

Pre-Conception Characteristics Predict Obstetrical and Neonatal Outcomes in Women With Polycystic Ovary Syndrome

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Context: Women with polycystic ovary syndrome (PCOS) are at increased risk for obstetric and perinatal complications. At present, it is unknown how characteristics of PCOS relate to the likelihood of these complications.

Objective: To evaluate which preconception features are associated with obstetric and perinatal disease among infertile women with PCOS.

Design: Data from two prospective cohort studies completed from January 2004 until January 2014 were linked to Dutch Perinatal national registry outcomes.

Setting: Two Dutch university medical centers.

Participants: 2768 women diagnosed with PCOS were included. Participants underwent an extensive standardized preconception screening. Exclusion criteria included: age <18 years or >45 years, language barrier, or failure to meet PCOS criteria.

Interventions: None.

Main Outcome Measures: Outcome measures were obtained from the Dutch Perinatal national registry and included: preeclampsia, preterm delivery, small for gestational age (SGA), low Apgar score, and any adverse outcome.

Results: 1715 (62% of participants) women with PCOS were identified as undergoing a pregnancy with live birth after screening. In fully adjusted models, prepregnancy free androgen index was associated with subsequent preeclampsia [OR (95% CI), 1.1 (1.0 to 1.1)]. Fasting glucose [1.4 (1.2 to 1.7)] and testosterone [1.5 (1.2 to 1.7)] predicted preterm delivery. Fasting insulin [1.003 (1.001 to 1.005)], and testosterone [1.2 (1.1 to 1.4)] predicted any adverse outcome. SGA was only predicted by features nonspecific to PCOS.

Conclusions: Primary disease characteristics of PCOS, chiefly hyperandrogenism and impaired glucose tolerance, predict suboptimal obstetric and neonatal outcomes. Increased surveillance during pregnancy should focus on women with PCOS and these features to help mitigate disease risk. (*J Clin Endocrinol Metab* 104: 809–818, 2019)

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of childbearing age (1). This heterogeneous syndrome is predominantly characterized by oligo-anovulation, hyperandrogenism, and polycystic ovarian morphology (PCOM) (2, 3). Additionally, women diagnosed with PCOS frequently suffer from metabolic dysfunction and are at increased risk for complications during pregnancy and the perinatal period (4–8).

Increased rates of gestational diabetes mellitus, pregnancy induced hypertension, preeclampsia, caesarean-section delivery, and preterm birth have been reported among pregnant women with PCOS (9–12). Neonates born to women with PCOS more frequently present with small for gestational age (SGA) birth weight, low Apgar score, postpartum admission to a neonatal intensive care unit, and even perinatal death (8, 9, 12–15). Complication data are not unequivocal, as some groups have failed to establish increased risk for preeclampsia (15), caesarean-section (10, 16), preterm delivery (16), and SGA (9, 12) among women with this syndrome. Variations between studies may be due to the limited sample size of individual studies and to the heterogeneity of included women with PCOS (17).

In the general population it is postulated that maternal features affect both obstetric and perinatal complication rates. Maternal health and risk behaviors determine the intrauterine environment, which in turn influences a child's future wellbeing and development (18, 19). Among women with PCOS, primary disease characteristics (*i.e.*, hyperandrogenism, menstrual irregularities, and insulin resistance) likely modify this group's risk of maternal and perinatal complications. The few studies available that have attempted to assess disease risk among these women suggest that variability in diagnostic criteria for PCOS, as well as some markers of metabolic dysfunction, may alter risk of adverse pregnancy and neonatal outcomes (15, 17, 20–23). Data between studies are conflicting, however, and there is a paucity of reports comprehensively evaluating the unique risk factors for obstetric and perinatal complications among women with PCOS.

