 1
Patient inclusion methodology and flowchart



A, Diagram of cohort construction. **B,** Flow diagram showing selection of the study population.

CPT, Current Procedural Terminology; *DRG*, Diagnosis-Related Group; *ICD*, International Classification of Diseases; *PCOS*, polycystic ovary syndrome.

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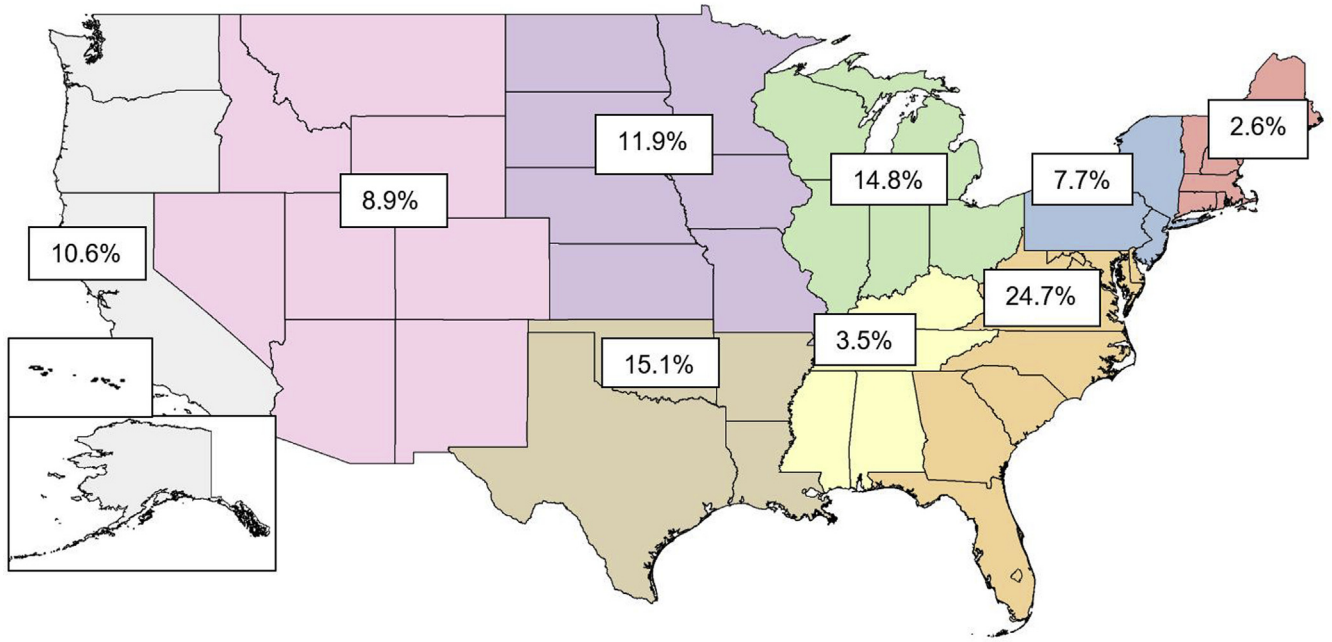
Outcome identification and definition

The definitions of the outcomes were based on the current recommendations in the literature. Postpartum PE and eclampsia were defined on the basis of ICD codes from date of delivery to 6 weeks after delivery[28] (Supplemental Table 2). Peripartum cardiomyopathy was defined as occurring within 1 month before delivery and up to 5 months after date of delivery.[29] The remaining postpartum cardiovascular complications (hypertensive heart disease, thrombotic disease, CHF, cerebrovascular accidents, and ischemic heart disease) were defined as occurring from date of delivery to 1 year after delivery, adapted from outcome definitions for pregnancy mortality data.[30] Perinatal depression was defined as occurring during pregnancy and up to 3 months after delivery.[23,24] Postpartum depression was defined as occurring after date of delivery up to 3 months postpartum.[23,24]

Statistical analysis

Continuous variables were compared between groups using Student *t*-test, and categorical variables were compared using Pearson chi-square tests. Separate multivariable logistic regression models were developed to evaluate the odds of developing each primary and secondary outcome. Racial differences in outcomes between black women and a reference group of white women were also assessed. Variables were identified a priori first, and the final set of covariates was then selected using a backward elimination strategy removing redundant variables. Variables evaluated included patient age, geographic division (Figure 2), obesity, smoking, race, ART use, history of prepregnancy depression,

FIGURE 2
Geographic distribution of study cohort by regions



PCOS, polycystic ovary syndrome.

