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A Comparison of Pregnancy and Neonatal Outcomes in Women with the Hyperandrogenic Disorders Polycystic Ovary syndrome and Cushing's Syndrome

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Abstract

Research Question: How does the risk for adverse obstetric outcomes differ among women with polycystic ovary syndrome (PCOS) and women with Cushing's syndrome (CUS)?

Design: A retrospective population-based study utilizing data from the Healthcare Cost and Utilization Project—Nationwide Inpatient Sample (HCUP-NIS), 2004-2014. 14, 881 deliveries to women with PCOS and 134 deliveries to women with CUS were identified. Associations between PCOS, CUS, pregnancy, delivery, and neonatal outcomes were analyzed with multivariate logistic regression analysis.

Results: At baseline, CUS was associated with a higher risk of chronic hypertension (P<0.001), pregestational diabetes mellitus (P=0.01), thyroid disease (P=0.004), and higher rates of smoking during pregnancy (P=0.02) whereas PCOS was associated with higher rates of obesity (P=0.01). In terms of obstetric outcomes, PCOS increased the prevalence of gestational diabetes mellitus (P=0.002, adjusted[a] OR 2.73; 95% CI 1.46 to 5.12), and cesarean section (P<0.001, aOR 2.63; 95% CI 1.81-3.83) in comparison to CUS. CUS increased the prevalence of operative vaginal delivery (P<0.001, aOR 0.10; 95% CI 0.06-0.14), and transfusion (P=0.002, aOR 0.25; 95% CI 0.11-0.59) in comparison to deliveries to women with PCOS. No significant differences were found in terms of pregnancy-induced hypertension (P=0.78), gestational hypertension (P=0.86), preeclampsia (P=0.25), preeclampsia or eclampsia superimposed on pre-existing hypertension (P=0.13).

Conclusion: PCOS increases the risk of gestational diabetes and cesarean section relative to CUS, whereas CUS increases the prevalence of operative vaginal delivery and blood transfusions.

Keywords: PCOS, Polycystic ovary syndrome, Cushing's syndrome, pregnancy complications, pregnancy, hyperandrogenic disorders, pregnancy outcomes

Introduction

Polycystic ovary syndrome (PCOS) is a common endocrine disorder affecting up to 18% of young women [1]. The disorder is associated with insulin resistance, type 2 diabetes mellitus, and increased cardiovascular disease risk factors [1]. Women diagnosed with PCOS have a greater inherent insulin resistance in comparison to body mass index matched normal controls and their insulin resistance is further exacerbated by the presence of obesity [1]. PCOS is associated with infertility as well as adverse obstetric outcomes [1]. Women with PCOS are at a higher risk of gestational diabetes mellitus, gestational hypertension, and preeclampsia [1]. In a meta-analysis of pregnancy complications among women with PCOS which included 40 studies, it was found that PCOS was associated with increased risk of gestational diabetes, preeclampsia,

pregnancy-induced hypertension, preterm delivery, cesarean delivery, miscarriage, hypoglycemia, and perinatal death [2]. There were no significant differences found for babies being small for gestational age, nor preterm premature rupture of membranes [2]. This study did not control for confounding effects in the baseline characteristics of the women with PCOS, as results were only stratified based on study design, mean age, and pre-pregnancy BMI [2]. In addition, substantial heterogeneity was found between the studies in terms of gestational diabetes mellitus, pregnancy induced hypertension and preterm delivery, however after sequentially excluding each study from the pooled analysis, there were no differences found in the overall conclusions.

Cushing's syndrome (CUS), in comparison to PCOS, is a much rarer metabolic disorder, with 2-4 cases per million people per year [3]. It is characterized by increased levels of glucocorticoids, contributing to insulin resistance. The most common cause of CUS in pregnancy are adrenal adenomas, followed by pituitary etiologies, and lastly adrenal carcinomas [4]. The presentation of CUS in pregnancies has similarities to that of PCOS, including the presence of hyperandrogenemia and insulin resistance. In a meta-analysis from 2016 including 168 manuscripts which compared pregnancies to women with active CUS vs treated CUS, it was found that women with active CUS had increased risk of gestational diabetes, pregnancy-induced hypertension, and preeclampsia- in comparison to women with treated Cushing's syndrome [5]. There were higher rates of fetal loss and fetal morbidity in the active CUS group when compared to the cured CUS group. This study contained 168 manuscripts, however, these consisted solely of case reports, and results were not adjusted for confounding factors.

