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Polycystic ovary syndrome and risk of adverse pregnancy outcomes: a registry linkage study from Massachusetts

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STUDY QUESTION: Do women with polycystic ovary syndrome (PCOS) have a greater risk of adverse pregnancy complications (gestational diabetes, preeclampsia, cesarean section, placental abnormalities) and neonatal outcomes (preterm birth, small for gestational age, prolonged delivery hospitalization) compared to women without a PCOS diagnosis and does this risk vary by BMI, subfertility and fertility treatment utilization?

SUMMARY ANSWER: Deliveries to women with a history of PCOS were at greater risk of complications associated with cardiometabolic function, including gestational diabetes and preeclampsia, as well as preterm birth and prolonged length of delivery hospitalization.

WHAT IS KNOWN ALREADY: Prior research has suggested that women with PCOS may be at increased risk of adverse pregnancy outcomes. However, findings have been inconsistent possibly due to lack of consistent adjustment for confounding factors, small samples size and other sources of bias.

STUDY DESIGN, SIZE, DURATION: Massachusetts deliveries among women ≥18 years old during 2013–2017 from state vital records linked to hospital discharges, observational stays and emergency department visits were linked to the Society for Assisted Reproductive Technology Clinic Outcome Reporting System (SART CORS) and the Massachusetts All-Payers Claims Database (APCD).

PARTICIPANTS/MATERIALS, SETTING, METHODS: PCOS was identified by ICD9 and ICD10 codes in APCD prior to index delivery. Relative risks (RRs) and 95% CI for pregnancy and delivery complications were modeled using generalized estimating equations with a log link and a Poisson distribution to take multiple cycles into account and were adjusted *a priori* for maternal age, BMI, race/ethnicity, education, plurality, birth year, chronic hypertension and chronic diabetes. Tests for homogeneity investigated differences between maternal pre-pregnancy BMI categories (<30, ≥30, <25 and ≥25 kg/m^2) and between non-infertile deliveries and deliveries that used ART or had a history of subfertility (defined by birth certificates, SART CORS records, APCD or hospital records).

MAIN RESULTS AND THE ROLE OF CHANCE: Among 91 825 deliveries, 3.9% had a history of PCOS. Women with a history of PCOS had a 51% greater risk of gestational diabetes (CI: 1.38–1.65) and a 25% greater risk of preeclampsia (CI: 1.15–1.35) compared to women without a diagnosis of PCOS. Neonates born to women with a history of PCOS were more likely to be born preterm (RR: 1.17, CI: 1.06–1.29) and more likely to have a prolonged delivery hospitalization after additionally adjusting for gestational age (RR: 1.23,

CI: 1.09–1.40) compared to those of women without a diagnosis of PCOS. The risk for gestational diabetes for women with PCOS was greater among women with a pre-pregnancy BMI <30 kg/m^2.

LIMITATIONS, REASONS FOR CAUTION: PCOS was defined by ICD documentation prior to delivery so there may be women with undiagnosed PCOS or PCOS diagnosed after delivery included in the unexposed group. The study population is limited to deliveries within Massachusetts among most private insurance payers and inpatient or observational hospitalization in Massachusetts during the follow-up window, therefore there may be diagnoses and or deliveries outside of the state or outside of our sample that were not captured.

WIDER IMPLICATIONS OF THE FINDINGS: In this population-based study, women with a history of PCOS were at greater risk of pregnancy complications associated with cardiometabolic function and preterm birth. Obstetricians should be aware of patients' PCOS status and closely monitor for potential pregnancy complications to improve maternal and infant perinatal health outcomes.

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Key words: polycystic ovary syndrome / gestational age / gestational diabetes / preterm birth / adverse pregnancy outcomes / PCOS / low birth weight / preeclampsia / pregnancy-induced hypertension

Introduction

Polycystic ovary syndrome (PCOS) is characterized by hyperandrogenism, ovarian dysfunction and polycystic ovarian morphology (Legro *et al.*, 2013; Teede *et al.*, 2018) and is the most common endocrine disorder in women, burdening approximately 6–15% of reproductive-aged women (Fauser *et al.*, 2012; Bozdag *et al.*, 2016). Phenotypic traits associated with PCOS, such as obesity, metabolic syndrome, impaired glucose tolerance, insulin resistance and infertility (Franks, 1995), are also associated with higher prevalence of adverse pregnancy outcomes. Therefore, there has been a great deal of interest in the influence of PCOS on adverse outcomes during pregnancy.

Prior meta-analyses and systematic reviews have suggested that deliveries to women with a history of PCOS are at an increased risk of pregnancy complications (Kjerulff *et al.*, 2011; Qin *et al.*, 2013; Palomba *et al.*, 2015; Yu *et al.*, 2016; Gilbert *et al.*, 2018; Bahri Khomami *et al.*, 2019; Sha *et al.*, 2019), including an elevated risk of gestational diabetes, pregnancy-induced hypertension (PIH) and preterm birth. However, findings from some studies have been inconsistent and not all analyses have adjusted for potential confounding factors, such as BMI or chronic diabetes (Palomba *et al.*, 2015). Moreover, many studies on PCOS and adverse pregnancy outcomes are conducted among a small number of women, limiting statistical power and generalizability. Among the most recent meta-analyses, 70% of the studies included had fewer than 100 deliveries to women with a history of PCOS (Yu *et al.*, 2016) and half of the studies were considered to have moderate to high risk of bias (Bahri Khomami *et al.*, 2019).