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history of prepregnancy hypertension, history of prepregnancy diabetes, hyperlipidemia, gestational hypertension in current pregnancy, gestational diabetes in current pregnancy, preterm delivery of current pregnancy, multiple gestation, and socioeconomic factors including personal net worth and highest education level.

We conducted the following sensitivity analyses: (1) including the date of delivery for appropriate outcomes, (2) using the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) definition of perinatal depression up to 4 weeks postpartum, and (3) expanding the definition of postpartum depression to up to 1 year after delivery. As we captured outcomes occurring in the postpartum period, it is possible that outcomes occurring after delivery but on the same day were filed along with other ICD codes as a package, making it difficult to distinguish if they were intrapartum or postpartum complications. Therefore, we conducted the first sensitivity analysis including date of delivery in outcome definitions. The last 2 analyses were conducted to account for varying definitions of peripartum depression using DSM-5 criteria and those recommended by national organizations.[31–33] Tests for interaction were also performed between obesity, prepregnancy depression, and the outcomes. Interaction was evaluated by adding multiplicative terms to the multivariable logistic regression models. The statistical significance of the interaction term was determined by a Wald-based test where $P<.05$ was considered significant. Joint Wald tests were employed for interactions with more than 1 term. If statistically significant, linear combinations were then calculated to determine coefficients and appropriate CIs for those with and without the variable of interest. Data were extracted from Optum files using R (R Core Team, Vienna, Austria), whereas statistical analysis was performed using STATA version 14.2 (StataCorp, College Station, TX). This study was deemed exempt after review by the University of Pennsylvania's Institutional Review Board.

Results

A total of 29,233,013 unique females were present over the 16 years of Optum data collection (Figure 1, B). After excluding ineligible patients, there were 42,391 women with PCOS and 795,480 without PCOS who had a delivery and were continuously enrolled in the Optum dataset, resulting in a prevalence of 5.06% for PCOS. Most of these patients (97.0%) met criteria by a PCOS diagnosis code as compared with a combination of codes. Overall, before pregnancy, women with PCOS were more likely to be obese and have a history of depression, hypertension, diabetes, and hyperlipidemia (Table 1). They were more likely to have used ART to achieve pregnancy and had a significantly higher prevalence of gestational hypertension, gestational diabetes, preterm delivery, multiple births,

TABLE 1
Demographic characteristics of women with and without PCOS

Characteristic	PCOS (n=42,391)	Non-PCOS (n=795,480)
Age at delivery, y (±SD)	31.2±4.7	30.9±5.5
Race		
White	26,832 (68.0)	499,534 (69.7)
Black	3403 (8.6)	67,756 (9.4)
Asian	3967 (10.1)	53,596 (7.5)
Hispanic	5262 (13.3)	96,549 (13.5)
Geographic division		
New England	852 (2.0)	21,063 (2.7)
East North Central	5865 (13.9)	118,163 (14.9)
West North Central	4536 (10.7)	95,208 (12.0)
East South Central	1434 (3.4)	28,227 (3.6)
West South Central	7417 (17.5)	118,933 (15.0)
Mid-Atlantic	4000 (9.4)	60,381 (7.6)
South Atlantic	11,110 (26.2)	195,568 (24.7)
Mountain	3890 (9.2)	70,546 (8.9)
Pacific	3250 (7.7)	85,937 (10.8)
Education level		
Less than 12th grade	206 (0.5)	6635 (0.9)
High school diploma	9261 (22.4)	175,150 (23.3)
Less than bachelor's degree	22,073 (53.4)	396,908 (52.9)
More than bachelor's degree	9809 (23.7)	171,996 (22.9)
Home owner	28,689 (69.1)	519,758 (68.9)
Net worth of individual		
>$500,000	3129 (9.0)	64,772 (10.2)
$250,000–$499,000	6166 (17.8)	119,548 (18.8)
$150,000–$249,000	5241 (15.1)	95,646 (15.1)
$25,000–$149,000	11,616 (33.5)	204,493 (32.2)
<$25	8505 (24.5)	150,234 (23.7)
Smokers	1342 (3.2)	23,008 (2.9)
Obese	6225 (14.7)	37,089 (4.7)
History of hyperlipidemia	4787 (11.3)	41,960 (5.3)
History of prepregnancy hypertension	2628 (6.2)	19,829 (2.5)
History of prepregnancy diabetes	2239 (5.3)	9196 (1.2)
History of ART use	2205 (5.2)	7865 (1.0)
History of depression prepregnancy	1824 (4.3)	24,915 (3.1)
Gestational hypertension in current pregnancy	5787 (13.7)	61,000 (7.7)
Gestational diabetes in current pregnancy	10,279 (24.3)	105,845 (13.3)
Preeclampsia in current pregnancy	2128 (5.0)	20,544 (2.6)
Preterm delivery in current pregnancy	7158 (16.9)	96,765 (12.2)
Multiple gestation in current pregnancy	2796 (6.6)	19,668 (2.5)