The objective of this study was to analyze the differences in baseline maternal characteristics between women with PCOS and CUS, given their commonality of insulin resistance and hyperandrogenemia and observe differences in pregnancy and neonatal outcomes among women with these disorders while accounting for confounding effects using the Healthcare Cost and Utilization Project Nationwide Inpatient Sample (HCUP-NIS) database.

Methods

This was a retrospective population-based study with data derived from the HCUP-NIS from the years of 2004-2014, inclusively. The HCUP-NIS database collects information on 7 million inpatient stays per year, being the largest inpatient sample database in the USA and geographically representing over 96% of the American Population. The data presents information on approximately 20% of admissions to US hospitals in 48 states as well as the District of Columbia.

To extract admissions related to pregnancy from the database, the International Classification of Diseases (ICD-9-CM) diagnostic codes and procedural codes were used. So as to include subjects only once per pregnancy the analysis was limited to hospital admissions that resulted either in a delivery or maternal death using the diagnostic codes: 650.xx, 677.xx, or 651.xx-676.xx, as well as the ICD-9-CM procedural codes of 72.x, 73.x, 74.0-74.2. Among this group, women with PCOS were identified using the diagnostic code 256.4, while women with CUS were identified with codes 255.0 and 255.3. ICD-9 codes were additionally used to identify demographic characteristics, pregnancy, delivery, and neonatal outcomes for all the women in the study population. The baseline maternal characteristics included patient age, race, income, insurance type, hospital type, previous cesarean section (CS), multiple gestation (MG), smoking history, obesity (BMI ≥ 30kg/ m^2) or not, preexisting HTN, preexisting diabetes, preexisting thyroid disease, and the use of *in vitro* fertilization (IVF). The maternal pregnancy complications included gestational diabetes mellitus (GDM), pregnancy-induced hypertension (PIH), gestational hypertension (GHTN), preeclampsia, eclampsia, preeclampsia or eclampsia superimposed on pre-existing HTN, and placenta previa. Delivery outcomes included PPROM (preterm rupture of membranes in the third trimester), preterm delivery (delivery before 37 weeks of completed gestation), placental abruption, chorioamnionitis, cesarean section, operative vaginal delivery, maternal infection, hysterectomy, postpartum hemorrhage, wound complications, maternal death, transfusion, maternal infection, deep vein thrombosis, pulmonary embolism, venous thromboembolism and disseminated intravascular coagulation. The neonatal outcomes studied included being small for gestational age (SGA), intrauterine fetal death (IUFD), and congenital anomalies. These outcomes are defined in **Table 1**.

Statistical analyses

Chi-squared tests were used to compare the baseline maternal characteristics among the PCOS and the CUS groups. Logistic regression analyses were used to analyze the individual associations between PCOS and CUS and adverse pregnancy outcomes. This comparison used estimation of odd ratios as well as 95% CI. The regression models were then adjusted for confounding effects of the maternal baseline demographic criteria (when $P<0.05$) and then presented as the adjusted odds ratios (aORs). All of the analyses were performed using SPSS 23.0 (IBM Corporation, Chicago, IL, USA) software. According to the Tri-Council Policy Statement (2018), institutional review board approval was not required as only publicly available anonymized data was used for this study.

Results

Between the years 2004 and 2014 inclusively, 9,096,788 births took place. Of these, 14,881 deliveries were to women with PCOS and 134 deliveries were to women with CUS. The baseline demographics of the women with PCOS and CUS who delivered throughout the given time frame are summarized in **Table 2**.

Table 1. Main obstetric outcomes and definitions.

