


ORIGINAL RESEARCH

Polycystic ovary syndrome and gestational diabetes mellitus association to pregnancy outcomes: A national register-based cohort study

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Abstract

Introduction: It is well known that both women with polycystic ovary syndrome (PCOS) and women with gestational diabetes mellitus (GDM) have increased risks of adverse pregnancy outcomes, but little is known whether the combination of these two conditions exacerbates the risks. We explored risk estimates for adverse pregnancy outcomes in women with either PCOS or GDM and the combination of both PCOS and GDM.

Material and Methods: Nationwide register-based historical cohort study in Sweden including women who gave birth to singleton infants during 1997–2015 ($N = 281\,806$). The risks of adverse pregnancy outcomes were estimated for women exposed for PCOS-only ($n = 40\,272$), GDM-only ($n = 2236$), both PCOS and GDM ($n = 1036$) using multivariable logistic regression analyses. Risks were expressed as odds ratios with 95% confidence intervals (CIs) and adjusted for maternal characteristics, including maternal BMI. Women with neither PCOS nor GDM served as control group. Maternal outcomes were gestational hypertension, preeclampsia, postpartum hemorrhage, and obstetric anal sphincter injury. Neonatal outcomes were preterm birth, stillbirth, shoulder dystocia, born small or large for gestational age, macrosomia, low Apgar score, infant birth trauma, cerebral impact of the infant, neonatal hypoglycemia, meconium aspiration syndrome and respiratory distress.

Results: Based on non-significant PCOS by GDM interaction analyses, we found no evidence that having PCOS adds any extra risk beyond that of having GDM for maternal and neonatal outcomes. For example, the adjusted odds ratio for preeclampsia in women with PCOS-only were 1.18 (95% CI 1.11–1.26), for GDM-only 1.77 (95% CI 1.45–2.15), and for women with PCOS and GDM 1.86 (95% CI 1.46–2.36).

Abbreviations: aOR, adjusted odds ratio; ART, assisted reproductive technology; BMI, body mass index; CI confidence interval; GDM, gestational diabetes mellitus; LGA, large for gestational age; OGTT, oral glucose tolerance test; OR, odds ratio; PCOS, polycystic ovary syndrome; SGA, small for gestational age.

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Corresponding adjusted odds ratio for preterm birth in women with PCOS-only were 1.34 (95% CI 1.28–1.41), GDM-only 1.64 (95% CI 1.39–1.93), and for women with PCOS and GDM 2.08 (95% CI 1.67–2.58). Women with PCOS had an increased risk of stillbirth compared with the control group (aOR 1.52, 95% CI 1.29–1.80), whereas no increased risk was noted in women with GDM (aOR 0.58, 95% CI 0.24–1.39).

Conclusions: The combination of PCOS and GDM adds no extra risk beyond that of having GDM alone, for a number of maternal and neonatal outcomes. Nevertheless, PCOS is still an unrecognized risk factor in pregnancy, exemplified by the increased risk of stillbirth.

KEYWORDS

gestational diabetes, neonatal outcomes, polycystic ovary syndrome, preeclampsia, pregnancy complications, preterm birth, stillbirth

1 | INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women, with a prevalence of 10%–13%.^{1,2} The symptoms of PCOS vary but commonly include irregular menstrual cycles, hirsutism and acne.² The majority of women with PCOS are overweight or obese and have difficulty losing weight.^{2,3} Women with PCOS have a long-term increased risk of type 2 diabetes mellitus, hypertension, cardiovascular disease, sleep apnoea and endometrial cancer.^{2,7} Infertility is common among women with PCOS due to ovulatory dysfunction but the prognosis for childbirth is overall good.^{2,6,8,9} Women with PCOS have an increased risk of adverse outcomes during pregnancy, particularly gestational diabetes, gestational hypertension, preeclampsia, preterm delivery and infants born small for gestational age (SGA).^{3,7}

Gestational diabetes mellitus (GDM) is the most frequent pregnancy complication in women with PCOS, with a two- to threefold risk compared to non-PCOS women, independent of BMI.^{2,3,5,10} GDM is defined as impaired glucose tolerance first diagnosed during pregnancy.¹¹ The prevalence of GDM is increasing due to increased obesity and is estimated globally to be 14%, varying between 1% and 28% depending on ethnicity, screening methods and diagnostic criteria.^{12,13} GDM is associated with adverse pregnancy outcomes for both the mother and the infant, such as preeclampsia, preterm birth, shoulder dystocia, macrosomia, large for gestational age (LGA) infant and neonatal hypoglycaemia.^{11,12,14}

Both women with PCOS and women with GDM have an increased risk of adverse pregnancy outcomes but little is known whether the combination of these two conditions exacerbates the risks for mothers and infants. Thus, this study aims to investigate pregnancy and neonatal outcomes among women with either PCOS-only, GDM-only or the combination of PCOS and GDM and estimate the risks.

Key message

Women with PCOS have increased risk of a number of adverse maternal and neonatal outcomes, but having the combination of PCOS and GDM does not exacerbate the risk associated with GDM.