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TABLE 1
Demographic characteristics of women with and without PCOS *(continued)*

Characteristic	PCOS (n=42,391)	Non-PCOS (n=795,480)
Cesarean delivery	19,116 (45.1)	261,196 (32.8)
Stillbirth of current pregnancy	563 (1.33)	5507 (0.69)

Data are presented as number (percentage) unless otherwise specified.

ART, assisted reproductive technology; *PCOS*, polycystic ovary syndrome.

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stillbirth, and cesarean delivery in the current pregnancy ($P<.001$).

Postpartum cardiovascular complications

Women with PCOS had a significantly higher prevalence of postpartum PE (OR, 1.81; 95% CI, 1.63−2.01), eclampsia (OR, 2.27; 95% CI, 1.81−2.84), peripartum cardiomyopathy (OR, 1.84; 95% CI, 1.52−2.23), hypertensive heart disease (OR, 2.09; 95% CI, 1.71−2.55), thrombotic disease (OR, 1.85; 95% CI, 1.50−2.28), CHF (OR, 2.00; 95% CI, 1.69−2.35), and cerebrovascular accidents (OR, 1.56; 95% CI, 1.47−1.65) (Table 2). In adjusted analyses controlling for age; history of hypertension; history of diabetes; ART use; preterm delivery; multiple pregnancy; gestational diabetes; gestational hypertension; hyperlipidemia; obesity; smoking; geographic division; and socioeconomic factors including education, net worth, and race, women with PCOS had increased odds of postpartum PE (adjusted odds ratio [aOR], 1.30; 95% CI, 1.17−1.45), eclampsia (aOR, 1.45; 95% CI, 1.14−1.86), peripartum cardiomyopathy (aOR, 1.26; 95% CI, 1.03−1.54), hypertensive heart disease (aOR, 1.32; 95% CI, 1.07−1.64), thrombotic disease (aOR, 1.50; 95% CI, 1.20−1.87), CHF (aOR, 1.35; 95% CI, 1.13−1.61), and cerebrovascular accidents (aOR, 1.21; 95% CI, 1.14−1.29) (Table 2).

In our study, black women had significantly higher odds of postpartum PE (aOR, 1.59; 95% CI, 1.45−1.74), peripartum cardiomyopathy (aOR, 1.95; 95% CI, 1.67−2.29), hypertensive heart disease (aOR, 2.00; 95% CI, 1.70−2.37), and CHF (aOR, 2.02; 95% CI, 1.76−2.32) than white women, adjusted for PCOS status.

Perinatal and postpartum depression

Women with PCOS had an increased risk of perinatal depression (OR, 1.40; 95%

TABLE 2
Postpartum complications in women with and without PCOS

Complication	PCOS (n=42,391)	Non-PCOS (n=795,480)	OR (95% CI)	aOR (95% CI)
Cardiovascular outcomes[a]				
Postpartum preeclampsia	390 (0.92)	4060 (0.51)	1.81 (1.63−2.01)	1.30 (1.17−1.45)
Postpartum eclampsia	85 (0.2)	705 (0.09)	2.27 (1.81−2.84)	1.45 (1.14−1.86)
Peripartum cardiomyopathy	116 (0.27)	1182 (0.15)	1.84 (1.52−2.23)	1.26 (1.03−1.54)
Hypertensive heart disease	109 (0.26)	979 (0.12)	2.09 (1.71−2.55)	1.32 (1.07−1.64)
Thrombotic disease	98 (0.23)	995 (0.13)	1.85 (1.50−2.28)	1.50 (1.20−1.87)
Congestive heart failure	157 (0.37)	1479 (0.19)	2.00 (1.69−2.35)	1.35 (1.13−1.61)
Cerebrovascular accidents	1263 (2.98)	15,366 (1.93)	1.56 (1.47−1.65)	1.21 (1.14−1.29)
Ischemic heart disease	11 (0.03)	166 (0.02)	1.24 (0.68−2.29)	—
Depression outcomes[b]				
Perinatal depression	2956 (6.97)	40,311 (5.07)	1.40 (1.35−1.46)	1.27 (1.22−1.33)
Postpartum depression	899 (2.12)	10,815 (1.36)	1.57 (1.47−1.68)	1.46 (1.36−1.57)

Data are presented as number (percentage) unless otherwise specified.

aOR, adjusted odds ratio; *ART*, assisted reproductive technology; *CI*, confidence interval; *OR*, odds ratio; *PCOS*, polycystic ovary syndrome.