To improve upon these previous limitations, we conducted an analysis among Massachusetts deliveries from 2013 to 2017. Specifically, we investigated whether women with a previous history of PCOS had greater risk of adverse maternal and pregnancy outcomes compared to women without a diagnosis of PCOS accounting for potential confounding factors. We also investigated effect modification by maternal pre-pregnancy BMI and by history of subfertility/infertility or ART usage.

Materials and methods

This analysis linked data from three sources: (i) Massachusetts Pregnancy to Early Life Longitudinal (PELL) data system, (ii) Society for Assisted Reproductive Technology Clinic Outcome Reporting System (SART CORS) and (iii) Massachusetts All-Payers Claims Database (APCD). The study had IRB approvals from the Massachusetts Department of Public Health and Dartmouth-Hitchcock Health.

As described in detail previously (Kotelchuck *et al.*, 2014), the Massachusetts Outcome Study of Assisted Reproductive Technology (MOSART) database was created by linking SART CORS deliveries from 1 July 2004 to 31 December 2017 to birth certificates and fetal death records using mother's first and last name, father's last name, mother's date of birth and date of delivery. Between 2004 and 2017, the linkage rates were 91.5% overall and 94.9% for those in which both ART cycle patient zip code and treatment clinic were located in Massachusetts.

APCD is comprised of insurance claims from most public and private insurance payers in Massachusetts. The APCD and MOSART data from 1 January 2013 to 31 December 2017 were linked, as described in detail previously (Stern *et al.*, 2021a,b). Mothers with MassHealth (Medicaid Program in Massachusetts) at any time during the study period were excluded. This linkage was executed through a Memorandum of Understanding among the Center for Health Information and Analysis (CHIA) that maintains and houses APCD, the Massachusetts Department of Public Health (MDPH) and project principal investigators. Maternal (date of birth, first name, last name and zip code) and infant (date of birth, first name, last name, sex and

zip code) information from the MOSART database was submitted to CHIA for linkage using the member eligibility file. CHIA matched and then extracted the APCD non-MassHealth medical claim records for the linked mothers and children and sent these de-identified data back to MDPH.

History of PCOS was categorized based on ICD9 and ICD10 codes reported to APCD (ICD9:256.4, ICD10: E28.2). Participants were categorized as having a history of PCOS if there was a date of service for the condition in APCD that was on or before their index delivery date.

Maternal, neonatal and infant outcomes

Maternal outcomes of interest included: gestational diabetes, gestational hypertension/preeclampsia/eclampsia, cesarean delivery and placental abnormalities. Data on gestational diabetes, hypertension during pregnancy including preeclampsia and eclampsia as well as placental abnormalities were identified in PELL from either the birth certificate, hospital discharge delivery record or pre-delivery (within 280 days before delivery) ICD9 and ICD10 codes (642.3–642.6, 642.9, O11, O13–O16 for pregnancy-related hypertension/preeclampsia/eclampsia; 648.8, O24.4, O24.9 for gestational diabetes; and 641.0–641.2, 663.5, 667.0, 762.1, O45, P02.1, O43.21, O44, O69.4 for placental abnormalities). Information on cesarean delivery was obtained from the birth certificate. Outcome diagnoses made in the outpatient setting were not available.

Neonatal outcomes investigated were large for gestational age, small for gestational age, low birthweight, prematurity and prolonged delivery hospital stay. Large and small for gestational age were defined as a *birthweight Z*-score above or below the 10th percentile, respectively and based on the SD score of the value for each individual from the mean value of the Massachusetts reference population divided by the SD for that reference population (Oken *et al.*, 2003). To calculate population-specific birthweight Z scores, we generated gender-, race/ethnicity- and gestation length-specific birthweight means and SDs using Massachusetts data for all live births from 1998 to 2017. Low birthweight was defined as <2500 g using information on birthweight from the birth certificate. The birth certificate provided information on length of gestation and was based on clinical estimates of first-trimester ultrasound or last menstrual period. Premature birth was defined as a gestational length of <37 weeks. Prolonged delivery hospital stay was defined as a hospital stay of >3 days for vaginal delivery or >5 days for cesarean delivery and was limited to deliveries in which gestational age was ≥ 35 weeks, and with known data on mode of delivery. Mode of delivery and gestational age were obtained from birth certificates and length of birth hospitalization was obtained from neonatal hospital discharge records.

We also investigated risk of infant conditions, including abnormalities of infectious disease, cardiovascular, respiratory, gastrointestinal/nutritional, neurologic and hematologic systems during the first year of life. These conditions were grouped by system based on ICD9 and ICD10 codes, as has been described in detail previously (Hwang *et al.*, 2018) and were restricted to live born infants in 2013–2016 to allow capture of conditions up to 1 year after birth. These diagnoses were identified from inpatient hospital stays (including hospital discharges, observational stays and Emergency Room visits) and did not include outpatient visits.