2 | MATERIAL AND METHODS

2.1 | Data sources

This study obtained data from five Swedish national registries linked through unique personal identity number.¹⁵ The Swedish National Board of Health and Welfare provided information on the National Patient Register, the Medical Birth Register and the Prescribed Drug Register. Statistics Sweden supplied information on the Education Register and the Total Population Register. The National Patient Register contains data on diagnoses and dates of in-patient hospital visits since 1964 and specialized outpatient visits, including visits to a gynecologist or reproductive specialist, since 2001. Diagnoses are classified according to the International Statistical Classification of Diseases and Related Health Problems, version 10 (ICD-10), since 1997.¹⁶ In addition, the Medical Birth Register covers over 98% of births in Sweden since 1973. It includes information on women's reproductive history and complications during pregnancy, delivery and the neonatal period (classified by ICD-codes when applicable).¹⁷

The Swedish Prescribed Drug Register contains data on drug prescriptions, including Anatomic Therapeutic Chemical (ATC) classification codes, daily doses and dates of filled prescriptions of drugs since 1 July 2005.¹⁸ The Education Register provides information on the highest completed level of education since 1985, while the Total

Population Register provides details on country of birth and residential municipality.¹⁹

2.2 | Study population and exposure

The study population consisted of women born between 1950 and 1999. For each woman with PCOS, five non-PCOS women, matched for age and geographic area at the time of PCOS diagnosis, were randomly selected as controls. Out of these, women with a singleton delivery after 22 completed gestational weeks and registered in the Medical Birth Register between the years 1997 and 2015 were included in the study population.

The PCOS group consisted of women with the diagnoses PCOS (E28.2), androgen excess from the ovary (E28.1) and anovulatory infertility (N97.0) in the National Patient Register between 1997 and 2017. Since PCOS is a chronic condition, and thus, the assumption was made that women with PCOS had their condition already at the start of the study period, that is, independently of whether they were diagnosed before or after their pregnancies.³ We included anovulatory infertility among the PCOS diagnoses since PCOS accounts for approximately 80%–95% of infertility cases due to anovulation.^{20,21} During the first years of the study period, PCOS was diagnosed according to the National Institutes of Health (NIH) criteria, which require the presence of clinical or biochemical hyperandrogenism and chronic oligo- or anovulation.²² From 2003 and onwards, most clinicians used the Rotterdam criteria, which added polycystic ovary morphology on ultrasound as an additional criterion. According to the Rotterdam criteria, two out of three of the following criteria must be fulfilled: polycystic ovary morphology, oligo- or anovulation or hyperandrogenism, either clinical or biochemical.⁴ We excluded all women diagnosed with hyperprolactinemia, primary ovarian insufficiency or congenital adrenal hyperplasia. Further, as PCOS is underdiagnosed and may be hidden among the non-PCOS women, we excluded women with pregnancies achieved by ovarian stimulation from the non-PCOS group.

Diabetes mellitus was identified by ICD-10 diagnoses given at discharge from the hospital after delivery. The study population was categorized as diagnosed with GDM, pre-gestational diabetes (diabetes mellitus type 1 or 2) and no diabetic disease (Supporting Information Table S1). Women with pre-gestational diabetes were excluded from the study population. During the study period the decision to screen for GDM, in most regions in Sweden, was based on known risk factors and a random capillary blood glucose ≥ 8 mmol/L or plasma glucose ≥ 9 mmol/L. Diagnosis of GDM was based on the result of a 75 g oral glucose tolerance test (OGTT) among those screened. No national consensus regarding GDM screening and diagnosing was in place in Sweden during the study period, resulting in varying cut-off values across regions within the country. The main diagnostic criteria for GDM during the study period were fasting venous plasma ≥ 7.0 mmol/L and a 2 h cut-off value after OGTT ≥ 10.0 mmol/L.^{23,24}

The final study population included 158 638 women with 281 806 singleton births. Participants could be included in the study

population several times if they had delivered more than once during the study period. Women were categorized as having PCOS-only, GDM-only and the combination of PCOS and GDM. The flow chart of the study population is presented in Figure 1.

2.3 | Outcomes

Maternal and neonatal outcomes were extracted from the Medical Birth Register and identified according to ICD-10 diagnosis (Table S1).

Maternal outcomes assessed were gestational hypertension, preeclampsia, postpartum hemorrhage and obstetric anal sphincter injury. Gestational hypertension was defined as newly onset hypertension (systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg measured at two subsequent occasions at least 4 h apart) after 20 weeks of gestation. Preeclampsia was defined as new onset hypertension and proteinuria (≥ 300 mg/24 h), superimposed preeclampsia and eclampsia were included as preeclampsia. Postpartum hemorrhage was defined as bleeding exceeding 1000 mL. Obstetrical anal sphincter injury included third- and fourth-degree perineal lacerations.

Neonatal outcomes explored were preterm birth, stillbirth, shoulder dystocia, SGA, LGA, macrosomia, Apgar score < 7 at 5 min, infant birth trauma, cerebral impact of the infant, neonatal hypoglycemia, meconium aspiration syndrome and infant respiratory distress. Preterm birth was defined as delivery before 37 completed gestational weeks. Spontaneous preterm birth was defined as a preterm birth with a spontaneous onset of labor, including spontaneous premature rupture of membranes. Stillbirth was defined as fetal death before or during labor (after 28 completed weeks prior to July 2008 and after 22 weeks onwards). SGA and LGA were defined as infants with birthweight above or below two standard deviations (± 2 SD) from the mean weight for gestational age and sex according to the Swedish intrauterine growth reference range.²⁵ Macrosomia was defined as birthweight ≥ 4500 g. Apgar score is registered at 1, 5 and 10 min after birth, among which we chose to report on Apgar score < 7 at 5 min. Neonatal hypoglycemia was defined as blood glucose < 2.6 mmol/L at least 3 h after birth and identified by ICD-10 codes. Infant birth trauma was defined as injury to the skeleton, peripheral and central nervous system and retinal hemorrhage. Cerebral impact of the infant included any of the following diagnoses: Intracranial lacerations and hemorrhage, intrauterine hypoxia, convulsions, other disturbances of cerebral status and hypoxic ischemic encephalopathy (Table S1).