[a] Adjusted analyses controlled for age; history of hypertension; history of diabetes; ART use; preterm delivery; multiple pregnancy; gestational diabetes; gestational hypertension; hyperlipidemia; obesity; smoking; geographic division; and socioeconomic factors including education, net worth, and race; [b] Adjusted analyses controlled for age; history of prepregnancy depression; obesity; smoking; geographic division; and socioeconomic factors including education, net worth, and race.

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CI, 1.35−1.46) and postpartum depression (OR, 1.57; 95% CI, 1.47−1.68). After controlling for age; history of prepregnancy depression; obesity; smoking; geographic division; and socioeconomic factors including education, net worth, and race, women with PCOS had higher odds of perinatal depression (aOR, 1.27; 95% CI, 1.22−1.33) and postpartum depression (aOR, 1.46; 95% CI, 1.36−1.57) (Table 2).

Black women had lower odds of perinatal (aOR, 0.78; 95% CI, 0.75−0.81) and postpartum (aOR, 0.91; 95% CI, 0.85−0.97) depression.

Sensitivity analysis

When using the definition of a given outcome first occurring on the date of delivery as compared with the day after delivery, the odds of postpartum PE (aOR, 1.19; 95% CI, 1.14−1.25), eclampsia (aOR, 1.35; 95% CI, 1.14−1.60), hypertensive heart disease (aOR, 1.35; 95% CI, 1.10−1.66), thrombotic disease (aOR, 1.50; 95% CI, 1.23−1.83), CHF (aOR, 1.23; 95% CI, 1.04−1.46), cerebrovascular accidents (aOR, 1.17; 95% CI, 1.11−1.25), and postpartum depression (aOR, 1.27; 95% CI, 1.21−1.34) remained elevated. As the definition of perinatal depression and peripartum cardiomyopathy includes the date of delivery, sensitivity analysis was not performed for these outcomes. The odds of perinatal depression remained higher when using the DSM-5 definition (aOR, 1.19; 95% CI, 1.14−1.25), and the odds of postpartum depression remained higher (aOR, 1.40; 95% CI, 1.33−1.48) when including episodes occurring after date of delivery and up to 1 year.

Interaction between prepregnancy obesity and outcomes

Approximately 70% of women with PCOS in the United States are obese,[6] and obesity is also associated with depression and CVD[14,34]; therefore, the interaction between obesity and outcomes was studied. In our dataset, the interaction between PCOS and obesity was statistically significant for the following CVD-related outcomes: postpartum eclampsia (P=.032), peripartum cardiomyopathy (P=.039), and cerebrovascular accidents (P=.002). When we included this interaction in the multivariable model, nonobese women with PCOS had higher odds of postpartum eclampsia (aOR, 1.72; 95% CI, 1.31−2.26), peripartum cardiomyopathy (aOR, 1.43; 95% CI, 1.14−1.79), and cerebrovascular accidents (aOR, 1.28; 95% CI, 1.19−1.38) than nonobese women without PCOS. Obese women with PCOS did not have significantly higher odds of postpartum eclampsia (aOR, 0.93; 95% CI, 0.56−1.53), peripartum cardiomyopathy (aOR, 0.86; 95% CI, 0.56−1.32), or cerebrovascular accidents (aOR, 1.02; 95% CI, 0.90−1.16) compared with those without PCOS (Supplemental Table 3).

Interaction between history of prepregnancy depression with outcomes

Given the association between PCOS and depression in the nonpregnant state, we examined the impact of depression before the incident pregnancy on the outcomes. The interaction between prepregnancy depression and PCOS was significant for perinatal depression (P<.001) and postpartum depression (P=.024). Including this interaction in the multivariable model, in women without prepregnancy depression, the odds of perinatal depression (aOR, 1.32; 95% CI, 1.26−1.39) and postpartum depression (aOR, 1.50; 95% CI, 1.39−1.62) were higher in women with PCOS than those without PCOS. However, in women with a history of prepregnancy depression, women with PCOS did not have higher odds of either perinatal depression (aOR, 1.06; 95% CI, 0.96−1.18) or postpartum depression (aOR, 1.13; 95% CI, 0.90−1.43) (Supplemental Table 4).

