INTRODUCTION

Polycystic ovary syndrome (PCOS) is a heterogeneous endocrine disorder affecting 5–13% of women of fertile age. PCOS is characterised by ovarian dysfunction, hyperandrogenism and polycystic ovary morphology. Common clinical manifestations of PCOS are obesity, menstrual irregularities, infertility and hyperandrogenic symptoms.

RESEARCH ARTICLE

Polycystic ovary syndrome and risk of pre-eclampsia: A national register-based cohort study

Ragnheidur Valdimarsdottir1 | Eszter Vanky2,3 | Evangelia Elenis1 | Linda Lindström1 | Katja Junus1 | Maria Jonsson1 | Inger Sundström Poromaa1 | Anna-Karin Wikström1

1Department of Women’s and Children’s Health, Uppsala University, Uppsala, Sweden
2Department of Clinical and Molecular Medicine, Norwegian University of Science and Technology, Trondheim, Norway
3Department of Obstetrics and Gynaecology, St. Olav’s Hospital, Trondheim University Hospital, Trondheim, Norway

Correspondence
Ragnheidur Valdimarsdottir, Department of Women’s and Children’s Health, Uppsala University, 751 85 Uppsala, Sweden. Email: ragnheidur.valdimarsdottir@khh.uu.se

Funding information
The Perinatal Foundation, Sweden; Swedish Research Council, Grant/Award Number: 2020-01640

Abstract

Objective: To explore whether the association between polycystic ovary syndrome (PCOS) and pre-eclampsia depends on treated clinical hyperandrogenism and whether PCOS is associated with different subtypes of pre-eclampsia.

Design: Nationwide register-based cohort study.

Setting: Sweden.

Population: Nulliparous women with PCOS (n = 22,947) and non-PCOS controls (n = 115,272) giving singleton birth at ≥22 gestational weeks during 1997–2015. Treated clinical hyperandrogenism was defined as filled prescriptions of anti-androgenic drugs during 2005–2017 (n = 2,301 among PCOS women).

Methods: The risk of pre-eclampsia was estimated with conditional logistic regression, expressed as adjusted odds ratio (OR) with 95% confidence interval (CI). Adjustments were performed individually for confounders and predictors.

Main outcome measures: Overall pre-eclampsia. Early/late (delivery <34/≥34 weeks) pre-eclampsia. Pre-eclampsia with or without a small-for-gestational-age (SGA) infant.

Results: Compared with controls, women with PCOS had a 29% increased risk of pre-eclampsia (predictor adjusted OR 1.29, 95% CI 1.20–1.39), with similar risk estimates for PCOS women with and without treated clinical hyperandrogenism. The association between PCOS and early pre-eclampsia seemed stronger than its association with late pre-eclampsia (predictor adjusted OR 1.64 (95% CI 1.33–2.02) and 1.26 (95% CI 1.17–1.37). Additionally, the association seemed slightly stronger between PCOS and pre-eclampsia in women with an SGA infant than without.

Conclusions: Women with PCOS face an increased risk for pre-eclampsia, especially early pre-eclampsia and pre-eclampsia with an SGA infant. We were unable to determine on the basis of available data, whether hyperandrogenism is associated with pre-eclampsia.

KEYWORDS

hyperandrogenism, polycystic ovary syndrome, pre-eclampsia, pregnancy complications, preterm birth, small for gestational age
such as hirsutism and acne. In addition, PCOS is strongly associated with insulin resistance, independent of obesity. Women with PCOS also have an increased risk of type 2 diabetes and cardiovascular disease. In non-pregnant women with PCOS, hyperandrogenism is associated with greater metabolic risk and higher prevalence of cardiovascular risk factors than normoandrogenism.

Pre-eclampsia is a severe pregnancy complication with a global incidence of 3–5%. Women with PCOS have a higher risk of developing pre-eclampsia, also after adjustment for body mass index (BMI). Clinical practice guidelines report several high and moderate risk factors for pre-eclampsia. These risk factors are used to guide caregivers when to offer aspirin for pre-eclampsia prevention and when to provide more intense surveillance during pregnancy.

PCOS is currently not included as a risk factor for pre-eclampsia in international guidelines. Recent evidence implies that current pre-eclampsia guidelines are unaligned with evidence that points to PCOS being a probable risk factor for pre-eclampsia.