Subfertility, infertility and ART treatment

We classified deliveries into groups of non-infertile, subfertile/infertile or ART as these groupings have been informative on previous analyses conducted by our research group. Index deliveries were classified as having utilized ART if the delivery was linked to an ART cycle in the SART CORS database. Cycles in the SART CORS database include IVF and related techniques that involve manipulation of eggs and embryos. They do not include ovulation induction, intrauterine insemination or other less invasive techniques. Deliveries were classified as 'subfertile' if they met one of the following criteria: (i) indicated infertility treatment on the birth or fetal death certificate but no linkage to SART CORS in the index delivery, (ii) utilized an ICD code for infertility (ICD codes 628 and V230; ICD 10 O09.00–O09.03 and N97.0–N97.9) during a prior hospitalization or (iii) had a prior delivery with either an indication of infertility treatment or linkage to SART CORS. Deliveries were considered 'infertile' if the delivery had a prior APCD outpatient or inpatient claim with provider-confirmed diagnosis of infertility. Subfertile and infertile deliveries were combined for this analysis. The subfertile/infertile category excluded those with ART treatment to conceive the index pregnancy. Deliveries were classified as 'non-infertile' if they did not fall into any of the other categories (Declercq *et al.*, 2014).

Statistical analyses

The relative risks (RRs) and 95% CIs of adverse outcomes were estimated using generalized estimating equations with a log-link and a Poisson distribution to account for multiple deliveries by the same women. Multivariable models were *a priori* adjusted for maternal age (continuous), maternal BMI prior to pregnancy (<25, ≥ 25 kg/m^2, unknown), maternal race/ethnicity (non-Hispanic White, other race/ethnicity, unknown), maternal education (high school and/or some college, completed college, unknown), plurality of delivery (singleton, multiple), birth year (2013–2017 ordinal categorical calendar years), history of chronic maternal hypertension, history of chronic maternal diabetes and gestational age (continuous), where appropriate. Information on maternal covariates, including pre-pregnancy BMI, was obtained from the birth certificate. Information on chronic hypertension and diabetes prior to pregnancy was obtained from both the birth certificate and the hospital discharge records. In sensitivity analyses for the outcome, gestational diabetes, we excluded women with a history of pre-existing diabetes.

We investigated effect modification by BMI using two categorizations to be consistent with prior analyses (BMI <30 versus BMI ≥ 30 kg/m^2; and BMI <25 versus BMI ≥ 25 kg/m^2) and infertility history overall (non-infertile, subfertile/infertile, ART delivery) and comparing non-infertile to other groups by stratifying deliveries into categories. We performed tests for homogeneity by using generalized estimating equations score tests with type 3 estimates. We also restricted our analyses to primiparous deliveries. In accordance with guidelines from CHIA, we suppressed any counts that were <11. Analyses were performed in SAS/STAT software 14.3 (SAS Institute, Cary NC, USA). A statistical significance threshold of <0.05 was used.

Results

Our sample included 3552 deliveries to women with a history of PCOS and 88 273 deliveries to women without a diagnosis of PCOS (Table I). We observed no meaningful difference in age at delivery between women with and without a diagnosis of PCOS. Women with a history of PCOS were more likely to be overweight or obese prior to pregnancy (51.0% versus 35.5%) and to have used ART (20.8% versus 7.9%) or to experience subfertility or infertility (47.7% versus 13.3%). Women with a history of PCOS were less likely to have a history of two or more previous births (43.7% versus 51.4%).

In multivariable models adjusted for maternal age, pre-pregnancy BMI, maternal education, maternal race/ethnicity, plurality, birth year and history of hypertension and diabetes, women with a history of PCOS had a 51% greater risk of gestational diabetes (RR: 1.51, 95% CI: 1.38–1.65) compared to women without a diagnosis of PCOS (Table II). In sensitivity analyses excluding women with pre-existing diabetes, this association remained consistent (RR: 1.56, 95% CI: 1.43–1.71). We also observed that women with a history of PCOS were at greater risk of PIH, preeclampsia and eclampsia (RR: 1.25, 95% CI: 1.15–1.35), as well as higher risk of cesarean section (RR: 1.07, 95% CI: 1.02–1.11) compared to women never diagnosed with PCOS. We did not observe an association between PCOS and placental abnormalities.