Discussion

Principal findings

This is the largest study using a nationwide cohort to examine the risk of perinatal and postpartum comorbidities in women with PCOS residing in the US. Our study, including over 42,000 women with PCOS, showed a higher prevalence of cardiometabolic and depression complications both before and during pregnancy.

Results

We show for the first time that women with PCOS are at increased risk of cardiovascular and psychiatric conditions during the postpartum period, including PE and eclampsia, peripartum cardiomyopathy, hypertensive heart disease, thrombotic disease, CHF, cerebrovascular accidents, and perinatal and postpartum depression, compared with women without PCOS. On performing sensitivity analyses, we found that nonobese women with PCOS appeared to drive the increased risk observed for postpartum eclampsia, cardiomyopathy, and cerebrovascular accidents. Further, in the subgroup without prepregnancy depression, women with PCOS had an increased risk of perinatal and postpartum depression. When evaluating the strength of variables that drive the risk, we observed that gestational hypertension strongly affected several cardiovascular complications, including PE, eclampsia, peripartum cardiomyopathy, hypertensive heart disease, and CHF; obesity strongly affected the odds of eclampsia, peripartum cardiomyopathy, thrombotic disease, CHF, cerebrovascular accidents, and perinatal and postpartum depression, whereas a history of depression impacted perinatal depression (data not shown). The postpartum findings are novel, whereas findings regarding comorbidities before pregnancy and in the antepartum period have been described previously in smaller cohort studies primarily outside the US.[11,35]

Clinical implications

Pregnancy is recognized as a stress test, and hypertensive diseases in pregnancy are linked to significant long-term consequences, such as chronic hypertension, CVD, heart failure, and stroke.[36−41] In 2018, AHA teamed with ACOG to release a Presidential Advisory highlighting the importance of multidisciplinary care in identifying, understanding, and preventing risk factors for CVD in women.[42] In addition to the higher prevalence of hypertensive

disease during pregnancy, our study found increased risk of hypertensive disease in the postpartum period. Although the prevalence of postpartum PE and eclampsia was lower than in the antepartum period, the diagnosis can be missed because of inconsistent follow-up during the postpartum period.[43] ACOG has redefined the postpartum period as the fourth trimester of pregnancy,[43] and new guidelines recommend early contact with the patient in the first 3 weeks after delivery and then an individualized comprehensive visit no later than 12 weeks postpartum.

Untreated perinatal and postpartum depression has been linked to increased risk of maternal psychiatric disease and suicide, low breastfeeding rates, and lower IQ in offspring.[44−47] The US Preventative Task Force recommends screening for depression in pregnant and postpartum women and then referring those at increased risk for first-line therapy.[48] In March 2019, the Food and Drug Administration approved the first medication specifically for use in postpartum depression, brexanolone, adding to nonpharmacologic options such as cognitive behavioral therapy.[49,50]

Racial disparities in perinatal complications have been described in the literature. A lower risk of depression in black women with PCOS may be related to decreased reporting of symptoms owing to stigma, reporting somatic symptoms more than mood symptoms, and protective factors such as strong family ties and religion.[51,52] These findings need to be confirmed in prospectively collected datasets.

Research implications

Current guidelines for PE and perinatal depression risk assessment do not include women with PCOS as an at-risk population.[31,53] Given the heterogeneity of PCOS, future studies should estimate the prevalence of perinatal and postpartum depression in different PCOS phenotypes. In accordance with ACOG recommendations for the general population, all women with PCOS should be screened for depression in both the prenatal and postpartum periods. The findings of our study underscore the need to evaluate the impact of early interventions on risk of long-term CVD complications and depression specifically in women with PCOS.[48,54]

Strengths

Although our study has inherent limitations associated with a health insurance database, it has several strengths. First, we found similar increases in PCOS-related prepregnancy comorbidities as described in other population-based datasets.[11,35,55] Second, this study includes the largest cohort of women with PCOS residing in the US. Our large sample size compared with other studies[11,56] allowed us to capture a racially and geographically diverse population and include significant postpartum complications that typically have a relatively low prevalence. Moreover, we were able to conduct sensitivity analyses varying outcome definitions, adding to the robustness of our findings.