Outcome	Definition
Gestational diabetes	Diabetes that develops during pregnancy.
Pregnancy-induced hypertension	Systolic blood pressure ≥140 mmHg and diastolic blood pressure ≥ 90 mmHg.
Gestational hypertension	Hypertension that develops at ≥ 20 + 0 weeks gestation [16].
Preeclampsia	Gestational hypertension with new-onset proteinuria and, potentially, other end-organ dysfunctions (Wagner, 2004).
Eclampsia	New onset of seizures in a woman with preeclampsia [16].
Preeclampsia and eclampsia superimposed hypertension	Preeclampsia or eclampsia in women with chronic hypertension [16].
Placenta previa	A condition in which the placenta directly covers the cervix.
Preterm premature rupture of the membranes	Preterm (before 37 weeks' gestation) rupture of the amniotic sac.
Preterm delivery	Delivery before 37 weeks' gestation.
Placental abruption	Preterm (before 37 weeks' gestation) rupture of the amniotic sac.
Chorioamnionitis	Infection of the chorion, amnion and amniotic fluid.
Operative vaginal delivery	Assisted vaginal birth requiring the use of instruments, including vacuum or forceps.
Caesarean delivery	Delivery of the fetus through incision in the abdomen and uterus.
Spontaneous vaginal delivery	Vaginal delivery that occurs without the use of instruments.
Hysterectomy	The need for hysterectomy after the fetal delivery.
Postpartum haemorrhage	Heavy bleeding of ≥1000 ml within 24 h after delivery of the fetus.
Wound complications	Including infection, dehiscence and hematomas.
Maternal death	Death occurring peripartum or postpartum.
Transfusion	Transfusion of red blood cells.
Maternal infection	Including maternal sepsis, endometritis, etc.
Deep vein thrombosis	Blood clot development in a deep vein.
Pulmonary embolism	Sudden blockage in a pulmonary artery of the lungs.
Venous thromboembolism	Involves deep vein thrombosis and pulmonary embolism.
Disseminated intravascular coagulation	Occurrence of disseminated intravascular coagulation during the perinatal period.
Small for gestational age	Neonatal weight below the 10th percentile.
Intrauterine fetal death	Fetus dies in the womb at ≥ 20 weeks gestation
Congenital anomalies	Structural or functional birth defects

Table 2. Maternal characteristics.

	CUS (N=134)	PCOS (N=14881)	P-value
Age (years)			<0.001
<25	24 (17.9%)	2295 (15.4%)	
25-34	58 (43.3%)	9770 (65.7%)	
≥35	52 (38.8%)	2812 (18.9%)	
Race			0.06
White	75 (65.8%)	9106 (71.2%)	
Black	15 (13.2%)	1098 (8.6%)	
Hispanic	18 (15.8%)	1288 (10.1%)	
Asian and Pacific	2 (1.8%)	741 (5.8%)	
Native American	0 (0.0%)	84 (0.7%)	
Other	4 (3.5%)	464 (3.6%)	
Income quartiles			0.59
Less than 39,000	20 (22.7%)	2117 (17.2%)	
$39,000-47,999	19 (21.6%)	2192 (23.6%)	
$48,000-62,999	24 (27.3%)	3536 (28.7%)	
$63,000 or more	25 (28.4%)	3756 (30.5%)	
Medical insurance plan type			<0.001
Medicare	7 (5.2%)	107 (0.7%)	
Medicaid	26 (19.4%)	2392 (16.1%)	
Private including HMO	88 (65.7%)	11748 (79.1%)	
self-pay	6 (4.5%)	155 (1.0%)	
No charge	1 (0.7%)	6 (0.0%)	
Other	6 (4.5%)	452 (3.0%)	
Obesity	17 (12.7%)	3293 (22.1%)	0.01
Previous CS	21 (15.7%)	2716 (18.3%)	0.44
Tobacco smoking	11 (8.2%)	631 (4.2%)	0.02
Chronic HTN	33 (24.6%)	1248 (8.4%)	<0.001
Pregestational DM	12 (9.0%)	673 (4.5%)	0.01
Illicit drug use	2 (1.5%)	106 (0.7%)	N/A
Multiple gestation	4 (3.0%)	880 (5.9%)	N/A
Thyroid disease	28 (20.9%)	1882 (12.6%)	0.004
HIV	0 (0.0%)	1 (0.0%)	N/A
IVF (AssisReproTech)	0 (0.0%)	360 (2.4%)	N/A

N/A: Not Applicable (listed for the P-value if the number of cases was so few that results were unreliable).