2.4 | Covariates

The following covariates were collected from the Medical Birth Register: Maternal age, maternal weight, height, involuntary childlessness before the present pregnancy, assisted reproductive technology (ART) treatment, cigarette smoking during pregnancy and year of delivery.

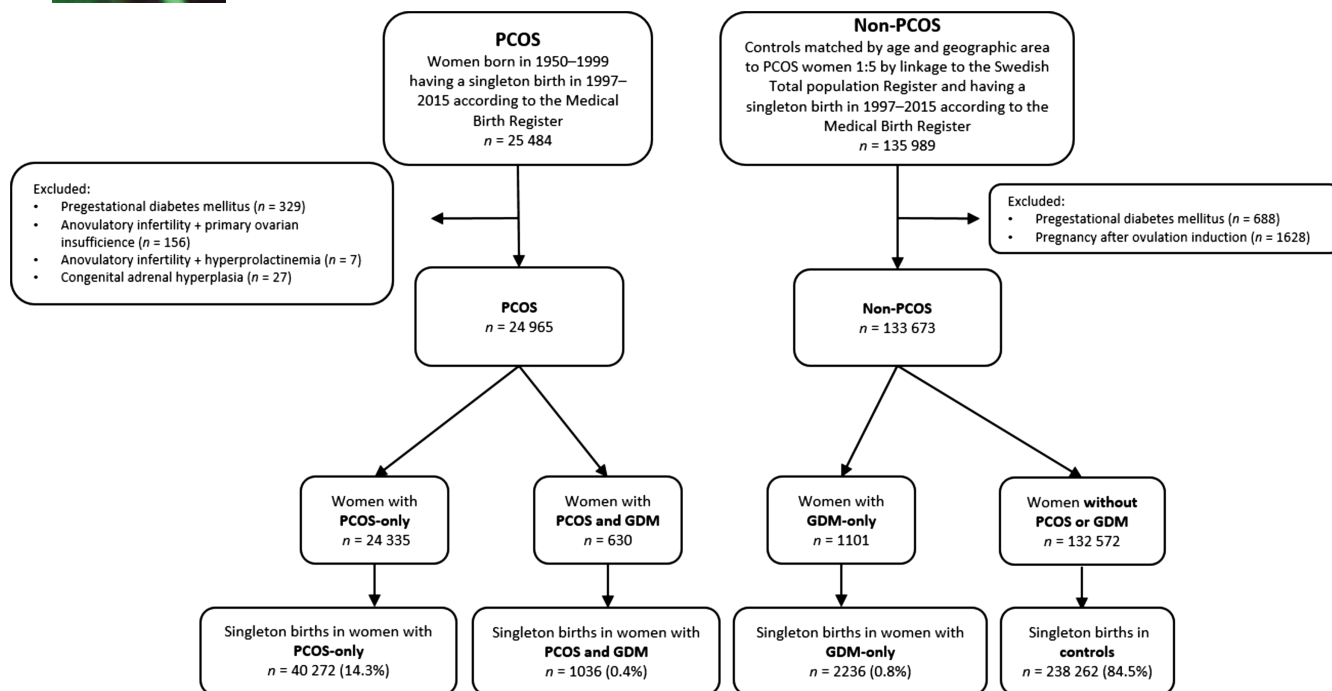


FIGURE 1 Flow chart of the study population. PCOS, Polycystic ovary syndrome defined as a diagnosis of PCOS, hyperandrogenism of ovarian origin or anovulatory infertility in the Patient register 1997–2017. GDM, Gestational diabetes mellitus.

Maternal age was recorded at the time of delivery. Maternal weight and height were recorded at the first antenatal visit (usually gestational week 7–10) and were either measured or self-reported. Early pregnancy maternal body mass index (BMI) was calculated using the equation weight (kg) / height (m)². Cigarette smoking during pregnancy was self-reported at the time of the first antenatal visit and/or at gestational week 30–32. Involuntary childlessness and conception through ovulation induction or ART treatment were self-reported and recorded in checkboxes by midwives.

Information on country of birth and years of formal education was collected from the Total Population Register and the Education Register, respectively.

Metformin use was identified by the ATC code A10BA02 after linkage to the Prescribed Drug Register and defined as at least two filled prescriptions within 3 months before conception and through the first trimester.

The covariates were categorized as presented in [Table 1](#).

2.5 | Statistical analyses

Multivariable logistic regression analysis was used to estimate the association between exposure and maternal and neonatal outcomes. Crude and adjusted odds ratios (OR and aOR) with 95% confidence intervals (CIs) were calculated using the generalized estimation equation method as observations were not independent in women giving birth more than once during the study period. Confounders were identified by a directed acyclic graph (DAG) which was constructed to obtain a systematic representation of

a possible causal relationship between exposure and outcome. Adjustments were calculated in two steps, first with the following confounders: maternal age, parity, educational level and country of birth (Adjusted Model 1), and in a second step, BMI was added to the model (Adjusted Model 2). Maternal BMI can both be considered as a confounder and a mediator in the association between PCOS and pregnancy outcomes. In the statistical models, covariates were included as continuous variables, where possible. Pregnancies with missing data on the chosen covariates were excluded from the multivariable analyses. In addition to the additive model (PCOS-only, GDM-only and PCOS + GDM) we also entered an interaction variable PCOS-only * GDM-only. A sensitivity analyses was performed for the outcome SGA where cases with preeclampsia were excluded. Similarly, sensitivity analyses were also performed for all outcomes by excluding all pregnancies through ART to estimate if the ART affected the associations. Due to the large number of statistical comparisons, we corrected for multiple testing by use of Bonferroni correction. Finally, information on BMI was missing in 8.8% of women. As BMI values during pregnancy are not missing at random, we refrained from imputation of missing values.