Limitations

Claims databases lack temporality to evaluate if certain variables are confounders vs mediators in a causal pathway. In addition, causality cannot be concluded, only associations. We recognize that both obesity and depression are undercoded in claims datasets,[23] and women with billable codes likely have more severe symptoms. These limitations precluded reliable assessment of women with morbid obesity, although this subset of women would likely have greater risk of complications. The low prevalence of these conditions could have contributed to some of the findings in the interaction analyses, although our results indicate that nonobese women with PCOS are also at an increased risk for some CVD-related outcomes. Nevertheless, the prevalence of chronic hypertension, gestational hypertension, PE, preterm delivery, and cesarean delivery mirror rates that have been reported in the general US population,[40,57−60] adding to the generalizability of our findings. We chose to restrict our analyses to the first pregnancy included in the database, as the risk of several of our outcomes is greater in subsequent pregnancies. As we did not have data on gravidity and parity, we were unable to account for pregnancies that occurred before the start of data collection in 2000 or pregnancies in women whose insurance may have changed during this time frame.

It has been reported that as many as 40% of women in the United States do not attend a postpartum visit,[43] thereby decreasing the availability of postpartum data in claims databases.[61] As we only included women with continuous eligibility during the study period, this may result in a selection bias toward women who seek postpartum care. The 2 cohorts were unlikely to be selected differentially for inclusion in the Optum database, minimizing the impact of selection bias. Misclassification bias could be present if women are incorrectly coded as having PCOS. However, regardless of the direction of misclassification, this would bias results toward the null and provide a more conservative estimate of increased risk. Despite these limitations, this is the largest cohort of women with PCOS in the US, allowing sufficient power to study postpartum outcomes.

Conclusion

This large study describes an increased risk of both cardiovascular and psychiatric postpartum complications in women with PCOS. Although the prevalence of individual postpartum cardiovascular outcomes is low, the collective burden and potential impact on long-term CVD risk supports the need for closer surveillance of this population. Our study results also indicate that women with PCOS have a higher risk of perinatal and postpartum depression and should be considered as a high risk group that would benefit from closer monitoring, early counseling, and interventions to ameliorate long-term health risks.[54] ■