This paper aims to identify the subgroup of women diagnosed with PCOS who are at greatest risk for obstetric and/or neonatal disease. We use two large data resources of 2768 prospectively phenotyped women diagnosed with PCOS before conception and the Dutch Perinatal national registry (24). These results may allow for the stratification of women with PCOS into either normal or high risk categories. In turn these findings may improve allocation of resources, monitoring strategies, and treatment burden.

Materials and Methods

Study design

A secondary analysis of two large prospective cohort studies, referred to as the cycle disturbances, oligo-amenorrhea and amenorrhea (COLA) screening (25) on menstrual cycle disturbances, as well as the complications of polycystic ovary syndrome pregnancy: evaluating risk (COPPER) (20) trial was completed. The COLA study recruited women with menstrual cycle irregularities and extensively evaluated relevant endocrine, metabolic, and phenotypic characteristics associated with subjects' menstrual disturbances. The COPPER trial prospectively evaluated pregnancy and perinatal outcomes among women with a diagnosis of PCOS. Women involved in the current analysis were recruited at the University Medical Center, Utrecht and Erasmus Medical Center, Rotterdam from 1 January 2004 to 1 January 2014. An extensive standardized screening was performed for all women as previously described (20, 26). PCOS was assigned according to the 2003 Rotterdam consensus criteria following standardized phenotyping (2, 3). Women were excluded in case of age <18 years or >45 years, language barrier, or failure to meet PCOS criteria.

Data obtained from the COLA and COPPER trials were subsequently linked to the Dutch Perinatal registry (Perined) by the Dutch Central Bureau of Statistics (CBS). The Perined registry consists of population-based data on ~96% of all deliveries and pregnancies carried to greater than 16 completed weeks of gestation in the Netherlands, as previously published (24). Data regarding spontaneous or terminated abortions were not included as the CBS only includes data on live births. Caregivers routinely record maternal, neonatal, and delivery characteristics using electronic registration forms. All data received by the national registry office are validated. If inconsistencies are noted, the data are returned to the caregivers for correction. Data were available from January 1995 to December 2016 at the time of linkage. Both data from our group and the Perined were uploaded to the Dutch CBS, whereby each person receives a unique, yet anonymous, identification code. Highly accurate coding is accomplished through the use of multiple identifiers unique to each subject. Data from our groups and from the Perined were then linked via these unique identification codes. The described linkage procedure is only possible under special conditions, after obtained permission from the Dutch CBS, which guarantees no legal privacy infringements are made to the interest of the patients/citizens. A validation of the Perined data set was possible through comparison of selected (coinciding) obstetric and perinatal data collected both in the COPPER trial, as research data, and in Perined records, through standard abstraction routinely collected in the Netherlands.

Study procedures were conducted with approval of the local institutional ethical review boards (IRB number 17-062). The ethics committee of the Perined and CBS approved the described linkage and subsequent use of the data. COLA and COPPER studies were registered on www.clinicaltrials.gov with trial numbers NCT02309047 and NCT00821379, respectively. All trial participants provided written informed consent.

Clinical assessments

All participants recruited from the outpatient infertility unit and diagnosed with PCOS underwent a standardized baseline screening. This included a lifestyle questionnaire with

socio-economic status, mental state, medical history, and family history of cardiovascular disease (CVD) and/or type 2 diabetes mellitus. Anthropometric measurements included height, weight, waist and hip circumference, as well as blood pressure (BP). Transvaginal ultrasound scans of the uterus and ovaries were completed and assessed for antral follicle count and ovarian volume. Metabolic and endocrine measurements were performed and analyzed in each center separately as previously outlined (27). To account for differences in assays across years of the study and between centers, previously reported conversion factors were used to standardize all laboratory measurements as necessary (25).

The 2003 Rotterdam criterion (2, 3) were assigned as follows: hyperandrogenism-free androgen index (FAI) ≥ 4.5 or Ferriman-Gallwey score of ≥ 9 (26), PCOM- ≥ 12 follicles per ovary or an ovarian volume ≥ 10 mL, oligo/anovulation-menstrual cycles ≥ 35 days.