The underlying mechanisms may comprise shared features such as insulin resistance, chronic inflammation and hyperandrogenism, but the results of previous studies on PCOS phenotypes and adverse pregnancy outcomes are inconsistent. The majority of published reports demonstrate that hyperandrogenism is associated with adverse pregnancy outcomes, such as pre-eclampsia, gestational diabetes, preterm delivery and a small-for-gestational-age (SGA) infant. Women with PCOS and high testosterone levels during pregnancy seem to have an even higher risk for pre-eclampsia.

The pathophysiology of pre-eclampsia is complex and differs between its subtypes. Pre-eclampsia of early onset and pre-eclampsia in women with an SGA infant are regarded as subtypes of pre-eclampsia that have a more evident placental component than late-onset pre-eclampsia and pre-eclampsia in women without an SGA infant. Placental studies show that the placenta of pregnant women with PCOS has an altered histological structure, even in uncomplicated pregnancies. The placental lesions described differ among the PCOS phenotypes, especially among hyperandrogenic women with PCOS, who have microscopic alterations in early trophoblast invasion and placentation. To the best of our knowledge, no study has evaluated whether the risk of pre-eclampsia in women with PCOS differs between subtypes of pre-eclampsia.

In this large population-based multi-register study, we examined the association between PCOS and risk of pre-eclampsia. The primary aim of the study was to confirm prior findings that suggest that hyperandrogenic women with PCOS have the highest risk of pre-eclampsia. The secondary aim was to determine whether the association between PCOS and pre-eclampsia varies depending on the pre-eclampsia subtype. There are two potential approaches, either a causal analysis or a prediction model; we present the results of both approaches in this work.

## METHODS

### 2.1 Data sources

The Swedish National Board of Health and Welfare provided information from the National Patient Register, the Medical Birth Register and the Prescribed Drug Register. Statistics Sweden provided data from the Education Register and the Total Population Register. The National Patient Register holds information on dates and diagnoses for in-patient hospital visits since 1964 and is considered to have complete coverage since 1987. Since 2001, the register also includes specialised outpatient visits, such as visits to a gynaecologist or reproductive specialist. Since 1997, diagnoses are classified according to the International Statistical Classification of Diseases and Related Health Problems, version 10 (ICD-10). The Medical Birth Register contains data on more than 98% of births in Sweden since 1973. Antenatal care is standardised and free of charge in Sweden, accounting for the high coverage. Demographic and clinical data are collected prospectively. The register includes information on reproductive history and complications during pregnancy, delivery and the neonatal period. Complications during pregnancy and delivery are classified according to ICD codes. The Swedish Prescribed Drug Register contains information on drug prescriptions according to Anatomic Therapeutic Chemical (ATC) classification codes, daily doses and the date of filled prescription of drugs since 1 July 2005. The Education Register contains information on the highest completed level of education of the Swedish population since 1985. The Total Population Register started in 1968 and provides information on country of birth and municipality of residence. Linkage between registries is possible through the personal identity number assigned to all residents in Sweden at birth or upon immigration.

### 2.2 Study population and exposure

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

Women with a PCOS-related diagnosis in the National Patient Register between 1997 and 2017 were considered as exposed to PCOS (n=23 150) (Figure 1). PCOS-related diagnoses were defined as ICD-10 codes reflecting PCOS (n=14 751) and the related diagnoses androgen excess from the ovary (n=44) and anovulatory infertility (n=8152) (diagnostic codes are presented in Table S1). PCOS diagnoses before, during and after the pregnancy were included as
POLYCYSTIC OVARY SYNDROME AND RISK OF PRE-ECLAMPSIA

exposures because PCOS affects women during their entire life span. The diagnosis of anovulatory infertility was included among the PCOS diagnoses because PCOS accounts for approximately 80–95% of infertility cases due to anovulation.33,34 At the beginning of the study period, PCOS was diagnosed according to the National Institutes of Health (NIH) criteria. From 2003, most clinicians used the Rotterdam criteria. The NIH criteria for PCOS require the presence of clinical or biochemical hyperandrogenism and chronic oligo- or anovulation.35 The Rotterdam criteria added polycystic ovary morphology on ultrasound as a new criterion and required the presence of two of the following three criteria: (1) polycystic ovary morphology, (2) oligo- or anovulation and (3) clinical or biochemical hyperandrogenism.5 We excluded all women diagnosed with both anovulatory infertility and either hyperprolactinaemia or primary ovarian insufficiency as well as women with congenital adrenal hyperplasia.

