Polycystic ovary syndrome and risk of stillbirth: a nationwide register-based study

H Valgeirsddottir, T Kunovac Kallak, I Sundström Poromaa, M Jonsson, N Roos, L Lindström, A-K Wikström

Department of Women’s and Children’s Health, Uppsala University, Uppsala, Sweden

Correspondence: H Valgeirsddottir, Uppsala Universitet, Kvinnors och barns hälsa, Akademiska sjukhuset, 75185 Uppsala, Sweden. Email: heiddis.valgeirsddottir@kbb.uu.se

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Objective To investigate whether polycystic ovary syndrome (PCOS) is associated with increased risk of stillbirth and whether any such association is linked to PCOS with a severe hyperandrogenic profile.

Design Nationwide register-based cohort study.

Setting Sweden.

Population The cohort consisted of women giving birth to singleton infants in 1997–2015. All women with a diagnosis of PCOS in the period 1997–2017 and a randomly selected reference group of women without PCOS diagnosis were included. PCOS with a severe hyperandrogenic profile was defined as a PCOS diagnosis with at least two dispensations of prescribed anti-androgens during 2005–2017.

Methods The risk of stillbirth in women with PCOS was estimated through multiple logistic regression, using women without PCOS as a reference. Risks were expressed as adjusted odds ratios (aORs) with 95% confidence intervals (95% CIs), adjusted for maternal age, parity, body mass index, type-1 diabetes, educational level and country of birth.

Main outcome measures Stillbirth, at ≥22 weeks of gestation in 2008–2015 and at ≥28 weeks of gestation in 1997–2007.

Results Compared with women without PCOS (n = 241 750), women with PCOS (n = 41 851) had a 50% increased risk of stillbirth (aOR 1.50, 95% CI 1.28–1.77). The incidence of stillbirth in women with PCOS was particularly increased at term. Women with PCOS and a severe hyperandrogenic profile (n = 13 713) did not have a stronger association with stillbirth than women with PCOS who did not have such a profile.

Conclusions PCOS is associated with stillbirth and should be considered as a possible risk factor in antenatal care. Further research is warranted to investigate possible causal mechanisms.

Keywords PCOS, pregnancy complications, stillbirth.

Tweetable abstract Women with PCOS have increased risk of stillbirth, and the incidence is particularly increased at term.

Linked article This article is commented on by Ø Lidegaard, p. 2083 in this issue. To view this mini commentary visit https://doi.org/10.1111/1471-0528.16895.

Introduction

Polycystic ovary syndrome (PCOS) is a common endocrine disorder, affecting 6–10% of women of fertile age.1 PCOS is characterised by oligo-anovulation, hyperandrogenism and polycystic morphology of the ovaries. Obesity is common in women with PCOS, as are insulin resistance, type-2 diabetes and chronic hypertension.2

Women with PCOS can be categorised into four phenotypes, with hyperandrogenism being present in three of them.3 In non-pregnancy, women with hyperandrogenic PCOS have a greater risk of insulin resistance and cardiovascular disease than women with normo-androgenic PCOS.4 Women with PCOS have increased risk of pregnancy complications such as preterm birth,5,6 gestational diabetes, pregnancy-induced hypertension and pre-eclampsia.7 Hyperandrogenism may further increase the risk of PCOS-related pregnancy complications.8

Stillbirth is a rare but devastating pregnancy complication. In Sweden, the stillbirth rate from 22 weeks of gestation onwards was 3.2 per 1000 births in 2019.9 Known risk factors of stillbirths in high-income countries are maternal age over 35 years, overweight and obesity, smoking, pre-existing hypertension and diabetes.10 Stillbirth is also strongly associated with fetal growth restriction.11 It is currently unclear whether PCOS is associated with an
increased risk of stillbirth. Earlier studies on this association were inconclusive, presumably as a result of few stillbirth events being included. In a rat model of hyperandrogenic PCOS, an association between PCOS and fetal loss was shown, where the underlying mechanisms were defective placental formation, reduced angiogenesis and mitochondrial dysfunction. It remains to be clarified whether women with PCOS suffer an increased risk of stillbirth compared with women who do not have PCOS.