In the CUS group, the subjects had a tendency to be older than the women with PCOS. Both groups had a majority of participants on private health insurance including health maintenance organizations (HMOs), however this was more predominant in the PCOS group (79.1% vs. 65.7%), while the percentage with Medicare was smaller in the PCOS group as compared to the CUS group (0.7% vs 5.2%). Women with CUS were more likely to be tobacco smokers during their pregnancy.

In terms of metabolic baseline characteristics, women in the PCOS group were more likely to have obesity (22.1% vs. 12.7%, P=0.01). At baseline, CUS was associated with a higher risk of chronic hypertension (24.6% vs. 8.4%, P<0.001), pregestational diabetes mellitus (9.0% vs. 4.5%, P=0.01), and thyroid disease (20.9% vs 12.6%, P=0.004) in contrast to PCOS.

The association between PCOS and CUS and adverse pregnancy and delivery outcomes, while controlling for confounding variables, are presented in **Table 3**. In terms of obstetric outcomes, PCOS increased the prevalence of gestational diabetes mellitus (P=0.002, adjusted[a] OR 2.73; 95% CI 1.46 to 5.12), and was also associated with a higher prevalence of cesarean section (P<0.001, aOR 2.63; 95% CI 1.81-3.83) in comparison to CUS. CUS increased the prevalence of operative vaginal delivery (P< 0.001, aOR 0.10; 95% CI 0.06-0.14), as well as transfusion (P=0.002, aOR 0.25; 95% CI 0.11-0.59) when compared to the deliveries to women with PCOS. No significant differences were found in terms of pregnancy induced hypertension (P=0.78), gestational hypertension (P=0.86), preeclampsia (P=0.25), and preeclampsia or eclampsia superimposed on pre-existing hypertension (P=0.13).

Table 3. Pregnancy and delivery outcomes.

	CUS (%)	PCOS (%)	Crude OR (95% CI)	Adjusted OR (95% CI)	Adjusted P-value
Pregnancy outcomes[a]					
Pregnancy induced hypertension	16.4	16.1	0.98 (0.62-1.55)	1.07 (0.67-1.71)	0.78
Gestational hypertension	5.2	6.6	1.28 (0.60-2.75)	1.07 (0.50-2.32)	0.86
Preeclampsia	8.2	7.1	0.85 (0.46-1.58)	0.69(0.37-1.30)	0.25
Eclampsia	0.0	0.1	N/A	N/A	N/A
Preeclampsia and Eclampsia superimposed HTN	3.7	2.7	0.71 (0.29-1.75)	2.13(0.80-5.63)	0.13
GDM	8.2	18.7	2.57 (1.38-4.77)	2.73(1.46-5.12)	0.002
Placenta previa	0	0.7	N/A	N/A	N/A
Delivery outcomes[a]					
PPROM	2.2	2.2	0.97 (0.31-3.05)	0.99 (0.31-3.16)	0.99
Preterm delivery	9.0	12.2	1.413(0.78- 2.56)	1.53 (0.84-2.79)	0.17
Placental abruption	1.5	1.6	1.05 (0.26-4.25)	1.18 (0.29-4.86)	0.82
Chorioamnionitis	0.7	3.0	4.18 (0.58-29.93)	4.17 (0.58-30.06)	0.16
Operative vaginal delivery	30.6	3.9	0.09 (0.06-0.13)	0.10 (0.06-0.14)	<0.001
CS	32.1	52.7	2.36 (1.64-3.39)	2.63 (1.81-3.83)	<0.001
SVD	37.3	43.5	1.29 (0.91-1.84)	1.19 (0.83-1.70)	0.35
Hysterectomy	0.0	0.1	N/A	N/A	N/A
PPH	1.5	3.4	2.29 (0.57-9.28)	2.15 (0.53-8.73)	0.29
Wound complications	0.7	0.8	N/A	N/A	N/A
Maternal Death	0.7	0.0	N/A	N/A	N/A
Transfusion	4.5	1.2	0.25 (0.11-0.57)	0.25 (0.11-0.59)	0.002
Others[b]					
Maternal infection	0.7	3.5	4.88 (0.68-34.99)	4.93 (0.69-35.47)	0.11