Further, by linkage to the Prescribed Drug Register, we identified women with PCOS with treated clinical hyperandrogenism, as a proxy for the hyperandrogenic PCOS phenotype. These women with PCOS had filled at least two prescriptions during 2005–2017 for anti-androgenic drugs identified with the following ATC codes: C03DA01 (spironolactone), D11AX10 (finasteride), D11AX16 (eflornithine), G03HB01 (combined oral contraceptives with ethinyl estradiol and cyproterone acetate), G04CB (finasteride and dutasteride), L02BB (bicalutamide) and L02BB01 (flutamide). Anti-androgenic drug treatment was either before or after pregnancy (these drugs are

FIGURE 1 Flowchart of the study population. *PCOS defined as a diagnosis of PCOS hyperandrogenism of ovarian origin or an ovulatory infertility in the patient register from 1997 to 2017.
contraindicated for use in pregnancy). The definition of two filled prescriptions was chosen to decrease to the risk of misclassification of normoandrogenic women in the treated group.

We identified 116,898 non-PCOS controls who gave birth to their first child during the study period. To decrease the risk of including undiagnosed cases of PCOS, we excluded pregnancies achieved by ovarian stimulation from the non-PCOS group, which reduced the non-PCOS population by 1.4% (n = 1626).

The study population was restricted to nulliparous women to increase the homogeneity of the study population. Further, we had no information on previous pregnancy complications in the population, which would have influenced the risk prediction in multiparas.

Pregnancies with missing gestational length or a gestational length of >44 weeks at birth were excluded from both groups.

The final study population included 138,219 nulliparous women delivering a child (n = 22,947 women with PCOS and n = 115,272 non-PCOS controls). The flow chart of the study population is presented in Figure 1.

2.3 | Outcome

The main outcome was pre-eclampsia registered in the Medical Birth Register with the corresponding ICD-10 codes: O14 (pre-eclampsia), O15 (eclampsia) and O11 (pre-eclampsia superimposed on chronic hypertension).

During the study period, pre-eclampsia was defined as new onset hypertension (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg measured on two subsequent occasions at least 4 hours apart) and proteinuria (≥300 mg/24 hours) after 20 weeks of gestation. A Norwegian validation study has concluded that specificity of pre-eclampsia during 1999–2010 is satisfactory for primiparous women, with a positive predictive value of 85.4%.

Although no Swedish validation study is available, there are strong similarities between the Swedish and Norwegian healthcare systems and birth registers.

Pre-eclampsia was further categorised by subtype into early (delivery <34 gestational weeks) or late (delivery at ≥34 gestational weeks) pre-eclampsia, and pre-eclampsia with or without the birth of an SGA infant. SGA was defined as a birthweight two standard deviations (−2 SD) or more below the mean weight for gestational age and sex according to the Swedish intrauterine growth reference range.

2.4 | Covariates

From the Medical Birth Register, the following covariates were collected: maternal age, weight, height, cigarette smoking during pregnancy, involuntary childlessness, assisted reproductive technology (ART) treatment, year of delivery as well as presence of any of the following diseases: type 1 or 2 diabetes mellitus, chronic hypertension, chronic kidney disease, systemic lupus erythematosus (SLE) and antiphospholipid syndrome (diagnostic codes are presented in Table S1).

Maternal age was the woman’s age at the time of delivery. Maternal weight was measured at the first antenatal visit (usually gestational weeks 7–10), whereas data on maternal height is generally self-reported. Early pregnancy maternal body mass index (BMI) was calculated as weight (kg)/height (m)². Cigarette smoking during pregnancy was self-reported at the time of the first antenatal visit and at gestational weeks 30–32. Involuntary childlessness and conception through ovulation induction or ART treatment were self-reported by the woman and were recorded in check boxes by the midwife.

Presence of type of diabetes mellitus, chronic hypertension, chronic kidney disease, SLE and antiphospholipid syndrome was identified by the ICD-10 codes collected at discharge from the hospital after delivery. Diabetes mellitus was categorised as no diabetic disease, type 1 or 2 diabetes and gestational diabetes.

Information on country of birth and years of formal education was collected from the Total Population Register and the Education Register, respectively. The covariates were categorised as presented in Table 1.

2.5 | Statistical analysis

Conditional logistic regression analysis was used to estimate the association between maternal PCOS and pre-eclampsia. Crude and adjusted odds ratios (OR) with 95% confidence intervals (CIs) were calculated, and non-PCOS controls were used as the reference. As associations are of interest both for increased pathophysiological knowledge and potential improved prediction of pre-eclampsia; we performed adjustments in two separate models, a confounding-adjusted model for causal analysis and a predictor-adjusted model.