The aim of this large population-based study was therefore to investigate whether PCOS is associated with an increased risk of stillbirth and whether severe symptoms of hyperandroge

Methods

Data sources

The Swedish National Board of Health and Welfare provided access to 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. Linkage between the registers was made possible through the use of each individual’s unique personal identity number, which is assigned to a Swedish resident at birth or immigration.

The National Patient Register includes information on diagnoses for inpatient hospital visits since 1964, with full national coverage since 1987. Since 2001, the register also includes all outpatient visits in public and private specialist care. Diagnoses by general practitioners are not included. Since 1997, diagnoses are classified in accordance with the International Classification of Diseases and Related Health Problems, version 10 (ICD-10). Women with PCOS are generally diagnosed by specialists in gynaecology or obstetric medicine.

The Medical Birth Register contains data on more than 98% of births in Sweden, from 1973 onwards. It includes prospectively collected demographic data, information on reproductive history and complications that occur during pregnancy, delivery and the neonatal period. Antenatal care is standardised and free of charge in Sweden, which is associated with high enrolment and participation. During the first antenatal care visit, usually in the first trimester, the mother is interviewed about her height, medical and obstetric history and current smoking habits. Maternal weight is measured at the first antenatal visit, with the mother wearing light indoor clothing. Relevant chronic diseases and complications during pregnancy and delivery are classified based on ICD codes. In Sweden, gestational age is assessed through ultrasound scans in more than 95% of women, usually performed at around 18–19 weeks of gestation. Information from standardised antenatal, obstetric and paediatric records is automatically forwarded to the Medical Birth Register.

The Swedish Prescribed Drug Register contains information on prescribed drugs dispensed at pharmacies based on the Anatomical Therapeutic Chemical (ATC) classification codes, daily doses and date of drug collection, since 1 July 2005. The Education Register contains information on the education of the population. The Total Population Register was started in 1968 and includes information on country of birth.

Study population and exposure

Women included in the PCOS group were identified from the Register of Total Population as being born in 1950–1999, with a PCOS-related diagnosis from 1997 to 2017 in the Patient Register and who had given birth to at least one singleton infant during 1997–2015, according to the Birth Register (Figure 1). PCOS-related diagnosis included diagnoses of PCOS, androgen excess from the ovary and anovulatory infertility, based on ICD-10 codes (Table S1); we included diagnoses prior to, during or after the index pregnancy. PCOS is a syndrome seen as affecting a woman’s reproductive life from puberty, although some women are not diagnosed until later in their reproductive lifespan. During the study period, PCOS was diagnosed based on the 1990 National Institutes of Health (NIH) criteria or the Rotterdam criteria (introduced in 2003). According to the Rotterdam criteria, the woman needs to fulfil two out of three criteria for PCOS diagnosis: oligo- or anovulation, clinical or biochemical hyperandrogenism and polycystic morphology of the ovaries. The NIH criteria required clinical or biochemical hyperandrogenism and chronic anovulation for PCOS diagnosis. Women with anovulatory infertility were included in the PCOS-related group, as 80–90% of them have PCOS based on the Rotterdam criteria. Women diagnosed with both anovulatory infertility and hyperprolactinaemia or premature ovarian insufficiency were excluded. We also excluded women with a diagnosis of congenital adrenal hyperplasia.

Further, women with PCOS and severe hyperandroge

and as having at least two dispensations of prescribed anti-androgenic drugs during 2005–2017, prior to, during or after the index pregnancy, according to the Prescribed Drug Register. Anti-androgenic drugs were identified using the following ATC codes: G03DA01 (spironolactone), D11AX10 (finasteride), D11AX16 (eflornithine), G04CB (finasteride and dutasteride), L02BB01 (flutamide), L02BB (bicalutamide) and G05HB01 (etinyl oestradiol (EE) and cyproterone acetate). Further, the following anti-androgenic combined oral contraceptives (COCs) were included: G03AA09 (EE and desogestrel), G03AA12 (EE and...
drosperinone) and G03AA16 (EE and dienogest). These COCs are not a first-line treatment in Sweden for women who have PCOS without hirsutism.