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Supplemental material

SUPPLEMENTAL TABLE 1
Delivery codes

Code set	Delivery codes
CPT codes	00946, 01960, 01961, 01962, 01963, 01968, 01969, 59409, 59410, 59414, 59514, 59515, 59525, 59610, 59612, 59614, 59618, 59620, 59622, 59899
DRG codes	765, 766, 767, 768, 774, 775
ICD 9 procedure codes	72, 720, 721, 722, 7221, 7229, 723, 7231, 7239, 724, 725, 7251, 7252, 7253, 7254, 726, 727, 7271, 7279, 728, 729, 73, 732, 7322, 733, 735, 7359, 736, 738, 739, 7392, 7393, 7394, 7399, 74, 740, 741, 742, 744, 749, 7499, 754, 755, 7550, 7551, 7552, 7562, 7569
ICD 10 procedure codes	10D00Z0, 10C00Z1, 10D00Z2, 10D07Z3, 10D07Z4, 10D07Z5, 10D07Z6, 10D07Z7, 10D07Z8, 10E0XZZ
ICD 9 diagnosis codes	650, 65101, 65102, 65111, 65112, 65121, 65122, 65181, 65182, 65191, 65192, 65201, 65202, 65211, 65212, 65221, 65222, 65231, 65232, 65241, 65242, 65251, 65252, 65261, 65252, 65271, 65272, 65281, 65291, 65282, 65292, 66131, 66132, 65311, 65312, 65321, 65322, 65331,65332, 65341,65342, 65351, 65352, 65361, 65362, 65371, 65372, 65381, 65382, 65391, 65392, 65401, 65402, 65411, 65412, 65421, 65422, 65431, 65432, 65441, 65442, 65451, 65452, 65461, 65462, 65471, 65472, 65481, 65482, 65491, 65492, 65501, 65502, 65511, 65512, 65521, 65522, 65531, 65532, 65541, 65542, 65551, 65552, 65561, 65562, 65571, 65572, 65581, 65591, 65582, 65592, 65601, 65602, 65611, 65612, 65621, 65622, 65631, 65632, 65641, 65642, 65651, 65652, 65661, 65662, 65671, 65672, 65681, 65682, 65691, 65692, 65701, 65702, 65801, 65802, 65811, 65812, 65821, 65822, 65831, 65832, 65841, 65842, 65891, 65881, 65882, 65892, 65901, 65902, 65911, 65912, 65921, 65922, 65931, 65932, 65941, 65942, 65951, 65952, 65961, 65971, 65981, 65991, 65982, 65992, 66001, 66002, 66011, 66012, 66021, 66022, 66032, 66041, 66042, 66051, 66052, 66061, 66062, 66071, 66072, 66081, 66091, 66082, 66092, 66101, 66102, 66111, 66112, 66121, 66122, 66131, 66132, 66141, 66142, 66191, 66192, 66201, 66202, 66211, 66212, 66221, 66222, 66231, 66232, 66301, 66302, 66311, 66312, 66321, 66331, 66322, 66332, 66341, 66342, 66351, 66352, 66361, 66362, 66381, 66391, 66382, 66392, 66401, 66402, 66411, 66412, 66421, 66422, 66431, 66432, 66441, 66442, 66451, 66452, 66461, 66462, 66481, 66491, 66482, 66492, 66501, 66502, 66511, 66512, 66521, 66522, 66531, 66532, 66541, 66542, 66551, 66561, 66552, 66562, 66571, 66572, 66581, 66591, 66582, 66592, 66601, 66602, 66591, 66592, 66701, 66702, 66902, 66911, 66912, 66921, 66922, 66941, 66942, 66951, 66952, 66961, 66962, 66971, 66972, V270, V271, V272, V273, V274, V275, V276, V277
ICD 10 diagnosis codes	0700, 0701, 0702, 0703, 0713, 0714, 0715, 0717, 0718, 0719, 0720, 0721, 080, 082, Z370, Z371, Z372, Z373, Z374, Z375, Z3750, Z3751, Z3752, Z3753, Z3754, Z3759, Z376, Z3760, Z3761, Z3762, Z3763, Z3764, Z3769, Z377, Z3801, Z383, Z3830, Z3831, Z3861, Z3862, Z3863, Z3864, Z3865, Z3866, Z3868, Z3869, 0601, 06010, 06010X0, 06010X1, 06010X2, 06010X3, 06010X4, 06010X5, 06010X9, 06012, 06012X0, 06012X1, 06012X2, 06012X3, 06012X4, 06012X5, 06012X9, 06013, 06013X0, 06013X1, 06013X2, 06013X3, 06013X4, 06013X5, 06013X9, 06014, 06014X0, 06014X1, 06014X2, 06014X3, 06014X4, 06014X5, 06014X9, 0602, 06020, 06020X0, 06020X1, 06020X2, 06020X3, 06020X4, 06020X5, 06020X9, 06022, 06022X0, 06022X1, 06022X2, 06022X3, 06022X4, 06022X5, 06022X9, 06023, 06023X0, 06023X1, 06023X2, 06023X3, 06023X4, 06023X5, 06023X9

CPT, Current Procedural Terminology; *DRG*, Diagnosis-Related Group; *ICD*, International Classification of Diseases.

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SUPPLEMENTAL TABLE 2
ICD codes for outcomes