Women enrolled in the COPPER study had additional follow-up antenatal visits 10 times from gestational age 6 to 8 weeks until 40 to 42 weeks of pregnancy. Maternal BP, body weight, and venous blood draws were completed at each visit. At 6 to 8 weeks' gestation, a transvaginal ultrasound examination was performed to detect fetal heart activity and measure crown-rump length. Crown-rump length was used to determine gestational age. A medical doctor collected pregnancy outcome data after delivery.

Study outcomes

All preconception data were obtained through the prospective COLA and COPPER cohort studies. Obstetric and neonatal outcomes of enrolled women with PCOS were obtained from the Perined database after database linkage. Primary outcome analyses were restricted to the first pregnancy after baseline screening. For the sole purpose of assessing the validity of outcomes in the Perined data set, data from a subset of women prospectively evaluated as part of the COPPER trial were compared with data provided by the Perined database. Occasionally data from second or greater pregnancies after screening were used for validity assessment alone.

Obstetric complications obtained from the Perined database included preeclampsia and duration of gestation. Development of preeclampsia is recorded in the Perined database through two methods. Either a woman may be coded as having developed preeclampsia or BP and presence or absence of proteinuria after 20 weeks' gestation may be recorded. If a woman either was coded as having preeclampsia or had a recorded diastolic BP of 90 or more as well as proteinuria, she was considered as having developed preeclampsia for analyses. This procedure is standard for Perined data. Dutch obstetric guidelines have adopted the definition of preeclampsia proposed by the International Society for the Study of Hypertension in Pregnancy defined as BP >140 mm Hg and proteinuria >300 mg/24 hours in the second half of pregnancy (28). Gestational age at delivery was also classified into preterm (<37.0 weeks), term (37.0 to 41.9 weeks), and post term (≥ 42.0 weeks).

Neonatal data obtained from the Perined included birth weight, 5-minute Apgar score, and gender. Birth weight percentiles were calculated for each child based on Dutch population normative curves using the gender, gestational age, parity of the mother, and birth weight of the child (29). Children were also classified as SGA (birth weight percentile $<10\%$) and large for gestational age (birth weight percentile $>10\%$). Apgar

scores were classified as "low Apgar score" if 5-minute Apgar scores were <7 .

A composite variable of any adverse outcome (preeclampsia, preterm delivery, SGA, and/or low Apgar score) was also calculated such that the development of any complication was coded as having an adverse outcome and the lack of development of any complication was coded as not having an adverse outcome.

Statistical analysis

For all variables of interest 89% of values were complete. Data were missing at random. Missing baseline values were imputed by conditional multiple imputation with 10 iterations and 5 imputations through predictive mean matching.

Baseline characteristics were compared between groups using χ^2 or Fisher's exact tests for categorical variables. In accordance with CBS protocol to protect individual citizen's privacy, groups with 10 or fewer participants are shown as $n < 10$.

To assess the accuracy of the linked Perined database, obstetric and neonatal outcomes recorded prospectively during the COPPER trial were compared with outcomes recorded in the Perined database. Kappa agreement statistics were calculated for categorical variables and intraclass correlation coefficients were calculated for continuous variables. In cases of discrepancy between the COPPER and Perined data sets, data provided by the Perined were used as per CBS protocol prohibiting auditing of individual participant data and to maintain homogeneity across outcomes in the data set.

To assess the relationship between preconception characteristics and obstetric and neonatal complications, first, each potential relevant baseline characteristic was entered into separate regression analyses with obstetric and neonatal outcomes as dependent variables. Univariate logistic regression analyses were used for binary obstetric outcomes. For outcomes utilizing offspring data, generalized estimating equations (GEEs) analysis was used, which controlled for correlations between siblings from multiple gestation pregnancies. Secondly, those baseline characteristics that were found to associate with outcomes of interest in regression analyses at the $P < 0.1$ level were then entered into multivariable logistic regression models, as well as multivariable GEE models, using a backward elimination technique with a threshold of $P < 0.1$ for inclusion in the final model. ORs were calculated for variables retained within the final models. ORs were expressed as an increase in odds for every 1-unit increase in continuous variables.