A non-PCOS group was randomly (1:5) selected among women born in the period 1950–1999 who did not have a PCOS-related diagnosis in the Patient Register during 1997–2017, but who had given birth to at least one singleton infant during 1997–2015, according to the Birth Register. Pregnancies after ovulation induction were excluded, as these mothers are expected to have anovulatory infertility and might represent undiagnosed PCOS cases.

Outcome
It is mandatory to register stillbirths in the Medical Birth Register. Until 30 June 2008, stillbirth was defined as fetal death before or during labour at ≥28 completed weeks of gestation. For deliveries from 1 July 2008 onwards, stillbirth was defined as fetal death from 22 completed weeks of gestation.

Covariates
We collected data on parity, maternal height, weight, smoking habits, cohabitation status, involuntary childlessness, ovulation induction and assisted reproduction from the Medical Birth Register, registered at the first antenatal visit. Further, we collected data on maternal age at delivery, year of delivery, presence of hypertensive and diabetic diseases, and the size and gestational age at birth of the offspring. Hypertensive and diabetic diseases were defined based on the corresponding ICD-10 codes (Table S1). Small (SGA) and large (LGA) for gestational age were defined as birthweights of less or more than two standard deviations from the mean for gestational age and sex. Early pregnancy maternal body mass index (BMI) was calculated as: weight (kg)/height squared (m²). Information on country of birth and education status in the year 2017 was collected from the Total Population Register and the Education Register, respectively. Covariates were categorised in accordance with Table 1.
Statistical analysis

Multiple logistic regression analysis was used to estimate the association between maternal PCOS and stillbirth. Crude and adjusted odds ratios (ORs and aORs, respectively) with 95% confidence intervals (95% CIs) were calculated, using the generalised estimation equation method, as observations were not independent in women who gave birth more than once during the study period. We drew a directed acyclic graph (DAG) to obtain a systematic representation of a possible causal relationship between PCOS diagnosis and stillbirth, and to choose which covariates should be considered as confounders and adjusted for (Figure S1). In model 1, adjustments were made for maternal age, parity, type-1 diabetes, educational level and country of birth. In model 2, we adjusted for the same covariates as in model 1 and also for BMI, as BMI can be regarded as both a mediator and a confounder. A high BMI may be part of the PCOS condition and can be seen as a mediator in the association between PCOS and stillbirth. Increasing BMI is also associated with a higher risk of presenting with PCOS symptoms, and can therefore be considered as a confounder. Information on the effect of smoking on PCOS is scarce in the literature, and therefore smoking was not considered as a confounder. Covariates were included as continuous or categorical in the statistical models. Cases with missing data on covariates were excluded from multiple analyses. Subsequently, crude and adjusted ORs were derived to assess the relationship between stillbirth and PCOS by androgenicity.

A sensitivity analysis was performed, where only women who had been diagnosed with PCOS prior to the index pregnancy were included, to estimate the association between maternal PCOS and stillbirth.

A plot of stillbirth risk by gestational age was constructed, stratified by PCOS. In this plot, pregnancies without known gestational age at birth were excluded (n = 168). The gestational age-specific risk was defined as the number of stillbirths during a time interval (from 22 weeks of gestation onwards, in 2-week intervals) divided by the total number of fetuses undelivered at the beginning of the interval. The proportion was multiplied by 10 000 to provide a gestational age-specific stillbirth rate per 10 000 undelivered fetuses. A 95% CI was calculated using the formula: 95% CI = ±1.96 × standard error. The standard error (SE) was calculated using the formula: SE = \sqrt{(rate of stillbirth during the 2-week interval) \times (1 – rate of stillbirth during the 2-week interval)/(number of undelivered pregnancies at the beginning of the 2-week interval))].

To quantify the proportion of stillbirths where PCOS might be the underlying cause, we calculated the population attributable fraction (PAF). The multiple logistic regression method was used to estimate adjusted ORs with 95% CIs. To calculate PAF, we used the formula: PAF = pd(\[(OR – 1)/OR\]). The pd value represents the proportion of total cases in the population arising from the ith category: in our case, women with PCOS. Data were analysed with SPSS 27 (IBM, Armonk, NY, USA).

The study was approved by the Regional Ethical Review Authority in Uppsala on 9 August 2017, registration number 2017/309. There was no active patient involvement in this study.