Diagnosis	ICD 9	ICD 10
Depression	2962, 29621, 29622, 29623, 29624, 29625, 29626, 2963, 29631, 29632, 29633, 29634, 29635, 29636, 29699, 3004, 30040, 6254, 6484, 64841, 64842, 64844	F320, F321, F322, F323, F324, F325, F3281, F3289, F329, F330, F331, F332, F333, F334, F3341, F3342, F338, F339, F341, F348, F3481, F53
Preeclampsia	64240, 64241, 64242, 64243, 64244, 64250, 64251, 64252, 64253, 64254, 64270, 64271, 64272, 64273, 64274	O1400, O140, O1402, O1403, O1404, O1405, O14, O1490, O1492, O1493, O1494, O1495, O149, O141, O1410, O1412, O1413, O1414, O1415, O11, O111, O112, O113, O114, O115, O119
Eclampsia	64260, 64261, 64262, 64263, 64264	O142, O1420, O1422, O1423, O1424, O1425, O15, O150, O1500, O1502, O1503, O151, O152, O159
Cardiomyopathy	67450, 67451, 67452, 67453, 67454	I425, I426, I427, I428, I429, I43, O903
Hypertensive heart disease	402, 4020, 40200, 40201, 4021, 40210, 40211, 4029, 40290, 40291	I11, I110, I119
Thrombotic disease	4150, 4151, 41513, 41519, 6732, 67320, 67321, 67322, 67323, 67324, 6738, 67380, 67381, 67382, 67383, 67284, 6713, 67130, 67131, 67132, 67133, 67134, 6714, 67140, 67141, 67142, 67143, 67144	O88211, O88212, O88213, O88219, O8822, O8823, O8881, O88811, O88812, O88813, O88819, O888, I26, I260, I2602, I2609, I269, I2692, I2699
Congestive heart failure	428, 4280, 4281, 4282, 42820, 42821, 423, 42830, 42831, 4284, 42840, 42841, 4289	I501, I502, I5020, I5021, I503, I5030, I5031, I504, I5040, I5041, I509
Cerebrovascular accident	430, 431, 432, 4320, 4321, 4329, 433, 4330, 43300, 43301, 4331, 43310, 43311, 4332, 43320, 43321, 4333, 43330, 43331, 4338, 43380, 43381, 4339, 43390, 43391, 4340, 43400, 43401, 4341, 43410, 43411, 4349, 43490, 43491, 436, 437, 4370, 4371, 4372, 4374, 4375, 4376, 4377, 4378, 4379, 6715, 67150, 67151, 67152, 67153, 67154, 6740, 67400, 67401, 67402, 67403, 67404	I600, I6000, I6001, I6002, I601, I6010, I6011, I6012, I602, I6020, I6021, I6022, I6030, I6031, I6032, I604, I605, I6050, I6051, I6052, I606, I607, I608, I609, I61, I610, I611, I612, I613, I614, I615, I616, I618, I619, I620, I6200, I6201, I6202, I6203, I621, I629, I630, I6300, I63011, I63012, I63013, I63019, I6302, I6303, I63031, I63032, I63033, I63039, I6309, I631, I6310, I63111, I63112, I63113, I63119, I6312, I63131, I63132, I63133, I63139, I6319, I632, I6320, I63211, I63212, I63213, I63219, I6322, I6323, I63231, I63232, I63233, I63239, I6329, I633, I6330, I6331, I63311, I63312, I63313, I63319, I6332, I63321, I63322, I63323, I63329, I6333, I63331, I63332, I63333, I63339, I6334, I63341, I63342, I63343, I63349, I6339, I634, I6340, I63411, I63412, I63413, I63419, I63421, I63422, I63423, I63429, I6343, I63431, I63432, I63433, I63439, I6344, I63441, I63442, I63443, I63449, I6349, I635, I6350, I6351, I63511, I63512, I63513, I63519, I6352, I63521, I63522, I63523, I63529, I6353, I63531, I63532, I63533, I63539, I6354, I63541, I63542, I63543, I63549, I6359, I636, I638, I639, I650, I6501, I6502, I6503, I6509, I651, I652, I6521, I6522, I6523, I6529, I658, I659, I66, I660, I6601, I6602, I6603, I6609, I661, I6611, I6612, I6613, I6619, I662, I6621, I6622, I6623, I6629, I663, I668, I669, I670, I671, I672, I673, I674, I675, I676, I677, I678, I6781, I6782, I6783, I67841, I67848, I6789, I679, I68, I680, I682, I688, O2250, O2251, O2252, O2253, O873
Ischemic heart disease	410, 4100, 41000, 41001, 41002, 4101, 41010, 41011, 41012, 4102, 41020, 41021, 41022, 4103, 41030, 41031, 41032, 4104, 41040, 41041, 41042, 4105, 41050, 41051, 41052, 4106, 41060, 41061, 41062, 4107, 41070, 41071, 41072, 4108, 41080, 41081, 41082, 4109, 41090, 41091, 41092	I21, I210, I2101, I2102, I2109, I211, I2111, I2119, I212, I2121, I2129, I213, I214, I219, I21A1, I21A9, I220, I221, I222, I228, I229

ICD, International Classification of Diseases.

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SUPPLEMENTAL TABLE 3
Stratified analysis by obesity

Complication	Obese women	Nonobese women
Postpartum eclampsia	0.93 (0.56–1.53)	1.72 (1.31–2.26)
Peripartum cardiomyopathy	0.86 (0.56–1.32)	1.43 (1.14–1.79)
Cerebrovascular accidents	1.02 (0.90–1.16)	1.28 (1.19–1.38)

Data are presented as adjusted odds ratio (95% confidence interval).

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SUPPLEMENTAL TABLE 4
Stratified analysis by history of depression

Complication	Women with a history of depression	Women without a history of depression
Perinatal depression	1.06 (0.96–1.18)	1.32 (1.26–1.39)
Postpartum depression	1.13 (0.90–1.43)	1.50 (1.39–1.62)

Data are presented as adjusted odds ratio (95% confidence interval).

Alur-Gupta et al. Postpartum complications increased in polycystic ovary syndrome. Am J Obstet Gynecol 2021.