DVT	0.0	0.0	N/A	N/A	N/A
Pulmonary embolism	0.0	0.0	N/A	N/A	N/A
VTE	0.0	0.1	N/A	N/A	N/A
DIC	0.0	0.2	N/A	N/A	N/A

[a]Adjusted for age, race, plan type, income quartiles, hospital type, drug use, previous caesarean delivery, chronic hypertension, smoking, multiple gestation and pregestational diabetes.

[b]Adjusted for age, race, plan type, income quartiles, hospital type, drug use, previous caesarean delivery, chronic hypertension, smoking, multiple gestation, pregestational diabetes, pregnancy-induced hypertension, gestation hypertension, preeclampsia, and gestational diabetes.

N/A: Not Applicable (listed for the OR and P-value if the number of cases was so few that results were unreliable).

Table 4. Neonatal outcomes.

	CUS (%)	PCOS (%)	Crude OR (95% CI)	Adjusted OR (95% CI)	Adjusted P-value
SGA	3.0	3.3	1.10 (0.41-2.99)	1.39 (0.51-3.82)	0.52
IUFD	0.7	0.5	0.70 (0.10-5.08)	0.93 (0.13-6.84)	0.94
Congenital anomalies	0.7	1.4	1.89 (0.26-13.55)	1.88 (0.26-13.60)	0.53

Adjusted for age, race, plan type, income quartiles, hospital type, drug use, previous caesarean delivery, chronic hypertension, smoking, multiple gestation, pregestational diabetes, pregnancy-induced hypertension, gestation hypertension, preeclampsia, and gestational diabetes.

The association between PCOS and Cushing's disease and neonatal outcomes, are presented in **Table 4**. The results showed no difference in the rate of women who gave birth to SGA infants (P=0.52), the rate of Intra-uterine fetal demises (P=0.94), and the rate of infants with congenital anomalies (P=0.53) between the PCOS and Cushing's groups.

Discussion

The aim of this study was to determine the differences in pregnancy, delivery, and neonatal outcomes in deliveries to women with PCOS and women with CUS using a large nation-wide database.

Maternal PCOS has previously been associated with increased risk of gestational diabetes, preeclampsia, pregnancy-induced hypertension, preterm delivery, cesarean delivery, miscarriage, hypoglycemia, and perinatal death [2]. In a review done by Palomba. *et al.* [6], maternal PCOS was associated with a 3 to 4 fold increased risk of gestational hypertension and pre-eclampsia, a 3-fold increased risk of gestational diabetes as well as a 2-fold increase in premature delivery. It is felt that these increased risks are induced by the inherent underlying issues of insulin resistance and hyperandrogenism. A review done assessing PCOS and endometrial function suggests that the endometrial dysfunction in PCOS in addition to abnormal trophoblast invasion and placentation, contributes to adverse pregnancy complications in this disorder [7].

Active CUS has been associated with an increased risk of gestational diabetes, pregnancy-induced hypertension, pre-eclampsia, fetal loss, and global fetal morbidity in comparison to women with cured Cushing's syndrome [5]. In addition, CUS increases the risk of operative vaginal delivery in comparison to non CUS patients, which is possibly linked to the finding that approximately sixty percent of CUS patients develop muscle atrophy to their type II muscle fibers, resulting in muscle weakness possibly affecting their labors [8]. A study using the HCUP-NIS database compared pregnancies in women with CUS to a control group of non- CUS pregnancies and found an increased risk of blood transfusion among women with CUS. In addition, after controlling for confounding factors, this study found a decreased risk of cesarean section in women with CUS compared to the control group. A review by Wang and colleagues demonstrated that patients with CUS undergoing pregnancy who were treated medically or surgically, or diagnosed for CUS early, had a better prognosis in terms of pregnancy and delivery outcomes [4]. According to a review done by Caimari *et al.* [5], women presenting with CUS are more likely to have hypertension, diabetes mellitus II, miscarriage, and gestational diabetes. In a different study, they had a 6-fold increased risk of preeclampsia and a 10-fold increased risk in fetal loss [9] when compared to those without CUS.