All statistical analyses were performed using IBM SPSS statistics version 28.0.

3 | RESULTS

[Table 1](#) illustrates the maternal characteristics of the study population. Age and BMI tended to increase across all exposed groups. Women with both PCOS and GDM were oldest, had the

TABLE 1 Maternal characteristics in a cohort of women giving birth in Sweden 1997–2015.

	Controls		PCOS-only		GDM-only		PCOS and GDM	
	n	%	n	%	n	%	n	%
	238262	84.5	40272	14.3	2236	0.8	1036	0.4
Age (years)								
Mean \pm standard deviation	28.9 \pm 4.8		30.1 \pm 5.1		30.7 \pm 4.8		31.7 \pm 5.2	
<25	43751	18.4	5892	14.6	240	10.7	93	9.0
25–34	165016	69.2	26382	65.5	1493	66.8	630	60.8
\geq 35	29495	12.4	7998	19.9	503	22.5	313	30.2
BMI in early pregnancy (kg/m ²)								
Mean \pm standard deviation	24.4 \pm 4.5		26.1 \pm 5.3		28.5 \pm 6.2		31.0 \pm 6.1	
<18.5	5794	2.4	641	1.6	32	1.4	3	0.3
18.5–24.9	135306	56.8	17865	44.4	639	28.6	161	15.5
25.0–29.9	52114	21.9	10339	25.7	622	27.8	279	26.9
30.0–34.9	16860	7.1	5487	13.6	427	19.1	279	26.9
\geq 35	6891	2.9	2632	6.5	325	14.5	245	23.7
Missing	21297	8.9	3308	8.2	191	8.6	69	6.7
Parity								
Nulliparous	113919	47.8	22191	55.1	860	38.5	505	48.7
Parous	124343	52.2	18081	44.9	1376	61.5	531	51.3
Involuntary childlessness (years)								
1–2	10155	4.3	7876	19.6	109	4.9	174	16.8
\geq 3	4354	1.8	6623	16.4	64	2.9	225	21.7
ART treatment								
Metformin*	117	0.05	1184	2.9	18	0.8	88	8.5
Cigarette smoking								
Missing	9375	3.9	1556	3.9	89	4.0	32	3.1
Country of birth								
Nordic countries	191637	80.4	31119	77.3	1373	61.4	586	56.6
Other countries in Europe	16292	6.9	2883	7.2	186	8.3	111	10.7
Remaining countries	30333	12.7	6270	15.5	677	30.3	339	32.7
Education (years)								
\leq 12	114225	47.9	18586	46.2	1331	59.5	602	58.1
>12	122948	51.6	21547	53.5	875	39.1	426	41.1
Missing	1089	0.5	139	0.3	30	1.4	8	0.8
Year of delivery in index pregnancy								
1997–2003	52626	22.1	6017	14.9	412	18.4	132	12.7
2004–2009	81410	34.2	13432	33.4	727	32.5	352	34.0
2010–2015	104226	43.7	20823	51.7	1097	49.1	552	53.3

Abbreviations: ART, assisted reproductive technology; BMI, body mass index; GDM, gestational diabetes mellitus; PCOS, Polycystic ovary syndrome.

*At least two filled prescriptions of metformin three months prior to conception through first trimester.

highest mean BMI and the highest proportion of obesity (BMI \geq 30 kg/m²). Women with PCOS (with or without GDM) were more often nulliparous, faced more often involuntary childlessness and used ART more frequently. Metformin use before or in the first trimester of pregnancy was most prevalent among women with both PCOS and GDM (8.5%), followed by women with PCOS-only (2.9%), and was lower in the GDM-only and control groups. Most women in

the control group were from the Nordic countries (80.4%), whereas fewer were born in the Nordic countries (56.6%) among women with both PCOS and GDM.

Maternal outcomes are presented in Table 2. Women with PCOS, GDM and the combination of PCOS and GDM had higher odds of both gestational hypertension and preeclampsia compared to unexposed individuals. The risk estimates were attenuated following adjustments

TABLE 2 Rates and odds ratios for maternal outcomes in a cohort of women giving birth in Sweden 1997–2015.