For the causal approach, a directed acyclic graph (DAG) was constructed to obtain a systematic representation of a possible causal relation between PCOS exposure and pre-eclampsia. We used DAG to identify covariates that should be considered true confounders and adjusted for these (Figure 2). Maternal age, educational level, country of birth and year of delivery were identified as confounders.

In the prediction approach we added all high and moderate risk factors for pre-eclampsia according to the NICE pre-eclampsia guidelines, except for a family history of pre-eclampsia, which was not available. Predictors were maternal age, educational level, country of birth, year of delivery, type 1 or 2 diabetes mellitus, chronic hypertension, chronic kidney disease, SLE and antiphospholipid syndrome. To evaluate the impact of high BMI in the association between PCOS and pre-eclampsia, we chose to calculate the adjusted OR in separate models. Covariates were included as continuous variables where possible.

In Model 1, we adjusted for confounders and predictors separately and, due to controversy as to whether BMI was a...
mediator or a confounder for the association between PCOS and pre-eclampsia, we chose to add BMI in Model 2. Due to non-random missing values for BMI and educational level in the first two models, Model 3 was enriched with multiple imputed values, using the same adjustments as in Model 2. We generated five multiple imputed datasets, making use of all available information on the women, and present the pooled estimates with confidence intervals. Available data

| TABLE 1 | Maternal characteristics in a cohort of nulliparous women giving birth in Sweden 1997–2015, stratified by PCOS status. |
| Non-PCOS | | PCOS |
| n | % | n | % |
| Maternal age at birth (years) | | | |
| Mean ± standard deviation | | | |
| <25 | 31 628 | 27.4 | 4695 | 20.5 |
| 25–34 | 76 407 | 66.3 | 15 079 | 65.7 |
| ≥35 | 7237 | 6.3 | 3173 | 13.8 |
| BMI in early pregnancy (kg/m²) | | | |
| Mean ± standard deviation | | | |
| <18.5 | 3255 | 2.8 | 398 | 1.7 |
| 18.5–24.9 | 69 035 | 59.9 | 10 682 | 46.6 |
| 25.0–29.9 | 22 763 | 19.7 | 5679 | 24.7 |
| ≥30.0 | 9 565 | 8.3 | 4 252 | 18.5 |
| Missing | 10 654 | 9.2 | 1 936 | 8.4 |
| Cigarette smoking in pregnancy | | | |
| Yes | 9 730 | 8.4 | 1 578 | 6.9 |
| Missing | 4 674 | 4.1 | 926 | 4.0 |
| Involuntary childlessness (years) | | | |
| 1–2 | 6 519 | 5.7 | 5 348 | 23.3 |
| ≥3 | 3 166 | 2.7 | 5 387 | 23.5 |
| ART treatment | | | |
| Yes | 3 325 | 2.9 | 4 852 | 21.1 |
| Diabetic disease | | | |
| Type 1 or 2 diabetes mellitus | 562 | 0.5 | 268 | 1.2 |
| Gestational diabetes mellitus | 860 | 0.7 | 505 | 2.2 |
| Chronic hypertension | 349 | 0.3 | 174 | 0.8 |
| Chronic kidney disease | 519 | 0.5 | 128 | 0.6 |
| Systemic lupus erythematosus | 140 | 0.1 | 37 | 0.2 |
| Antiphospholipid syndrome | 13 | 0.01 | 2 | 0.009 |
| Country of birth | | | |
| Nordic countries | 94 938 | 82.4 | 17 822 | 77.7 |
| Other countries in Europe | 7 528 | 6.5 | 1 654 | 7.2 |
| Remaining countries | 12 806 | 11.1 | 3 471 | 15.1 |
| Education (years) | | | |
| ≤12 | 51 529 | 44.7 | 10 218 | 44.5 |
| >12 | 63 284 | 54.9 | 12 644 | 55.1 |
| Missing | 459 | 0.4 | 85 | 0.4 |
| Year of delivery | | | |
| 1997–2003 | 27 940 | 24.2 | 3 910 | 17.0 |
| 2004–2009 | 40 602 | 35.2 | 7 943 | 34.6 |
| 2010–2015 | 46 730 | 40.5 | 11 094 | 48.3 |

Abbreviations: ART, assisted reproductive technology; BMI, body mass index; PCOS, polycystic ovary syndrome.
on BMI and education followed a multivariate normal distribution according to p-plots.