Women with a history of PCOS were more likely to deliver prematurely (<37 weeks gestation) (RR: 1.17, 95% CI: 1.06–1.29) compared to women without a diagnosis of PCOS (Table II). Infants born to mothers with a history of PCOS were more likely to be low birthweight in crude models (RR: 1.49, 95% CI: 1.27–1.74). However, this association attenuated and was no longer statistically significant in adjusted models (RR: 1.07, 95% CI: 0.96–1.19), which was primarily driven by adjustment for history of hypertension and diabetes and adjustment for fertility groups. While the association between PCOS and low birthweight did not vary overall by fertility groups (Table III) (*P*-value 0.12), we did observe differences between fertile and ART groups when assessed separately (*P*-value, test for homogeneity: 0.03). Among ART pregnancies, PCOS was not associated with low birthweight (RR: 1.05, 95% CI: 0.88–1.24), while among fertile deliveries PCOS was associated with low birthweight (RR: 1.28, 95% CI: 1.01–1.61). We observed a more modest, association between history of PCOS and risk of having an infant that is small for gestational age (RR: 1.11, 95% CI: 0.99–1.25) that did not meet the threshold of statistical significance. We also observed that infants born to mothers with a history of PCOS were more likely to have a prolonged neonatal hospital stay (RR: 1.23, 95% CI: 1.09–1.40) and to be diagnosed with infectious disease conditions (RR: 1.40, 95% CI: 1.05–1.88) or respiratory conditions (RR: 1.09, 95% CI: 1.01–1.19) in multivariable models additionally adjusted for gestational age. When analyses were restricted to primiparous deliveries, the majority of findings remained consistent (Supplementary Table SI). The association with PCOS and risk of cesarean section attenuated and was no longer statistically significant (RR: 1.01, 95% CI: 0.95–1.07).

We observed that the association between PCOS and maternal morbidity varied by BMI (<30 versus ≥30 kg/m^2) for gestational diabetes (*P*-value, test for homogeneity: <0.01) (Table IV). Specifically, among women with a BMI <30 kg/m^2, PCOS was associated with a greater risk of gestational diabetes (RR: 1.60, 95% CI: 1.42–1.80), than among women with a BMI ≥30 kg/m^2 (gestational diabetes RR: 1.37, 95% CI: 1.21–1.57). When stratifying by BMI <25 versus ≥25 kg/m^2, we observed that the risk of PIH/eclampsia/preeclampsia varied by BMI (Supplementary Table SII). Among women with a BMI ≥25 kg/m^2, PCOS diagnosis was associated with a 35% greater risk of PIH/eclampsia/preeclampsia (95% CI: 1.23–1.48), while among women with a BMI <25, we observed no association between PCOS and PIH/eclampsia/preeclampsia (RR: 1.04, 95% CI: 0.88–1.24).

The association between history of PCOS and risk of maternal and neonatal outcomes did not vary within each fertility group (Table III).

Discussion

Overall, we observed that women with a history of PCOS were more likely to experience gestational diabetes, PIH/eclampsia/preeclampsia and cesarean delivery. Neonates born to women with history of PCOS were more likely to be born premature, and require a prolonged neonatal hospital stay. Infants born to women with a history of PCOS were more likely to experience infectious disease conditions or respiratory conditions. The association between PCOS and gestational diabetes was strongest among women with a pre-pregnancy BMI <30 kg/m^2. We did not observe any statistically significant effect modification in the association between PCOS and adverse pregnancy outcomes by fertility groups.

Insulin resistance and hyperinsulinemia are intrinsic in the pathophysiology of PCOS (Palomba *et al.*, 2015) and occur independently of obesity (Stepto *et al.*, 2013). Our findings are in agreement with previous research which found that women with PCOS are at a 2- to 4-fold increased risk of gestational diabetes during pregnancy (Kjerulff *et al.*, 2011; Qin *et al.*, 2013; Bahri Khomami *et al.*, 2019; by Mills *et al.*, 2020b). Our observed effect estimate is more modest (RR: 1.51) and closer to the effect size in a recently published population-based cohort study by Mills *et al.* (2020b) (RR: 2.19). Both analyses were able to adjust for important confounding factors (Correia *et al.*, 2020), such as pre-pregnancy BMI, hypertension and diabetes, which may contribute to lower adjusted effect estimates. In analyses stratified by BMI, we observed that the association between PCOS and gestational diabetes was stronger among women with a pre-pregnancy BMI <30 kg/m^2 (RR: 1.60). However, among women with a pre-pregnancy BMI ≥30 kg/m^2 we still observed a statistically significant, yet more modest association (RR: 1.37). Similarly, prior meta-analyses have observed stronger associations among women with a BMI <30 kg/m^2 (meta-analysis odds ratio (OR): 3.25) compared to women with a BMI ≥30 kg/m^2 (meta-analysis OR: 1.43) (Bahri Khomami *et al.*, 2019), suggesting that the influence of PCOS diagnosis on gestational diabetes risk is less among women with BMI ≥30 kg/m^2 who may have other competing factors influencing risk. The individual and combined influence of BMI synergistic with insulin resistance on pregnancy outcomes is an important topic for continued research.

We observed that women with PCOS had a modest increased risk of hypertensive disorders of pregnancy (RR: 1.25), consistent with prior meta-analyses (Kjerulff *et al.*, 2011; Qin *et al.*, 2013; Yu *et al.*, 2016; Bahri Khomami *et al.*, 2019) and recent studies (Mills *et al.*, 2020b). We observed that the association with hypertensive disorders varied by pre-pregnancy BMI when 25 kg/m^2 was used as the categorization (*P*-value, test for homogeneity: <0.05; Supplementary Table

Table I Characteristics of study sample deliveries to women aged ≥18 between 1 October 2013 and 31 December 2017.