Maternal Outcomes	n	%	Odds Ratio (95% confidence interval)		
			Crude	Adjusted model 1 ^a	Adjusted model 2 ^b
Gestational hypertension	3232	1.1			
Controls	2507	1.1			
PCOS-only	633	1.6	1.50 (1.37–1.65)	1.38 (1.26–1.51)	1.17 (1.06–1.29)
GDM-only	61	2.7	2.64 (2.02–3.49)	2.89 (2.20–3.81)	1.98 (1.48–2.64)
PCOS and GDM	31	3.0	2.90 (2.01–4.19)	2.82 (1.93–4.11)	1.61 (1.08–2.39)
PCOS by GDM interaction			0.73 (0.46–1.16)	0.71 (0.44–1.13)	0.69 (0.43–1.13)
Preeclampsia	8428	3.0			
Controls	6513	2.7			
PCOS-only	1679	4.2	1.55 (1.46–1.64)	1.44 (1.36–1.53)	1.18 (1.11–1.26)
GDM-only	143	6.4	2.43 (2.03–2.91)	2.63 (2.19–3.16)	1.77 (1.45–2.15)
PCOS and GDM	93	9.0	3.51 (2.81–4.37)	3.47 (2.76–4.36)	1.86 (1.46–2.36)
PCOS by GDM interaction			0.93 (0.70–1.25)	0.92 (0.68–1.23)	0.89 (0.65–1.22)
Postpartum hemorrhage	14309	5.1			
Controls	11943	5.0			
PCOS-only	2181	5.4	1.09 (1.03–1.14)	1.05 (1.00–1.10)	1.03 (0.98–1.09)
GDM-only	137	6.1	1.24 (1.03–1.48)	1.22 (1.01–1.46)	1.15 (0.98–1.09)
PCOS and GDM	48	4.6	0.92 (0.68–1.24)	0.87 (0.64–1.18)	0.86 (0.64–1.17)
PCOS by GDM interaction			0.69 (0.48–0.98)	0.69 (0.48–0.98)	0.73 (0.51–1.04)
Obstetric anal sphincter injury*	8328	3.5			
Controls	7013	3.4			
PCOS-only	1219	3.8	1.10 (1.03–1.17)	0.98 (0.91–1.04)	0.98 (0.92–1.05)
GDM-only	70	4.1	1.21 (0.94–1.55)	1.24 (0.96–1.60)	1.22 (0.93–1.59)
PCOS and GDM	26	3.7	1.08 (0.72–1.62)	0.96 (0.64–1.44)	1.01 (0.66–1.53)
PCOS by GDM interaction			0.81 (0.50–1.31)	0.79 (0.49–1.29)	0.84 (0.51–1.39)

Note: Bolded estimates and confidence intervals survived Bonferroni correction for multiple testing. Confidence intervals have not been Bonferroni corrected.

Abbreviations: GDM, gestational diabetes mellitus; PCOS, polycystic ovary syndrome.

^aAdjusted for maternal age, parity, education and country of birth.

^bAdjusted for maternal age, parity, education, country of birth and BMI.

*Only vaginal deliveries.

and only remained significant for preeclampsia in all diagnostic groups when BMI was added to the models (Model 2). Women with PCOS who developed GDM had an increased risk of preeclampsia in comparison with PCOS-only (aOR 1.86, 95% CI 1.46–2.36 vs. aOR 1.18, 95% CI 1.11–1.26). Risk estimates and CIs were similar between women with GDM-only (aOR 1.77, 95% CI 1.45–2.15) and the combination of PCOS and GDM (see above), suggesting no increased risk of preeclampsia with the combination in relation to having GDM-only, Table 2. In line with this, we found no significant PCOS by GDM interaction regarding the maternal outcomes. No increased odds for postpartum hemorrhage or sphincter injury was found in any of the groups.

Table 3 presents the neonatal outcomes. The likelihood of overall and spontaneous preterm birth was higher in all diagnostic groups compared with the control group. Women with both PCOS and GDM had the highest odds for overall preterm birth (aOR 2.08, 95% CI 1.67–2.58) compared with controls, while the odds were increased

by 34% in women with PCOS-only (aOR 1.34, 95% CI 1.28–1.41) and 64% in GDM-only (aOR 1.64, 95% CI 1.39–1.93) (Adjusted model 2, BMI included).

Women with PCOS-only had a 52% increased risk of stillbirth compared with the control group (aOR 1.52, 95% CI 1.29–1.80), whereas no increased risk was noted among women with GDM (aOR 0.58, 95% CI 0.24–1.39) (Adjusted model 2). Also, increased risk for shoulder dystocia was found in women with PCOS-only and GDM-only compared with the controls.

All groups had an increased risk of giving birth to an LGA infant compared with the control group, especially the groups with GDM diagnoses. The same trend was seen for macrosomia. Among women with PCOS the risk of having an LGA infant increased if they developed GDM. Further, once they had developed GDM, their risk of LGA became ever greater than the risk of women with GDM-only (Table 3), although the latter finding did not survive adjustment for BMI.

TABLE 3 Rates and odds ratios for neonatal outcomes in a cohort of women giving birth in Sweden 1997–2015.