Next, we stratified women with PCOS into treated and non-treated clinical hyperandrogenism and repeated the analyses. Finally, we calculated the association between PCOS and pre-eclampsia stratified by subtype: early and late pre-eclampsia and pre-eclampsia with and without an SGA infant.

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

3 | RESULTS

Overall, 6172 (4.5%) women in the study population had pre-eclampsia; of these, 154 (2.5%) developed eclampsia and 100 (1.6%) had superimposed pre-eclampsia.

Among the 22,947 included women with PCOS, 2301 (10.0%) had filled two prescriptions for anti-androgenic drugs and were consequently assigned to the group PCOS with treated clinical hyperandrogenism.

Table 1 illustrates maternal characteristics by PCOS exposure. Women with PCOS were older and had a higher mean BMI compared with non-PCOS controls. Women with PCOS more often reported involuntary childlessness (≥1 year) and were more likely to conceive by ART treatment. They also had a higher rate of both gestational and pre-gestational diabetes mellitus compared with non-PCOS controls. Almost half of the births within the PCOS group took place during the final years of the study period, 2010–2015.

Table S2 illustrates maternal characteristics by pre-eclampsia status. Women with pre-eclampsia had a higher mean BMI than women without pre-eclampsia and were less often smokers. Women diagnosed with pre-eclampsia more often had pre-gestational or gestational diabetes mellitus.

Table 2 illustrates rates and risks of pre-eclampsia by PCOS status. Women with PCOS had higher rates of pre-eclampsia compared with non-PCOS controls (5.7 and 4.2%, respectively, $P < 0.001$). In the causal approach, women with PCOS had a 33% higher risk of pre-eclampsia after adjustments for confounders. In the prediction model, women with PCOS had a 29% higher risk of pre-eclampsia after adjustment for the predictors maternal age, education, country of birth, year of delivery, type 1 or 2 diabetes mellitus, chronic hypertension, chronic kidney disease, SLE and antiphospholipid syndrome (Model 1). No association was found when BMI was added to the adjustments (Model 2). With imputation of missing values, women with PCOS had a 10% higher risk for pre-eclampsia in the causal model but we found no association in the prediction model (Model 3). When separating PCOS into treated vs non- treated clinical hyperandrogenism, we found similar associations with pre-eclampsia.

Table 3 illustrates rates and risks of early and late pre-eclampsia and pre-eclampsia in women with or without an SGA infant by PCOS status. In comparison with
### TABLE 2 Rates and odds ratios for pre-eclampsia in a cohort of nulliparous women giving birth in Sweden 1997–2015, stratified by PCOS and treated clinical hyperandrogenism.

<table>
<thead>
<tr>
<th>PCOS status</th>
<th>n</th>
<th>Pre-eclampsia (n %)</th>
<th>Odds ratio (95% confidence interval)</th>
<th>n (%</th>
<th>n (%</th>
<th>n (%)</th>
<th>n (%)</th>
<th>n (%)</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Crude</td>
<td>Confounders&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td>Predictor&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-PCOS</td>
<td>115272</td>
<td>4860 (4.2)</td>
<td>Reference</td>
<td>1306 (5.7)</td>
<td>1.33 (1.23–1.43)</td>
<td>1.29 (1.20–1.39)</td>
<td>1184 (5.2)</td>
<td>1.08 (0.994–1.17)</td>
<td>1.06 (0.98–1.15)</td>
</tr>
<tr>
<td>PCOS (all)</td>
<td>22947</td>
<td>1312 (5.7)</td>
<td>1.36 (1.32–1.49)</td>
<td>1306 (5.7)</td>
<td>1.33 (1.23–1.43)</td>
<td>1.29 (1.20–1.39)</td>
<td>1184 (5.2)</td>
<td>1.08 (0.994–1.17)</td>
<td>1.06 (0.98–1.15)</td>
</tr>
<tr>
<td>Treated</td>
<td>2301</td>
<td>130 (5.6)</td>
<td>1.45 (1.31–1.59)</td>
<td>130 (5.6)</td>
<td>1.49 (1.17–1.90)</td>
<td>1.39 (1.09–1.78)</td>
<td>119 (5.2)</td>
<td>1.07 (0.82–1.40)</td>
<td>1.12 (0.88–1.44)</td>
</tr>
<tr>
<td>Non-treated</td>
<td>20646</td>
<td>1182 (5.7)</td>
<td>1.35 (1.31–1.39)</td>
<td>1176 (5.7)</td>
<td>1.31 (1.21–1.41)</td>
<td>1.28 (1.18–1.38)</td>
<td>1065 (5.2)</td>
<td>1.06 (0.99–1.17)</td>
<td>1.09 (1.01–1.18)</td>
</tr>
</tbody>
</table>

Note: Model 1: Adjusted for confounders/predictors. Model 2: BMI added to adjustments in Model 1. Model 3: Same adjustments as in Model 2 with multiple imputed values for missing data.