Results

Description of study groups

Altogether, we included 25 323 women with PCOS who gave birth to a singleton infant in the period 1997–2015, with a total of 41 851 births. Among these births, the distribution of diagnoses included as PCOS was as follows: PCOS, n = 27 323 (65.3%); androgen excess from the ovaries, n = 94 (0.2%); and anovulatory infertility, n = 14 434 (34.5%). A total of 8543 women with PCOS and severe hyperandrogenism were identified, corresponding to 13 713 births. We included 134 458 women without PCOS giving birth to a singleton infant in 1997–2015, representing 241 750 births (Figure 1).

A total of 1005 stillbirths occurred, giving an overall rate of 3.5/1000 births. Among women who had stillbirths, 25.9% had a PCOS diagnosis, compared with 14.7% of women who had live births.

Women with PCOS had generally a higher maternal age, were more often primiparous and had higher BMIs than women without PCOS (Table S2). Further, they had more often conceived after ovulation induction or other assisted reproduction treatment, and had higher rates of pregnancy-induced hypertension and gestational diabetes.

Table 1 illustrates maternal characteristics in the study population, based on whether they had a stillbirth or a live birth. Women with stillbirth were on average shorter, had higher BMIs, were more often smokers, had higher rates of pre-gestational diabetes, were more often born outside the Nordic countries and had lower educational levels, as compared with women who had live births. Of women who had stillbirths, 26.8% had SGA infants, compared with 2.3% of women who had live births.

PCOS and risk of stillbirth

The rates of stillbirth were 6.2/1000 in women with PCOS and 3.1/1000 in women without PCOS. The risk of stillbirth was twice as high in women with PCOS (OR 2.02, 95% CI 1.76–2.33), remaining at the same level after adjustment for maternal age, parity, type-1 diabetes, educational level and country of birth (model 1). Additional adjustment for maternal BMI (model 2) slightly attenuated
Table 1. Maternal and infant characteristics and rates of stillbirth in a cohort of women giving birth to singleton infants in Sweden, 1997–2015

| Maternal characteristics                                      | Stillbirth | P     |
|--------------------------------------------------------------|------------|-------|
|                                                             | No         | %     | Yes   | %     |       |
| Maternal characteristics                                     | n          | %     | n     | %     |       |
| Polycystic ovary syndrome (PCOS) Yes                         | 41 590     | 14.7  | 261   | 25.9  | <0.01 |
| Age (years)                                                  |            |       |       |       |       |
| Mean ± standard deviations                                   |            |       |       |       |       |
| <25                                                          | 50 028     | 17.7  | 185   | 18.3  | <0.01 |
| 25–34.9                                                      | 194 090    | 68.7  | 636   | 63.0  |       |
| ≥35                                                          | 38 474     | 13.6  | 188   | 18.6  |       |
| Parity                                                       |            |       |       |       |       |
| 1                                                            | 137 748    | 48.7  | 569   | 56.4  | <0.01 |
| ≥2                                                           | 144 844    | 51.3  | 440   | 43.6  |       |
| Height (cm)                                                  |            |       |       |       |       |
| Mean ± standard deviations                                   |            |       |       |       |       |
| <164                                                         | 89 723     | 33.4  | 346   | 39.4  | <0.01 |
| 164–171                                                      | 122 328    | 45.6  | 366   | 41.7  |       |
| ≥172                                                         | 56 350     | 21.0  | 166   | 18.9  |       |
| Missing                                                      | 14 191     |       | 131   |       |       |
| Body mass index in early pregnancy (kg/m²)                   |            |       |       |       |       |
| Mean ± standard deviations                                   |            |       |       |       |       |
| <18.5                                                        | 6472       | 2.5   | 7     | 0.8   |       |
| 18.5–24.9                                                    | 154 289    | 59.9  | 388   | 45.8  |       |
| 25.0–29.9                                                    | 63 601     | 24.7  | 249   | 29.4  |       |
| ≥30                                                          | 33 391     | 13.0  | 204   | 24.1  |       |
| Missing                                                      | 24 839     |       | 161   |       |       |
| Daily cigarette smoking in early pregnancy                   |            |       |       |       |       |
| Yes                                                          | 23 736     | 8.7   | 111   | 12.2  | <0.01 |
| Missing                                                      | 11 136     |       | 100   |       |       |
| Cohabitation                                                 |            |       |       |       |       |
| Yes                                                          | 253 473    | 94.1  | 821   | 92.6  | 0.06  |
| Missing                                                      | 13 135     |       | 122   |       |       |
| Involuntary childlessness before index pregnancy (years)     |            |       |       |       |       |
| <1                                                           | 252 836    | 89.5  | 882   | 87.4  | 0.03  |
| 1–2                                                          | 18 395     | 6.5   | 71    | 7.0   |       |
| ≥3                                                           | 11 361     | 4.0   | 56    | 5.6   |       |
| Ovulation induction                                          |            |       |       |       |       |
| Yes                                                          | 4723       | 1.7   | 30    | 3.0   | <0.01 |
| Assisted reproduction treatment                              |            |       |       |       |       |
| Yes                                                          | 11 185     | 4.0   | 44    | 4.4   | 0.51  |
| Hypertensive disease                                         |            |       |       |       |       |
| Chronic hypertension                                         | 1134       | 0.4   | 6     | 0.6   | 0.21  |
| Pregnancy-induced hypertension*                              | 11 691     | 4.1   | 51    | 5.1   |       |
| Diabetic disease                                             |            |       |       |       |       |
| Type-1 diabetes                                              | 1451       | 0.5   | 22    | 2.2   | <0.01 |
| Type-2 diabetes                                              | 277        | 0.1   | 1     | 0.1   |       |
| Gestational diabetes                                          | 13         | 0.0   | 0     | 0.0   |       |
| Country of birth                                             |            |       |       |       |       |
| Sweden                                                       | 221 876    | 78.5  | 754   | 74.7  | 0.01  |
| Other Nordic country                                         | 3601       | 1.3   | 14    | 1.4   |       |
| Non-Nordic country                                           | 57 115     | 20.2  | 241   | 23.9  |       |
the association to an aOR of 1.50 (95% CI 1.28–1.77; Table 2).