Neonatal Outcomes	n	%	Odds Ratio (95% confidence interval)		
			Crude	Adjusted model 1 ^a	Adjusted model 2 ^b
Preterm birth overall	14460	5.1			
Controls	11386	4.8			
PCOS-only	2777	6.9	1.48 (1.41–1.54)	1.42 (1.35–1.48)	1.34 (1.28–1.41)
GDM-only	180	8.1	1.74 (1.49–2.04)	1.70 (1.45–1.99)	1.64 (1.39–1.93)
PCOS and GDM	117	11.3	2.52 (2.06–3.09)	2.37 (1.93–2.91)	2.08 (1.67–2.58)
PCOS by GDM interaction			0.98 (0.76–1.27)	0.99 (0.76–1.28)	0.94 (0.72–1.24)
Spontaneous preterm birth	9011	3.2			
Controls	7168	3.0			
PCOS-only	1672	4.2	1.41 (1.33–1.49)	1.36 (1.29–1.45)	1.34 (1.26–1.43)
GDM-only	101	4.5	1.55 (1.27–1.90)	1.58 (1.29–1.94)	1.61 (1.30–1.99)
PCOS and GDM	70	6.8	2.40 (1.85–3.11)	2.32 (1.79–3.02)	2.26 (1.71–2.98)
PCOS by GDM interaction			1.10 (0.79–1.53)	1.08 (0.77–1.51)	1.05 (0.74–1.48)
Stillbirth	986	0.3			
Controls	725	0.3			
PCOS-only	245	0.6	2.01 (1.73–2.32)	1.87 (1.61–2.16)	1.52 (1.29–1.80)
GDM-only	7	0.3	1.03 (0.49–2.17)	0.89 (0.42–1.88)	0.58 (0.24–1.39)
PCOS and GDM	9	0.9	2.87 (1.49–5.55)	2.29 (1.19–4.43)	1.59 (0.79–3.23)
PCOS by GDM interaction			1.39 (0.51–3.79)	1.38 (0.51–3.76)	1.81 (0.58–5.63)
Shoulder dystocia*	692	0.3			
Controls	523	0.3			
PCOS-only	146	0.5	1.77 (1.47–2.13)	1.78 (1.48–2.15)	1.52 (1.25–1.85)
GDM-only	18	1.1	4.17 (2.60–6.69)	3.55 (2.20–5.72)	2.60 (1.57–4.32)
PCOS and GDM	5	0.7	2.79 (1.16–6.73)	2.37 (0.98–5.77)	1.34 (0.50–3.61)
PCOS by GDM interaction			0.38 (0.14–1.04)	0.38 (0.14–1.03)	0.34 (0.11–1.04)
Small for gestational age (-2SD)	6638	2.4			
Controls	5483	2.3			
PCOS-only	1098	2.7	1.19 (1.11–1.27)	1.08 (1.01–1.15)	1.08 (1.01–1.16)
GDM-only	36	1.6	0.70 (0.50–0.97)	0.55 (0.38–0.78)	0.53 (0.36–0.77)
PCOS and GDM	21	2.0	0.88 (0.56–1.38)	0.67 (0.42–1.06)	0.61 (0.38–0.98)
PCOS by GDM interaction			1.06 (0.60–1.88)	1.14 (0.64–2.04)	1.07 (0.58–1.97)
Large for gestational age (+2SD)	9604	3.4			
Controls	7448	3.1			
PCOS-only	1644	4.1	1.32 (1.24–1.40)	1.41 (1.33–1.50)	1.15 (1.08–1.23)
GDM-only	326	14.6	5.29 (4.64–6.04)	5.47 (4.78–6.26)	3.88 (3.37–4.47)
PCOS and GDM	186	18.0	6.78 (5.71–8.06)	7.83 (6.56–9.35)	4.45 (3.71–5.35)
PCOS by GDM interaction			0.97 (0.78–1.21)	1.01 (0.81–1.27)	0.99 (0.79–1.26)
Macrosomia (≥4500g)	10264	3.6			
Controls	8402	3.5			
PCOS-only	1604	4.0	1.14 (1.07–1.21)	1.21 (1.14–1.28)	1.02 (0.96–1.09)
GDM-only	167	7.5	2.21 (1.87–2.60)	2.37 (2.01–2.80)	1.76 (1.48–2.10)
PCOS and GDM	91	8.8	2.63 (2.11–3.29)	3.11 (2.48–3.89)	1.88 (1.49–2.37)
PCOS by GDM interaction			1.05 (0.79–1.39)	1.09 (0.82–1.44)	1.05 (0.78–1.40)
Apgar <7 at 5 min^c	2528	1.0			
Controls	2026	0.9			

(Continues)

TABLE 3 (Continued)

Neonatal Outcomes	n	%	Odds Ratio (95% confidence interval)		
			Crude	Adjusted model 1 ^a	Adjusted model 2 ^b
PCOS-only	457	1.2	1.37 (1.24–1.52)	1.28 (1.15–1.42)	1.16 (1.04–1.30)
GDM-only	26	1.3	1.42 (0.96–2.10)	1.38 (0.94–2.05)	1.21 (0.81–1.81)
PCOS and GDM	19	2.1	2.33 (1.48–3.68)	2.10 (1.33–3.33)	1.64 (1.03–2.60)
PCOS by GDM interaction			1.20 (0.66–2.19)	1.19 (0.65–2.18)	1.16 (0.63–2.15)
Infant birth trauma^{a,c}	1591	0.7			
Controls	1288	0.7			
PCOS-only	273	0.9	1.37 (1.20–1.56)	1.39 (1.22–1.59)	1.21 (1.05–1.39)
GDM-only	16	1.0	1.55 (0.92–2.61)	1.54 (0.91–2.61)	1.15 (0.65–2.02)
PCOS and GDM	14	2.2	3.46 (1.97–6.10)	3.50 (1.98–6.18)	2.33 (1.34–4.06)
PCOS by GDM interaction			1.64 (0.75–3.57)	1.63 (0.75–3.54)	1.68 (0.76–3.72)
Cerebral impact of the infant^c	803	0.3			
Controls	651	0.3			
PCOS-only	136	0.4	1.27 (1.05–1.52)	1.15 (0.95–1.39)	1.07 (0.88–1.30)
GDM-only	9	0.4	1.53 (0.79–2.95)	1.54 (0.80–2.97)	1.28 (0.63–2.59)
PCOS and GDM	7	0.8	2.67 (1.26–5.62)	2.41 (1.14–5.11)	1.98 (0.92–4.24)
PCOS by GDM interaction			1.38 (0.50–3.79)	1.36 (0.50–3.75)	1.45 (0.51–4.09)
Neonatal hypoglycemia^c	4583	1.7			
Controls	3537	1.6			
PCOS-only	745	2.0	1.28 (1.18–1.39)	1.19 (1.09–1.29)	1.07 (0.98–1.16)
GDM-only	202	9.8	6.88 (5.90–8.02)	6.84 (5.84–8.01)	5.65 (4.79–6.68)
PCOS and GDM	99	10.8	7.62 (6.15–9.44)	7.00 (5.61–8.73)	5.16 (4.08–6.53)
PCOS by GDM interaction			0.87 (0.66–1.14)	0.86 (0.65–1.14)	0.86 (0.80–0.92)
Meconium aspiration syndrome^c	350	0.1			
Controls	290	0.1			
PCOS-only	54	0.1	1.13 (0.84–1.51)	1.01 (0.75–1.36)	0.85 (0.62–1.17)
GDM-only	5	0.2	1.90 (0.79–4.61)	2.00 (0.82–4.89)	1.36 (0.50–3.70)
PCOS and GDM	1	0.1	0.85 (0.12–6.07)	0.75 (0.10–5.46)	0.54 (0.07–3.98)
PCOS by GDM interaction			0.40 (0.05–3.47)	0.37 (0.04–3.27)	0.46 (0.05–4.25)
Infant respiratory distress^c	4831	1.8			
Controls	3965	1.7			
PCOS-only	770	2.1	1.18 (1.09–1.28)	1.11 (1.02–1.20)	1.02 (0.94–1.11)
GDM-only	64	3.1	1.81 (1.41–2.32)	1.91 (1.48–2.45)	1.62 (1.24–2.11)
PCOS and GDM	32	3.5	2.03 (1.43–2.88)	2.00 (1.40–2.84)	1.64 (1.14–2.36)
PCOS by GDM interaction			0.95 (0.62–1.48)	0.95 (0.61–1.47)	0.99 (0.63–1.56)