Based on the literature, both PCOS and CUS have been shown to result in an increased risk of gestational diabetes, pregnancy-induced hypertension, preeclampsia, as well as fetal loss. This study analyzed the magnitude of the effects of these disorders on these outcomes and compared them.

From the literature, outcomes which were more prevalent in women with PCOS and not CUS were cesarean delivery, preterm delivery, as well hypoglycemia. Based on a previous study done with the HCUP-NIS database, when deliveries to women with CUS were compared to a control group of deliveries to women without CUS, outcomes which were more prevalent in CUS, unlike in PCOS, were operative vaginal delivery as well as blood transfusion [8]. This published study found that there was an increased risk of preeclampsia in the CUS group compared to the controls, yet there was no significant difference in the rates of gestational diabetes. 30.4% of the CUS group underwent operative vaginal delivery in comparison to 6.5% of the controls. 4.5% of the CUS group required blood transfusion in comparison to 1% of the control group. [8]

An analysis of the baseline characteristics demonstrated that women among the PCOS group were more likely to be obese (22.1% vs. 12.7%). To date, there is little research that analyzes the difference in the prevalence of obesity among the two disorders. According to a meta-analysis consisting of 106 studies, Women with PCOS had a 2.8 fold increase in obesity rates compared to women without PCOS [10], however the studies involved demonstrated substantial heterogeneity. In another review, it was found that the prevalence of obesity in women with PCOS can be as high as 80% in the United States, however studies performed outside of the United States demonstrate rates as low as 20%. This is likely related to lifestyle factors which play a large role in the development of obesity in women with PCOS [9]. It has been shown that the presence of obesity in women with PCOS exacerbates many adverse pregnancy outcomes seen in women with PCOS, such as hypertensive disorders, chorioamnionitis, GDM, and cesarean section [11]. A prominent feature seen in patients with CUS is central obesity. Despite this, out of the 134 deliveries to women with CUS studies, only 12.7% were obese. It should be noted that these findings may be related to rates of treatment in the CUS group and may be different in an older patient population, than in pregnant women. Clearly, the pregnancy itself will also modify these rates such that the results of obesity in this study would not be extrapolatable to other populations with PCOS or CUS. It should be noted that in this study we controlled rates of obesity when comparing CUS and PCOS.

The maternal baseline characteristics demonstrated that those in the CUS group were more likely to have thyroid disease, chronic hypertension and pregestational diabetes mellitus. Our study suggests that there is more than a 2-fold increase in the likelihood of developing GDM in the PCOS population when compared to the CUS population. This may reflect a difference in the magnitude of insulin resistance when comparing these two syndromes. On the other hand, this could represent an under diagnosis of pre-gestational diabetes in the PCOS population. One study demonstrated that about 50% of women presenting with PCOS and diabetes mellitus II have not been diagnosed [12].

Our study found that there was more than a 2-fold increase in the likelihood of CS in the PCOS population when compared to the CUS population (P<0.001, aOR 2.63; 95% CI 1.81-3.83). In a separate study using the same database, deliveries to women with CUS were compared to a control group consisting of deliveries to women without CUS, and there was found to be no significant difference in the rates of cesarean section. However, after adjusting for confounding factors, cesarean section became less likely in the CUS group with an adjusted odds ratio of 0.59 [8]. In another study using the same database, deliveries to women with PCOS were compared to a control group of deliveries to women without PCOS, and there was found to be a significant increase in the likelihood of cesarean section among the PCOS group, concluding that PCOS is an independent risk factor for cesarean delivery [13]. The reasons for the increased risk of CS in women with PCOS is not exactly clear, however it could be related to increased risks of fetal macrosomia, particularly with higher rates of GDM in the PCOS population seen [11].