The rate of stillbirth in women without and with anti-androgen drug treatment was 6.9/1000 and 4.9/1000, respectively (Table 2). Compared with women without PCOS, women with PCOS but without severe hyperandrogenism had an association with an increased risk of stillbirth (adjusted model 2, aOR 1.59, 95% CI 1.33–1.91). However, we could not find a significant association between PCOS and stillbirth in women with severe hyperandrogenism in the adjusted model 2 (aOR 1.26, 95% CI 0.95–1.68).

A sensitivity analysis including only women with PCOS who had received the PCOS diagnosis before or during the

### Table 2. Risk of stillbirth in a cohort of women giving birth in Sweden during 1997–2015, by PCOS diagnosis

| Stillbirth | OR (95% CI) |
|------------|-------------|
| **Non-PCOS (n = 241 750)** | 1.00 | 1.00 | 1.00 |
| PCOS (n = 41 851) | 2.24 (1.91–2.62) | 1.99 (1.69–2.34) | 1.59 (1.33–1.91) |
| Number included in analysis | 261 (6.2) | 258 649 | 244 879 |
| **Non-PCOS (n = 241 750)** | 1.58 (1.23–2.03) | 1.52 (1.18–1.96) | 1.26 (0.95–1.68) |
| PCOS, no anti-A treatment (n = 28 138) | 283 601 | 282 329 | 257 468 |
| Number included in analysis | 748 (3.1) | 1.00 | 1.00 |
| **PCOS, with anti-A treatment (n = 13 713)** | 269 888 | 268 649 | 244 879 |
| Number included in analysis | 67 (4.9) | 1.58 (1.23–2.03) | 1.52 (1.18–1.96) | 1.26 (0.95–1.68) |

*Anti-A treatment: at least two dispensations of an anti-androgen drug during the years 2005–2017.
**Adjusted for maternal age, parity, type-1 diabetes, education level and country of birth.
**Adjusted for same covariates as adjusted 1 plus BMI.
index pregnancy \((n = 28,969, 69.2\% \text{ of all women with a PCOS diagnosis})\) showed a similar association between PCOS and stillbirth as found in the main analysis. Compared with women without PCOS, women with PCOS had an OR for stillbirth of 1.70 (95% CI 1.42–2.02). When adjusted for maternal age, parity, type-1 diabetes, educational level and country of birth (adjusted model 1), the aOR for stillbirth was 1.55 (95% CI 1.30–1.86), and when adjusted for BMI as well, the aOR was 1.22 (95% CI 1.00–1.49).