Note: Bolded estimates and confidence intervals survived Bonferroni correction for multiple testing. Confidence intervals have not been Bonferroni corrected.

Abbreviations: GDM, gestational diabetes mellitus; PCOS, polycystic ovary syndrome.

^aAdjusted for maternal age, parity, education and country of birth.

^bAdjusted for maternal age, parity, education, country of birth and BMI.

^cGestational length $\geq 37 + 0$.

*Only vaginal deliveries.

The odds of having an infant with an Apgar score <7 at 5 min was increased in women with PCOS-only compared with the controls. Infants of mothers with PCOS, with and without GDM, had higher odds of having birth trauma compared with controls. However, these two findings depended on BMI and did not remain after adjustment.

Increased odds of neonatal hypoglycemia were found in all diagnostic groups compared with the control group, but depended on maternal BMI among women with PCOS-only. The odds of infant respiratory distress were higher in both GDM exposure groups compared with the control group.

Overall, no significant PCOS by GDM interactions were found across the neonatal outcomes, meaning that PCOS did not add to the risk of having GDM-only.

A sensitivity analysis excluding pregnancies by ART treatment gave similar risk estimates in all analyses.

4 | DISCUSSION

In this large population-based cohort study, we found that women with PCOS have increased risk of a number of adverse maternal and neonatal outcomes, but having the combination of PCOS and GDM does not change the risks associated with GDM.

There are limited studies on the coexistence of PCOS and GDM regarding maternal and neonatal outcomes and results are inconsistent. A recent population-based Finnish study which was the first to suggest a higher risk of both spontaneous and overall preterm birth in women with both PCOS and GDM compared to women without PCOS or GDM.²⁶ On the contrary, in a randomized trial in Norway, no increased risk was found in women with both PCOS and GDM for pregnancy complications other than late miscarriage compared with women with PCOS-only.²⁷ One explanation of these divergent results could be found in different study designs. This study, and the Finnish study, are both register studies where PCOS and GDM are more likely to be underdiagnosed and underreported. Therefore the exposed group represents the most severe cases with highest probability of adverse outcome. The Norwegian study by Fougher et al. is a randomized controlled trial with PCOS diagnosis as an inclusion criteria and probably included a broader spectrum of women with PCOS.

It has been reported previously by our group and others, that women with PCOS have higher risk of stillbirth compared with non-PCOS.²⁸⁻³⁰ In this study, we found no increased risk of stillbirth in women with GDM-only, or the combination of PCOS and GDM, in concordance with previous meta-analyses.^{31,32} This could be explained by closer follow-up of women with GDM diagnosis with earlier induction of labor and tight surveillance during labor.

GDM has a major impact on the risk of giving birth to an LGA infant and macrosomia, confirmed also in this study. Contrary to the systematic meta-analysis in the 2023 guidelines, women with PCOS-only had a small but increased risk of having an LGA infant. Similar results regarding both LGA and macrosomia in women with both PCOS and GDM were found in another Swedish study during same time period.³³ Although we do not know the exact mechanism behind the excessive foetal growth in women with PCOS in our study, we assume that it is partly because of insulin resistance, since maternal weight, GDM and assisted reproduction were accounted for in the analyses. The pathophysiology for adverse pregnancy outcomes in women with PCOS is not fully understood yet, but is considered to be a combination of oxidative stress and activated immune response.^{28,34,35}

Placentas from women with PCOS show alterations associated with an increased hypoxic state.³⁶ Due to the low prevalence of GDM in the Swedish population, it is also highly plausible that many women with PCOS may have had undiagnosed GDM.

The risk of shoulder dystocia was increased in both PCOS-only and GDM-only compared with controls. The risk was highest among women with GDM, which correlates well with the risk of having an LGA infant and neonatal macrosomia. However, the association was non-significant for women with both conditions, which most likely is the result of low statistical power since only five cases of shoulder dystocia were observed within that group.