Our study demonstrates that CUS was associated with about a 10-fold increased risk of operative vaginal delivery when compared to the PCOS group. (P< 0.001, aOR 0.10; 95% CI 0.06-0.14). 30.6% of the CUS group underwent operative vaginal delivery, in comparison to 3.9% of the PCOS group. When pregnancies to women with CUS were studied in reference to a control group of deliveries to women without CUS, it was determined that CUS is an independent risk factor for operative vaginal delivery (P<0.0001) with an adjusted odds ratio of 6.49 [8]. This is likely due to the muscular atrophy found in patients with CUS.

In addition, this study found that CUS increased the risk of transfusion in comparison to PCOS (4.5% vs. 1.2%). We hypothesize that the inherent muscle weakness of CUS could induce increased risks of post-partum hemorrhage [8].

This study demonstrated no significant differences in terms of hypertensive disorders of pregnancy between the two groups. These include GHTN (diagnosed after 20 weeks gestation), PEC, eclampsia or PEC superimposed on pre-existing chronic HTN. This finding would suggest that both PCOS and CUS are at similarly increased risks of these pregnancy complications.

The study demonstrated that there were no significant differences in the neonatal outcomes of SGA, IUFD, and congenital anomalies among the births to women with PCOS and CUS. The meta-analysis conducted by Kjerulff *et al.* [14], concluded that PCOS significantly increased the rates of SGA. Contrasting this, a systematic review and meta- analysis by Yu. *et al.* [2], determined that PCOS had little to no effect on neonates being small for gestational age, nor having

congenital malformations. That study demonstrated an association between PCOS and an increased risk for IUFD with a risk ratio of 1.83 [2]. A retrospective population study done in England found that maternal PCOS was associated with reduced risk for small gestational age babies and postulated that previous association between PCOS and low birthweight babies is likely due to preterm delivery and lower gestational age at birth [15]. CUS has been associated with greater risk of global fetal mortality and overall fetal loss compared to women with treated hypercortisolemia at the time of gestation [5]. In a study using the HCUP-NIS database comparing deliveries to women with CUS to non CUS pregnancies, there were no significant differences found for SGA, IUFD, nor congenital anomalies among the CUS and control group. Despite these results, there was only one case (0.7%) of IUFD and congenital anomalies amongst the CUS group, therefore these disease processes must be investigated in a larger study to draw further conclusions [8].

Strengths and Limitations

To our knowledge, this study is the first study to compare the adverse pregnancy outcomes between women with PCOS and with CUS. In addition, our results were adjusted for the confounding effects of maternal demographic baseline characteristics and concurrently occurring characteristics (age, race, income level, insurance type, obesity, IVF use, previous CS, chronic HTN, pregestational diabetes, thyroid disease, tobacco smoking and recreational drug use). Our study validity is limited by the fact that it is a retrospective study that uses a database which relies on the accuracy of the individuals collecting the data. It is possible that certain PCOS and CUS phenotypes were missed when identifying study participants. In addition, we were unable to analyze the HCUP database beyond the year of 2014, since in 2015, the database switched from ICD-9 codes to ICD-10 codes with different classification, therefore the data was not comparable. We did not have access to information on the treatments received by the patients as well as information once they were discharged from the hospital. We recognize that patients in both CUS and PCOS groups may have had multiple deliveries and therefore may be included in the data more than once. The large discrepancy in the number of individuals with CUS and PCOS may also play an effect on the results.

One strength is that the entire group of women was analyzed according to one methodology, therefore limiting the heterogeneity that is present in most meta-analyses published on either topic. Our study consisting of over 9 million pregnancies allowed for the analysis of 134 pregnancies to women with CUS and around 15 000 pregnancies to women with PCOS. Being that CUS is a very rare disease and a minority of women with this disorder can conceive, most of the research on pregnancies to women with CUS is in the form of case reports.

Conclusion

In conclusion, both CUS and PCOS are associated with mostly similar adverse obstetric outcomes rates. PCOS was associated with an increased risk of cesarean delivery and gestational diabetes mellitus as compared to CUS. CUS was associated with an increased risk of operative vaginal delivery and blood transfusion. Both disorders have previously been associated with increased risk of hypertensive disorders of pregnancy, however when compared, there were no significant differences in the rates of hypertensive disorders of pregnancy among the two disorders. This study may further elucidate how hypertensive disorders with associated insulin resistance alter pregnancy complications.

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