Figure 2 shows the rate of stillbirth by 10,000 pregnancies, in 2-week intervals from 22 weeks of gestation onwards, stratified by PCOS. Compared with women without PCOS, women with PCOS seem to have a higher rate of stillbirth in mid-pregnancy and after 38 weeks of gestation.

Anticipating a causal influence from PCOS on the risk of stillbirth, the PAF was found to be 4.9%, suggesting that 4.9% of stillbirths in pregnant women in Sweden might be associated with a diagnosis of PCOS.

**Discussion**

**Main findings**

In this large population-based cohort study, we found a doubled risk of stillbirth in women with PCOS compared with women without PCOS. The risk was attenuated after adjustment for BMI, but remained significantly increased, with an odds ratio of 1.5. The increased risk of stillbirth in women with PCOS was particularly apparent after 38 weeks of gestation. However, we could not confirm our hypothesis that severe hyperandrogenism in PCOS influenced the association with stillbirth.

**Strengths and limitations**

The main strength of this study was the large cohort of women with PCOS, delivering over 40,000 births, which enabled the highly precise estimates of the rare outcome of stillbirth. Further, the large cohort enabled a comparison of the risk of stillbirth in women with PCOS, with or without severe hyperandrogenism. Information on maternal characteristics was collected prospectively, which reduced recall bias. The diagnoses of PCOS and PCOS-related conditions were entered by a physician, and hence were not self-reported. It is mandatory to report stillbirth to the Medical Birth Register from 22 completed weeks of gestation onwards (until July 2008, stillbirths were recorded from 28 completed weeks of gestation), and the register includes information on over 98% of all births in Sweden, thereby reducing the risk for misclassification of the studied outcome.

We chose to include women with anovulatory infertility in our PCOS classification, as PCOS is the major cause of anovulation. This approach may have introduced misclassification bias, with some women experiencing anovulation but without PCOS being included in the PCOS group. To minimise this bias, we excluded women with anovulation and a concurrent diagnosis of hyperprolactinaemia or primary ovarian failure. However, our PCOS classification might have diluted the association found between PCOS and stillbirth, meaning that the strength of the association might have been underestimated. Further, women with PCOS who never sought medical care and therefore were not diagnosed with PCOS would be wrongly classified as women without PCOS. This misclassification is also expected to dilute the association found between PCOS and stillbirth. To reduce this misclassification bias, births after ovulation induction were excluded from the...
non-PCOS group, as they might represent undiagnosed PCOS cases. We used drug dispensation of prescribed anti-androgenic drugs as a proxy for severe hyperandrogenism. However, we were not able to capture dispensations from the whole study period as the Prescribed Drug Register was initiated in mid-2005, and nor could we capture all treatments for hyper-androgenic symptoms, such as laser treatment for hair removal. Also, not all women with severe symptoms seek medical care. Therefore, we have probably misclassified some women with PCOS and severe hyperandrogenic symptoms as non-severe. Further, women with a prescription of anti-androgenic COCs might have got them for birth control and not for the treatment of hyperandrogenism. This might explain why we could not show a stronger association between severe hyperandrogenism and stillbirth than was found for women with PCOS but without severe hyperandrogenism. Another explanation is that there may be no difference between the groups as regards to risk of stillbirth.

Interpretation
To our knowledge, this is the first study showing an association between PCOS and increased risk of stillbirth and risk in relation to severity of PCOS-related hyperandrogenism. Prior studies in this field report trends of an association. The largest of these studies included only 3787 women with PCOS, which may explain why no association with the rare outcome of stillbirth was found. Two meta-analyses have shown an association between PCOS and risk of perinatal death. Perinatal death includes both stillbirth and early neonatal death. However, the aetiology behind neonatal death partly differs from that of stillbirth, with the major cause of early neonatal death being extreme preterm birth. The rate of stillbirth has been constant in Sweden for many years. Thus, an increased knowledge of risk factors for stillbirth is of great importance to enable prevention.