	No diagnosis of PCOS		Diagnosis of PCOS	
	n	%	n	%
Total	88 273	100.0	3552	100.0
Maternal age (years)				
Range	18–56		18–50	
Mean (SD)	33.11 (4.12)		33.23 (3.80)	
18–29	15 613	17.7	522	14.7
30–34	41 511	47.0	1778	50.1
35–37	18 782	21.3	764	21.5
38–40	8917	10.1	379	10.7
>40	3450	3.9	109	3.1
Race/Ethnicity				
Hispanic	4085	4.6	173	4.9
Non-Hispanic White	66 535	75.4	2678	75.4
Non-Hispanic Black	2967	3.4	118	3.3
Non-Hispanic Asian	12 594	14.3	492	13.9
Other non-Hispanic	386	0.4	10	0.3
Unknown	1706	1.9	81	2.3
BMI (kg/m^2)				
<22.5	33 916	38.4	986	27.8
22.5 to <25.0	20 274	23.0	648	18.2
25.0 to <30.0	19 580	22.2	834	23.5
30.0+	11 746	13.3	978	27.5
Unknown	2757	3.1	106	3.0
Highest level of education				
<HS/HS graduate	2871	3.3	106	3.0
Some college	10 760	12.2	443	12.5
College graduate	72 637	82.3	2897	81.6
Unknown	2005	2.3	106	3.0
Health insurance at delivery				
Private	78 541	89.0	3159	88.9
Public/Free Care	4318	4.9	138	3.9
Self-pay	5363	6.1	249	7.0
Unknown	51	0.1	6	0.2
Gravidity[a]				
1	34 131	38.7	1508	42.5
2	29 409	33.3	1138	32.0
3–18	24 378	27.6	891	25.1
Unknown	355	0.4	15	0.4
Parity				
1	42 811	48.5	1997	56.2
2	32 737	37.1	1215	34.2
3–15	12 624	14.3	338	9.5
Unknown	101	0.1	2	0.1
Plurality				
Singletons	86 199	97.7	3404	95.8
Multiples	2074	2.3	148	4.2
Fertility group				
ART	6949	7.9	740	20.8
Subfertile/infertile	11 736	13.3	1696	47.7
Non-infertile	69 588	78.8	1116	31.4
Year of birth				
2013	5547	6.3	84	2.4
2014	21 983	24.9	526	14.8
2015	21 379	24.2	799	22.5
2016	20 382	23.1	1059	29.8
2017	18 982	21.5	1084	30.5

PCOS, polycystic ovary syndrome; HS, high school.
[a]No gravidity data from fetal deaths.

SII), but not when 30 kg/m^2 was used (*P*-value, test for homogeneity: 0.74; Table IV). Women with a pre-pregnancy BMI ≥25 kg/m^2 had a greater risk (RR: 1.35) than women with a lower pre-pregnancy BMI (RR: 1.04). PCOS is associated with metabolic syndrome (Palomba *et al.*, 2015; Bahri Khomami *et al.*, 2019), which may increase the risk of hypertensive disorders during pregnancy.

We observed no association between history of PCOS and placental abnormalities, which is in contrast with one published study which observed an increased risk of placental abruption among women with PCOS (OR: 1.63) (Mills *et al.*, 2020a). Women with PCOS have been hypothesized to have problems with placentation that may lead to negative downstream pregnancy outcomes (Palomba *et al.*, 2015). Future research is needed to understand whether PCOS has any influence on placental abnormalities as well as normal placental function.

Among neonatal outcomes, we observed that women with a history of PCOS had a 20% increased risk of low birthweight among full-term deliveries and an 11% increased risk of small for gestational age. We also observed that women with a history of PCOS had an increased risk of preterm delivery (RR: 1.17). Elevated risk of small for gestational age has been observed in some (Kjerulff *et al.*, 2011; Yu *et al.*, 2016; Foroozanfard *et al.*, 2020) but not all analyses (Boomsma *et al.*, 2006; Mills *et al.*, 2020a). These differences may be influenced by plurality and adjustment for potential confounding factors. Preterm delivery has been shown to be associated with PCOS history in most recent studies and meta-analyses (Boomsma *et al.*, 2006; Kjerulff *et al.*, 2011; Qin *et al.*, 2013; Naver *et al.*, 2014; Mills *et al.*, 2020a; Valgeirsdottir *et al.*, 2021). Again, our findings are of a smaller magnitude of effect (RR: 1.17) compared to previous reports from meta-analyses (ORs range: 2.20–1.75) (Boomsma *et al.*, 2006; Kjerulff *et al.*, 2011; Qin *et al.*, 2013) but similar in magnitude to a recently published

Table II Association between history of polycystic ovary syndrome (PCOS) prior to delivery and adverse pregnancy outcomes among deliveries to women in study sample aged ≥18 between 1 October 2013 and 31 December 2017.