Abbreviations: ART, assisted reproductive technology; BMI, body mass index; PCOS, polycystic ovary syndrome.

<sup>a</sup>Confounder adjusted models. Confounders: maternal age, educational level, country of birth, year of delivery.

<sup>b</sup>Predictor adjusted models. Predictors: maternal age, educational level, country of birth, year of delivery, type 1 or 2 diabetes mellitus, chronic hypertension, chronic kidney disease, systemic lupus erythematosus and antiphospholipid syndrome.

<sup>c</sup>Treatment for clinical hyperandrogenism defined as two dispensations of prescribed anti-androgenic drugs during 2005–2017.

### DISCUSSION

#### 4.1 Main findings

This large population-based cohort study corroborates previous findings of increased risk of pre-eclampsia in women with PCOS, both in causal and prediction approaches, after adjustment for confounders and known risk factors for pre-eclampsia. Although BMI was added to the adjustments in Model 1, the association diminished. We could not confirm our hypothesis that treated clinical hyperandrogenism in women with PCOS, defined as treatment with anti-androgenic drugs, further increased the risk for pre-eclampsia. Interestingly, we found a stronger association between PCOS and early-onset than late-onset pre-eclampsia and the same tendency was seen for pre-eclampsia without an SGA infant.

#### 4.2 Strengths and limitations

The main strength of the study is its large population-based sample size, comprising approximately 23,000 births among nulliparous women with a PCOS-related diagnosis, thus decreasing the risk of selection bias. The study design and sample size enabled stratified analyses of PCOS with and without treated clinical hyperandrogenism, as well as the study of subtypes of pre-eclampsia with more severe outcomes and low prevalence. As the majority of women with anovulatory infertility also have PCOS, we decided to include women with this diagnosis in the study of subtypes of pre-eclampsia without an SCA infant.

PCOS exposure was based on ICD-10 codes registered by physicians and was not self-reported by study participants. The study was not able to include women with PCOS, defined as treated clinical hyperandrogenism in women with PCOS, defined as treatment with anti-androgenic drugs, as such women were not included in the study sample. Additionally, the study did not include women with PCOS without treated clinical hyperandrogenism, as such women were not included in the study sample. The study did not include women with PCOS without treated clinical hyperandrogenism, as such women were not included in the study sample.

As the majority of women with anovulatory infertility also have PCOS, we decided to include women with this diagnosis in the study of subtypes of pre-eclampsia without an SCA infant. The study was not able to include women with PCOS, defined as treated clinical hyperandrogenism in women with PCOS, defined as treatment with anti-androgenic drugs, as such women were not included in the study sample.
TABLE 3  Rates and odds ratios for early (<34 gestational weeks at delivery) and late (≥34 gestational weeks at delivery) onset pre-eclampsia and pre-eclampsia with or without an infant born small for gestational age, in a cohort of nulliparous women giving birth in Sweden 1997–2015, by PCOS status.