Women with PCOS, especially women with a hyperandrogenic phenotype, have a higher risk of pregnancy complications, such as induced preterm birth, gestational diabetes and lower birthweight. Possible explanations could be that the placenta morphology in women with PCOS and hyperandrogenism is more often aberrant than in women with PCOS without hyperandrogenism, and that women with hyperandrogenic PCOS generally have greater insulin resistance than women with PCOS but not hyperandrogenism. However, in this study we could not find a stronger association between PCOS and stillbirth in women who had been prescribed anti-androgenic drugs. Our definition of hyperandrogenic PCOS was different from the hyperandrogenic phenotype used clinically and may also encompass women who do not match the clinical phenotype.

Women with PCOS are more likely to be overweight or obese, which are known risk factors for stillbirth. There are likely to be multiple mechanisms linking overweight and obesity to stillbirth, and pre-pregnancy obesity has been associated with hypertensive disorder, placental diseases (even without current hypertensive disorder), fetal anomalies and umbilical cord abnormalities, which are all risk factors for stillbirth. In our study, the risk of stillbirth in women with PCOS was attenuated but still significant after adjustment for BMI, suggesting that other factors are also involved in the pathogenesis.

One possible explanation for the increased risk of stillbirth in women with PCOS might be mediation by fetal growth restriction. In agreement with earlier studies, women with PCOS seemed to have an increased prevalence of giving birth to SGA infants. SGA is frequently a consequence of fetal growth restriction. Fetal growth restriction has a strong association with stillbirth, and oxidative stress is considered to play an important role in the development of fetal growth restriction. PCOS is associated with chronic inflammation, oxidative state and mitochondrial dysfunction in non-pregnant women, conditions that might also prevail during pregnancy. Women with PCOS have an increased risk of gestational hypertension and pre-eclampsia, which are associated with similar placental lesions as those found in stillbirth. According to recent rodent studies, fetal loss in PCOS-like dams is associated with oxidative stress because of an elevated production of reactive oxygen species and the inactivation of antioxidative proteins in the uterus and placenta. In addition, Zhang et al. have shown that ferroptosis, which is regulated cell death dependent on iron, is a potential mechanism leading to uterine and placental dysfunction in PCOS-like dams, subsequently leading to fetal loss. Based on these data, we speculate that increased inflammation and oxidative stress in women with PCOS might contribute to their increased risk of stillbirth. The PAF for PCOS in stillbirths is 4.9%, raising the question of whether PCOS requires more attention in antenatal care.

Conclusion
In this study, we found a doubled risk of stillbirth in women with PCOS. The increased risk was only partly explained by higher BMIs in women with PCOS. The risk of stillbirth seemed to be increased most in late pregnancy. During antenatal care, it might be valuable to highlight the association of PCOS and adverse pregnancy outcomes, including stillbirth. Further research is warranted to confirm this association between PCOS and stillbirth and to investigate possible causal mechanisms. More knowledge is important for developing evidence-based guidance on the further monitoring of women with PCOS during pregnancy and identifying women at increased risk of stillbirth.
Disclosure of interests
None declared. Completed disclosure of interests form available to view online as supporting information.

Contribution to authorship
HV and AKW were the principal investigators and drafted the article. AKW, HV and ISP formulated the study. ISP contributed to the acquisition of the data. HV performed the statistical analysis. NR, TKK, LL and MJ contributed to the process of writing the manuscript and critically revised the article. All authors contributed to the intellectual content and study design and approved the final version of the article for publication.

Details of ethics approval
The study was approved by the Regional Ethical Review Authority in Uppsala on 9 August 2017, registration number 2017/309.

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Data availability
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 license for this study. Data are available from Prof. Inger Sundström Poromaa (inger.sundstrom@kbh.uu.se) for qualified, interested researchers with the permission of The Swedish National Board of Health and Welfare and Statistics Sweden.

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

Figure S1. Directed acyclic graph (DAG) to estimate causal inference for the association of PCOS and stillbirth.

Table S1. Classification of diseases according to the International Classification of Diseases (ICD), 10th version.

Table S2. Maternal and infant characteristics in a cohort of women, with and without PCOS, giving birth in Sweden, 1997–2015.

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