	No diagnosis of PCOS		Diagnosis of PCOS		Relative risk (95% CI)[1]	
	n	%	n	%	Crude	Adjusted[2]
Total deliveries	88 273	100.0	3552	100.0		
Maternal outcomes						
Gestational diabetes	6690	7.6	490	13.8	1.85 (1.70–2.02)	1.51 (1.38–1.65)
PIH/eclampsia/preeclampsia	9077	10.3	576	16.2	1.57 (1.45–1.70)	1.25 (1.15–1.35)
Caesarean section[3]	28 084	31.8	1273	35.8	1.14 (1.10–1.20)	1.07 (1.02–1.11)
Placental abnormalities	2521	2.9	102	2.9	1.01 (0.83–1.22)	1.06 (0.87–1.28)
Infant outcomes						
Total infants	90 373	100.0	3704	100.0		
Total live births	90 129	99.7	3690	100.0		
Large for gestational age[4]	8251	9.4	350	9.7	1.05 (0.95–1.17)	0.97 (0.87–1.07)
Small for gestational age[4]	6337	7.2	291	8.1	1.10 (0.98–1.24)	1.11 (0.99–1.25)
Low birthweight (<2500 g)[5]	5800	6.4	378	10.2	1.49 (1.27–1.74)	1.07 (0.96–1.19)
Low birthweight (<2500 g)[5] full-term only	1670	2.0	100	3.1	1.53 (1.24–1.88)	1.20 (0.97–1.47)
Preterm birth (<37 weeks)	6880	7.7	435	11.9	1.14 (0.65–2.01)	1.17 (1.06–1.29)
Neonatal prolonged hospital stay[4,6,7]	3762	4.3	232	6.7	1.52 (1.32–1.74)	1.23 (1.09–1.40)
Neonatal conditions						
Infectious disease conditions[7,8]	815	1.2	56	2.2	1.89 (1.44–2.49)	1.40 (1.05–1.88)
Cardiovascular conditions[7,8]	1534	2.2	81	3.1	1.43 (1.14–1.80)	1.17 (0.93–1.46)
Respiratory conditions[7,8]	11 688	16.5	536	20.8	1.26 (1.17–1.37)	1.09 (1.01–1.19)
Gastrointestinal/nutritional conditions[7,8]	4448	6.3	247	9.6	1.53 (1.34–1.76)	1.13 (0.96–1.32)
Neurologic conditions[7,8]	2836	4.0	127	4.9	1.23 (1.03–1.46)	1.14 (0.95–1.36)
Hematologic conditions[7,8]	9751	13.8	486	18.9	1.39 (1.28–1.52)	1.01 (0.93–1.10)

[1]Crude and adjusted relative risk approximated using general estimating equations with a log link and Poisson distribution to take into account multiple deliveries by the same women.
[2]Multivariate models adjusted for maternal age (continuous), BMI (<25.0, 25.0+, unknown), race (non-Hispanic White, other race/ethnicity, unknown), education (high school + some college, completed college, unknown), plurality (singleton, multiples), birth year (2013–2017 ordinal categorical variable) and history of hypertension or diabetes.
[3]Excluding those with unknown mode of delivery.
[4]Limited to live births only.
[5]Multivariable model additionally adjusted for fertility treatment.
[6]Limited analysis to those whose gestational age ≥35 weeks, with known data on mode of delivery and birth hospital records. Prolonged stay defined as >3 days for vaginal delivery or >5 days for C-section.
[7]Relative risk additionally adjusted for gestational age (continuous variable, range 17–44), excluding those with unknown GA.
[8]Limited to live births 1 October 2013–31 December 2016 (to allow 1-year follow-up).
PIH, pregnancy-induced hypertension.

large, retrospective analysis using administrative claims data (RR: 1.37) (Mills *et al.*, 2020a). Future work should focus on disentangling whether the consistently observed association between PCOS and preterm birth is driven by spontaneous or medically indicated preterm birth.

We observed that infants born to women with a history of PCOS had a 29% greater risk for prolonged neonatal delivery hospital stay, defined as >3 days for vaginal deliveries and >5 days for cesarean section, compared to infants born to women without a history of PCOS. Prior research has suggested that neonates born to women with a history of PCOS are more likely to be admitted to the neonatal intensive care unit and have a lower Apgar score following delivery (Palomba *et al.*, 2015).

When we investigated infant health conditions associated with PCOS we observed that liveborn infants born to mothers with a history of PCOS were more likely to be diagnosed with respiratory conditions or infectious conditions within the first year of life. A recent meta-analysis reported that babies born to people with PCOS were 24% more likely to have respiratory distress than those born to people without PCOS, but this finding did not reach statistical significance (95% CI: 0.80–1.93) and only included four studies. There is also research suggesting that children born to women with PCOS may have a higher risk for asthma later in life (Doherty *et al.*, 2015). Recent research has suggested that women with PCOS are more likely to develop maternal infections (Koster *et al.*, 2015; Mills *et al.*, 2020a); however, there has been limited research on childhood infectious disease outcomes. Future research should focus on understanding early life outcomes for children born to mothers with PCOS.