<table>
<thead>
<tr>
<th>PCOS status</th>
<th>n</th>
<th>Odds ratio (95% confidence interval)</th>
<th>n (%)</th>
<th>Model 1</th>
<th>n (%)</th>
<th>Model 2</th>
<th>n (%)</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early onset pre-eclampsia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-PCOS</td>
<td>115272</td>
<td>441 (0.4)</td>
<td>Reference</td>
<td>168</td>
<td>0.7</td>
<td>138</td>
<td>0.6</td>
<td>1.49</td>
</tr>
<tr>
<td>PCOS</td>
<td>22947</td>
<td>169 (0.7)</td>
<td>1.84</td>
<td>1.40–2.13</td>
<td>138 (0.6)</td>
<td>1.29</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Late onset pre-eclampsia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-PCOS</td>
<td>113421</td>
<td>4419 (3.9)</td>
<td>Reference</td>
<td>1138</td>
<td>5.1</td>
<td>1046</td>
<td>4.7</td>
<td>1.07</td>
</tr>
<tr>
<td>PCOS</td>
<td>22213</td>
<td>1143 (5.1)</td>
<td>1.33</td>
<td>1.20–1.40</td>
<td>1046 (4.7)</td>
<td>1.07</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-eclampsia in women with a small-for-gestational-age infant</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-PCOS</td>
<td>115272</td>
<td>572 (0.5)</td>
<td>Reference</td>
<td>1124</td>
<td>4.9</td>
<td>1025</td>
<td>4.5</td>
<td>1.07</td>
</tr>
<tr>
<td>PCOS</td>
<td>22947</td>
<td>1128 (4.9)</td>
<td>1.32</td>
<td>1.21–1.41</td>
<td>1025 (4.5)</td>
<td>1.08</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-eclampsia in women without a small-for-gestational-age infant</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-PCOS</td>
<td>115272</td>
<td>428 (3.7)</td>
<td>Reference</td>
<td>1124</td>
<td>4.9</td>
<td>1025</td>
<td>4.5</td>
<td>1.07</td>
</tr>
<tr>
<td>PCOS</td>
<td>22947</td>
<td>1128 (4.9)</td>
<td>1.32</td>
<td>1.21–1.41</td>
<td>1025 (4.5)</td>
<td>1.08</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: Model 1: Adjusted for confounders/predictors. Model 2: BMI added to adjustments in Model 1. Model 3: Same adjustments as in Model 2 with multiple imputed values for missing data.

Abbreviations: ART, assisted reproductive technology; BMI, body mass index; PCOS, polycystic ovary syndrome.

*aConfounder adjusted models. Confounders: maternal age, educational level, country of birth, year of delivery.

*bPredictor adjusted models. Predictors: maternal age, educational level, country of birth, year of delivery, type 1 or 2 diabetes mellitus, chronic hypertension, chronic kidney disease, systemic lupus erythematosus and antiphospholipid syndrome.
in our PCOS population. To decrease the risk of misclassification, women with a concurrent diagnosis of primary ovarian insufficiency or hyperprolactinemia as well as women with congenital adrenal hyperplasia were excluded from the exposed group. In the non-exposed group, pregnancies after ovulation induction were excluded. Whereas PCOS is nowadays regarded as a risk factor for pre-eclampsia, this was not the case during the study period. Therefore the increased risk of pre-eclampsia seen in our study should not be ascribed to an increased surveillance of the PCOS population.

The major limitation of this study lies in the chosen definition of treated clinical hyperandrogenism, as a proxy for hyperandrogenic PCOS phenotype. The definition was based on two filled anti-androgenic prescriptions and not on detailed clinical data due to the lack of relevant ICD codes. It has been estimated that approximately 60–80% of women with PCOS are hyperandrogenic. This proportion may be slightly lower in the Nordic countries but we cannot overlook the fact that only 10% of the PCOS group in our study was assigned to the group with treated clinical hyperandrogenism. Further, biochemical hyperandrogenism, which may show no clinical signs of hirsutism, was not captured by our definition. In addition, we do not have information on other treatments for hirsutism, such as laser treatment. Overall, we undoubtedly have misclassified hyperandrogenic PCOS women in the non-treated group, which may have obscured relevant findings.

Another limitation in this study is that BMI was missing in 9.1% of the study population; subsequently, Model 2 with BMI adjustments may have been underpowered. With imputation of missing values in Model 3 we only noted increased risk for early pre-eclampsia for women with PCOS. BMI clearly affects the association between PCOS and pre-eclampsia, therefore BMI should be considered separately in screening tools and prediction models.

An additional limitation is the restriction of the study population to nulliparous women. Potentially, as women with PCOS give birth to fewer children, this restriction could have led to a selection of more severe cases of PCOS, overestimating the associations.

### 4.3 Interpretation

Our finding of an increased risk of pre-eclampsia among women with PCOS is in concordance with systematic reviews and meta-analyses. The risk estimates, however, vary between studies depending on the study population, PCOS criteria and adjustments for confounding factors. Despite higher odds of pre-eclampsia in women with PCOS in BMI-matched studies, the results of the present study suggest that the comorbid overweight/obesity often affects the association between PCOS and pre-eclampsia.

The pathophysiologic mechanism of this association is probably multifactorial. Obesity is a strong risk factor for pre-eclampsia, and women with PCOS are more often obese than women without PCOS. Obesity and pre-eclampsia are both associated with insulin resistance, inflammation and oxidative stress, factors that may affect the association.