In Sweden, all term born infants to mothers with diabetes are screened for neonatal hypoglycemia approximately 3h after birth, which entails a risk of surveillance bias. In our study, the proportion of infants with neonatal hypoglycemia was higher among mothers diagnosed with GDM-only and the combination of PCOS and GDM. Infants of women with PCOS-only had 28% increased odds in unadjusted analysis of having neonatal hypoglycemia compared with controls, although the finding did not survive correction for multiple testing. Again, this finding could be explained by undiagnosed cases of GDM or not yet diagnosed type 2 diabetes mellitus in the PCOS group, underpinning the importance of screening with OGTT prior and during pregnancy as recommended in the newly updated PCOS guidelines.²

Term infants of mothers with GDM-only have almost a two-fold risk for respiratory distress, in adjusted analysis (Model 1), and similar probability when the mother had both PCOS and GDM. Our findings corroborate those of others,³⁷ and indicate that neonatal respiratory morbidity is not fully explained by physiologic immaturity due to preterm delivery but support the concept that GDM, with and without PCOS, being an independent risk factor for respiratory distress.³⁸

The main strength of this study is its large population-based sample size, consisting of more than 280000 births, of which 40272 births in women with PCOS only, 2236 in women with GDM-only and 1036 in women with both PCOS and GDM. The large sample size yielded the opportunity to explore rare outcomes and to adjust for several confounders. Furthermore, the data originate from well-validated registers and are collected prospectively, limiting the risk of information bias.

Women diagnosed with anovulatory infertility were classified as having PCOS, as the majority of women with that diagnosis have PCOS. Further, to decrease the risk of misclassification, women with a concurrent diagnosis of primary ovarian insufficiency or hyperprolactinemia and those diagnosed with congenital adrenal hyperplasia were excluded from the PCOS groups.

There is an inherent risk of undiagnosed women with PCOS within the control group, meaning that the association of PCOS with adverse pregnancy outcomes could be, in reality, even stronger than presented in our results.

The low prevalence of GDM in the study population of 1.2%, concurs with the previously reported 1%–3% prevalence in Sweden during the same time period.²⁴ The low prevalence can be explained by higher cut-off levels for GDM diagnosis than WHO recommended in 2013 along with the fact that screening with OGTT was based on risk factors in almost all regions in Sweden. The prevalence has increased after implementing the updated WHO diagnostic criteria from 2013, where the global prevalence of GDM increased to approximately 14% and the European prevalence to 7.8%.¹³

Metformin use in pregnancy was defined as two filled prescriptions to decrease the risk of misclassification of women with one filled prescription who nevertheless stopped taking medication during pregnancy. Metformin use could possibly have affected our results by reducing the risk of preterm birth, but has limited effect on glucose metabolism in pregnant women and has not shown to decrease rates of GDM.^{2,30,39} In our study 8.5% of women with both PCOS and GDM did fill two prescriptions of metformin during the 3 months prior to pregnancy or during first trimester, while it was 2.9% in women with PCOS-only. PCOS is the most likely indication for metformin use in these women as GDM is typically diagnosed later in pregnancy and women with type 2 diabetes mellitus were excluded. Sweden had no national recommendations regarding metformin use in pregnancy during the study period, but according to our data the use increased over the study period.

Women with PCOS are at increased risk of a number of adverse maternal and neonatal outcomes, but having PCOS also does not change the risks associated with GDM. For some outcomes, like stillbirth, women with PCOS seem to have an increased risk in comparison with controls whereas women with GDM have not. This phenomenon is possibly due to already intensified surveillance of GDM pregnancies, whereas PCOS has not yet been recognized as a risk factor in pregnancy. Thus, it is important to increase awareness about risk for adverse pregnancy outcomes in women with PCOS both among the general population and healthcare professionals. According to newly updated guidelines, women with PCOS should be offered OGTT when planning a pregnancy or seeking fertility treatment. If not performed before pregnancy, it could be offered at the first antenatal visit and all women with PCOS should be offered OGTT at gestational week 24–28.² This screening method would contribute to the early identification of PCOS women with insulin resistance who have not yet developed overt diabetes. Early detection could be beneficial for both the mother and her infant, either through increased and frequent monitoring or through antidiabetic treatment.

The increased risk for adverse pregnancy outcome in women with both PCOS and GDM should be examined further.

5 | CONCLUSION

The combination of PCOS and GDM adds no extra risk of adverse pregnancy outcomes for neither mother nor infant in comparison to the risks associated with having only GDM. Nevertheless, PCOS is still an unrecognized risk factor in pregnancy, exemplified by the increased risk of stillbirth. With increased awareness of PCOS, precise diagnosis of PCOS prior to pregnancy as well as early screening and diagnosis of diabetes and hypertensive disorders during pregnancy, neonatal outcomes could be improved.

AUTHOR CONTRIBUTIONS

Ragnheidur Valdimarsdottir, Anna-Karin Wikströmand Inger Sundström Poromaa were the principal investigators and drafted this article. Anna-Karin Wikström, Ragnheidur Valdimarsdottir,

Eszter Vanky and Inger Sundström Poromaa formulated the study. Inger Sundström Poromaa contributed to data acquisition. Ragnheidur Valdimarsdottir performed statistical analysis. Eszter Vanky, Evangelia Elenis, Fredrik Ahlsson, Linda Lindström, and Katja Junus contributed to the process of manuscript writing and critically revised the article. All authors contributed to the intellectual content, study design, and approved the final version of this article.

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CONFLICT OF INTEREST STATEMENT

Inger Sundström Poromaa has, over the past years, served occasionally on advisory boards or acted as an invited speaker at scientific meetings for Bayer Health Care, Gedeon Richter, Novartis, and Sandoz. Evangelia Eleni has received lecture fee from Gedeon Richter, research grant from Ferring Pharmaceuticals and serves as the medical advisor of Tilly AB. The rest of authors have no conflicts of interest to declare.

ETHICS STATEMENT

The study was approved by the Regional Ethical Review Authority in Uppsala, Sweden, on August 7, 2017 (diary number 2017/309). The need for oral or written informed consent was waived since all data received from the Swedish registries were anonymized.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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