While this study has many strengths including its large sample size and ability to control for several potential confounding factors, there are also important limitations that must be considered. PCOS can be challenging to diagnose, with varying criteria necessary for diagnosis,

Table III Association between history of polycystic ovary syndrome (PCOS) and adverse pregnancy outcomes among deliveries by study sample women aged ≥18 between 1 October 2013 and 31 December 2017, stratified by history of subfertility/infertility treatment.

	No diagnosis of PCOS		Diagnosis of PCOS		Adjusted relative risk (95% CI)[1]	*P*-value test for homogeneity[2]
	n	%	n	%		
Gestational diabetes						
Non-infertile	5001	7.2	135	12.1	1.37 (1.17–1.61)	0.51
Subfertility/infertility	1005	8.6	235	13.9	1.54 (1.34–1.76)	
ART	684	9.8	120	16.2	1.42 (1.17–1.72)	
PIH/eclampsia/preeclampsia						
Non-infertile	6707	9.6	168	15.1	1.27 (1.10–1.47)	0.24
Subfertility/infertility	1272	10.8	236	13.9	1.13 (0.99–1.28)	
ART	1098	15.8	172	23.2	1.25 (1.08–1.46)	
Cesarean section[3]						
Non-infertile	20 395	29.3	363	32.5	1.07 (0.99–1.16)	0.16
Subfertility/infertility	4307	36.7	575	33.9	0.96 (0.90–1.03)	
ART	3382	48.7	335	45.3	0.98 (0.90–1.06)	
Small for gestational age[4]						
Non-infertile	4715	6.8	81	7.4	1.11 (0.89–1.39)	0.52
Subfertility/infertility	894	7.6	141	8.3	1.11 (0.93–1.32)	
ART	728	9.5	69	8.7	1.00 (0.78–1.28)	
Large for gestational age[4]						
Non-infertile	6470	9.3	107	9.8	0.93 (0.78–1.12)	0.66
Subfertility/infertility	1149	9.8	176	10.3	1.01 (0.86–1.17)	
ART	632	8.3	67	8.4	0.90 (0.70–1.15)	
Low birthweight (<2500 g)						
Non-infertile	3489	5.0	72	6.4	1.28 (1.01–1.61)	0.12
Subfertility/infertility	958	7.9	167	9.5	1.14 (0.97–1.33)	
ART	1353	17.2	139	16.9	1.05 (0.88–1.24)	
Preterm birth (<37 weeks)						
Non-infertile	4179	6.0	83	7.4	1.21 (0.97–1.52)	0.29
Subfertility/infertility	1135	9.5	184	10.6	1.04 (0.89–1.21)	
ART	1566	20.1	168	20.6	1.11 (0.94–1.30)	
Neonatal prolonged hospital stay[4,5]						
Non-infertile	2582	3.8	59	5.5	1.25 (0.99–1.59)	0.52
Subfertility/infertility	535	4.7	98	5.9	1.20 (0.98–1.46)	
ART	645	9.1	75	10.2	1.11 (0.88–1.41)	

[1]Crude and adjusted relative risk approximated using general estimating equations with a log link and Poisson distribution to take into account multiple deliveries by the same women; multivariate models adjusted for maternal age (continuous), BMI (<25.0, 25.0+, unknown), race (non-Hispanic White, other race/ethnicity, unknown), education (high school + some college, completed college, unknown), plurality (singleton, multiples), birth year (2013–2017 ordinal categorical variable) and history of hypertension or diabetes.
[2]Based on generalized estimating equations type 3 estimates.
[3]Excluding those with unknown mode of delivery.
[4]Limited to live births only.
[5]Limited analysis to those whose gestational age ≥35 weeks, with known data on mode of delivery and birth hospital records.
PIH, pregnancy-induced hypertension.

leaving the possibility of misdiagnosis of those defined as having PCOS. It is also likely that there are undiagnosed women erroneously included in our unexposed group who do have a history of PCOS. This underdiagnosis may be increased by our reliance on ICD codes for PCOS diagnosis, and therefore our data may miss any clinical documentation of PCOS that did not include an ICD billing code before delivery. This underdiagnosis may explain the relatively low prevalence of history of PCOS (4%) observed in this general population sample. Additionally, our data set is inherently restricted to women with PCOS who gave birth following their PCOS diagnosis. Therefore, we may expect the prevalence of PCOS among this sample to be lower than the general population prevalence of PCOS given the restriction

Table IV Association between history of polycystic ovary syndrome (PCOS) and adverse pregnancy outcomes among deliveries in study sample women aged ≥18 between 1 October 2013 and 31 December 2017, stratified by BMI.*