Based on our previous study, we hypothesised that hyperandrogenism might be the link between PCOS and pre-eclampsia. In fact, the risk for pre-eclampsia was reported to correlate positively with androgen levels among pregnant PCOS women and women without PCOS. However, the findings of the current study did not confirm our hypothesis. The most reasonable explanation is that most previous studies are based on biochemical hyperandrogenism and not clinical hyperandrogenism. Further, Palomba et al. found that adverse pregnancy outcomes in PCOS women seemed to be associated with biochemical hyperandrogenism rather than clinical hyperandrogenism. We therefore suggest performing further studies of PCOS and pre-eclampsia in which hyperandrogenism is based on both clinical and biochemical phenotyping.

To our knowledge, we are the first to report that women with PCOS seem to have a stronger association with early pre-eclampsia and pre-eclampsia with an SGA infant than their association with late pre-eclampsia and pre-eclampsia without an SGA infant.

The various subtypes of pre-eclampsia may have different but sometimes overlapping pathophysiological pathways. For example, early pre-eclampsia as opposed to late has more often been related to placental hypoperfusion, angiogenic disturbance, oxidative stress, fetal growth restriction and long-term risk of cardiovascular disease. In addition, pre-eclampsia in women with an SGA infant has more often been linked to placental hypoperfusion and risk of maternal cardiovascular disease compared with pre-eclampsia without an SGA infant, even among pregnancies ending at term. Indeed, placenta from women with PCOS display alterations associated with an increased hypoxic state.

Placental thrombosis was increased in women with PCOS who developed gestational hypertension or pre-eclampsia, compared with PCOS women with uncomplicated pregnancies, which might reflect vascular damage and fetal hypoxia.

Pre-eclampsia, especially the early onset subtype, may be prevented in some women by use of aspirin. Today, aspirin prophylaxis is offered to women at high risk for pre-eclampsia, risk calculation being based on either individual risk factors or multifactorial algorithms. PCOS has not been included in the most commonly used prediction models for pre-eclampsia. In line with newly updated PCOS guidelines and recent findings suggesting that the set of pre-eclamptic risk factors in current clinical practice guidelines are inadequately aligned with available evidence, we suggest PCOS should be included as a risk factor in obstetrical guidelines and prediction models for pre-eclampsia. Further research is needed on the association between PCOS and the more severe subtypes of pre-eclampsia as well to confirm whether the increased risk is independent of BMI.
Women with PCOS face a higher risk of pre-eclampsia compared with non-PCOS controls; however, this risk seems partly dependent on comorbid overweight/obesity. Further, on the basis of available data, the study was unable to determine whether hyperandrogenism in PCOS increased the risk of pre-eclampsia. The association between PCOS and pre-eclampsia was stronger when we restricted the outcomes to early pre-eclampsia and pre-eclampsia in women with an SGA infant, suggesting that pre-existing PCOS impacts placentaion in early pregnancy. Similar results were achieved in models with causal and prediction approaches.

AUTHOR CONTRIBUTIONS
RV and AKW were the principal investigators and drafted this article. AKW, RV and ISP formulated the study. ISP contributed to data acquisition. RV performed statistical analysis. EV, EE, LL, KJ and MJ contributed to the process of writing and critically reviewing the article. All authors contributed to the intellectual content and study design and approved the final version of this article.

ACKNOWLEDGEMENTS
None.

FUNDING INFORMATION
The Perinatal Foundation, Sweden, and the Swedish Research Council 2020-01640. Funders had no role in study design, data collection and analysis, decision to publish or preparation of the article.

CONFLICT OF INTEREST STATEMENT
Over the past years, ISP has served occasionally on advisory boards or acted as an invited speaker at scientific meetings for Bayer Health Care, Gedeon Richter, Novartis and Sandoz. EE has received lecture fees from Gedeon Richter, research grants from Ferring Pharmaceuticals and serves as the medical advisor of Tilly AB, none of which is in any way related to this article. The other authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from The Swedish National Board of Health and Welfare and Statistics Sweden. Restrictions apply to the availability of these data, which were used under licence for this study. Data are available from Prof. Inger Sundström Poromaa (inger.sundstrom@kkh.uu.se) for qualified, interested researchers with the permission of The Swedish National Board of Health and Welfare and Statistics Sweden.

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

REFERENCES