	No diagnosis of PCOS		Diagnosis of PCOS		Adjusted relative risk (95% CI)[1]	*P*-value test for homogeneity[2]
	n	%	n	%		
Gestational diabetes						
BMI < 30	4657	6.3	259	10.5	1.60 (1.42–1.80)	<0.01
BMI ≥ 30	1802	15.3	213	21.8	1.37 (1.21–1.57)	
PIH/eclampsia/preeclampsia						
BMI < 30	6317	8.6	274	11.1	1.16 (1.03–1.31)	0.74
BMI ≥ 30	2458	20.9	282	28.8	1.30 (1.17–1.44)	
Cesarean section[3]						
BMI < 30	21 908	29.7	762	30.9	1.05 (0.99–1.11)	0.96
BMI ≥ 30	5289	45.0	465	47.5	1.04 (0.99–1.11)	
Small for gestational age[4]						
BMI < 30	5474	7.4	233	9.3	1.14 (1.00–1.30)	0.28
BMI ≥ 30	725	6.1	62	6.3	0.96 (0.74–1.24)	
Large for gestational age[4]						
BMI < 30	6237	8.4	193	7.7	0.93 (0.81–1.07)	0.75
BMI ≥ 30	1729	14.7	134	13.6	0.94 (0.79–1.11)	
Low birthweight (<2500 g)						
BMI < 30	4708	6.2	262	10.2	1.22 (1.08–1.38)	0.32
BMI ≥ 30	833	6.9	105	10.3	1.15 (0.93–1.43)	
Preterm birth (<37 weeks)						
BMI < 30	5570	7.4	299	11.7	1.22 (1.08–1.37)	0.15
BMI ≥ 30	1077	9.0	123	12.2	1.11 (0.91–1.35)	
Neonatal prolonged hospital stay[4,5]						
BMI < 30	3078	4.2	152	6.2	1.13 (0.97–1.31)	0.63
BMI ≥ 30	570	5.0	72	7.6	1.30 (1.04–1.64)	

*Analyses are limited to those with known BMI.
[1]Crude and adjusted relative risk approximated using general estimating equations with a log link and Poisson distribution to take into account multiple deliveries by the same women; multivariate models adjusted for maternal age (continuous), race (non-Hispanic White, other race/ethnicity, unknown), education (high school + some college, completed college, unknown), plurality (singleton, multiples), birth year (2013–2017 ordinal categorical variable) and history of hypertension or diabetes.
[2]Based on generalized estimating equations type 3 estimates.
[3]Excluding those with unknown mode of delivery.
[4]Limited to live births only.
[5]Limited analysis to those whose gestational age ≥35 weeks, with known data on mode of delivery and birth hospital records.
PIH, pregnancy-induced hypertension.

to women of reproductive age and further exclusion of those whose PCOS diagnosis occurred after their index delivery. We would expect any misclassification of our PCOS phenotype to attenuate toward the null for any reported associations in our analysis, suggesting that our findings would be underestimates and not overestimates of the true associations between PCOS and adverse pregnancy outcomes. We were also unable to include data for anyone who had MA Health (Medicaid) during the study period although women both with and without PCOS would have been part of that study population. Given the nature of the linked data in our analysis, people who delivered outside of Massachusetts or who received a PCOS diagnosis outside of Massachusetts may not have been accurately captured in our data. However, we would expect this misclassification to attenuate any reported findings. Our analysis was not able to incorporate information on details related to the PCOS diagnosis, such as phenotype, which has led to heterogeneous findings in previous analyses (Bahri Khomami *et al.*, 2019). Another limitation is that these data come from a single state in the USA and may not reflect conditions found in other states or countries. While we were able to adjust for important confounders such as pre-existing diabetes, hypertension and maternal BMI we do not have information on other important covariates such as gestational weight gain.

In summary, we observed that ~4% of deliveries in our sample of women with deliveries were to those who had a previous diagnosis of PCOS. While our ability to capture PCOS diagnoses using our linked data source is a considerable strength compared to prior research, this may also be an underestimate of the true disease prevalence, as discussed in detail in the study's limitations. We observed that women with PCOS were at increased risk of gestational diabetes, hypertensive disorders of pregnancy and cesarean section. Additionally, neonates

born to women with a history of PCOS were at increased risk of low birthweight status among full-term deliveries, small for gestational age, preterm birth, prolonged neonatal hospital stay and infectious and respiratory conditions within the first year of life. Prior consensus documents have recognized that women with PCOS may be at increased risk of adverse pregnancy and neonatal outcomes (Fauser *et al.*, 2012; Teede *et al.*, 2018) and the 2018 'Recommendations from the international evidence-based guideline for the assessment and management of PCOS' recommends increased monitoring for women with PCOS during pregnancy given increased risk of adverse offspring outcomes (Teede *et al.*, 2018). Pregnant women should discuss their gynecologic history with their providers and may benefit from additional screening and/or early intervention.

Supplementary data

Supplementary data are available at *Human Reproduction* online.

Data availability

Due to restrictions on release of vital records data by the Massachusetts Department of Public Health we are unable to provide our dataset.

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Authors' roles

L.V.F., S.A.M. and J.E.S. conceived, designed and supervised the study. C.L.-L. and H.J.C. performed and oversaw the statistical analysis. L.V.F., J.E.S., C.L.-L., H.J.C., C.C.C., H.D., D.D., S.H. and S.A.M. drafted and critically reviewed the manuscript and approved the final version.

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Conflict of interest

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