Multiple gestation pregnancies were accounted for in two ways: (i) for two-sample nonadjusted comparisons, women with multiple gestation pregnancies were excluded to eliminate the effects of multiple gestations on outcomes of interest; (ii) for multivariable adjusted regression analyses presence or absence of a multiple-gestation pregnancy was included as a dependent variable for each participant and included in final multivariable models if found to associate with the outcome of interest at the $P < 0.1$ level.

Multiple testing was controlled for using the Holm-Bonferroni correction method, whereby tests are ranked in order of ascending significance level and adjusted α levels, below which a test is considered significant, is calculated based on each test's rank and the number of overall tests. This was completed for two sample comparisons, such that P values were only considered significant if less than the adjusted α level (30). In the exploratory context of finding candidate predictive

factors, we refrained from Bonferroni adjustments for simple logistic regression and GEE analyses. Thus, two sample comparisons were adjusted for a total of 12 tests.

All data were analyzed using IBM SPSS Statistics (version 20.0; IBM SPSS, Inc., Chicago, IL).

Results

Linkage results

In total, 2768 women with PCOS were screened at University Medical Center Utrecht and Erasmus University Medical Centre Rotterdam over the 10-year inclusion period. Linkage to the CBS national database was successful for 97% of these women. Data on 4,235,994 pregnancies from 1995 to 2016 were uploaded from the Perined. Excluding cases of miscarriage, 98% of uploaded pregnancies were accurately identified and linked to the CBS national database. After linkage of the Perined data set to the Copper/COLA data set a total of 1715 (62% of the total number of women with PCOS screened during that time period) women were identified as having a pregnancy after screening that resulted in live birth and were thus included in the analyses. Seventy (4%) women had multiple gestation pregnancies, resulting in a total of 1786 offspring included in the final analyses (Table 1).

Utilizing intraclass correlation (r) and Kappa (κ) statistics for continuous and categorical variables, respectively, concordance between data recorded in the COPPER trial and reported by the Perined was $\kappa = 0.920$ for pre-eclampsia, $r = 0.997$ for birth weight, and $r = 0.940$ for 5-minute Apgar score. A threshold of κ or $r > 0.9$ was used to represent a high level of agreement.

Baseline characteristics

Of the 1715 women included, the average age at screening was 28.7 years; 1432 (84%) women were Caucasian, 506 (30%) women had a history of a previous pregnancy, and 363 (21%) women had a history of a previous delivery. Ninety-eight percent of included women had oligo-anovulation, 95% had PCOM, and 50% had hyperandrogenism (Table 1). Among recorded obstetric outcomes, 64 women (4%) were recorded as developing preeclampsia. One hundred seventy-four women (10%) delivered preterm, whereas 12 (1%) women delivered post term. Offspring were born at an average gestational age of (mean \pm SD) 39.1 ± 2.4 weeks, with an average birth weight of 3268.0 ± 666.0 g and an average birth weight percentile of $51\% \pm 28\%$. One hundred fifty-one (9%) offspring were SGA. One hundred seventy-two (10%) offspring were LGA. Average 5-minute Apgar was $9.4 \pm$

Table 1. Baseline Characteristics of 1715 Enrolled Infertile Women Diagnosed With PCOS With a Recorded Pregnancy Following Initial Diagnosis (%)

Patient History		Diagnostic Criteria	
Age, y	28.7 \pm 4.3	Oligo-amenorrhea	1675 (98)
Ethnicity		PCOM	1584 (95)
Caucasian	1432 (84)	Hyperandrogenism	854 (50)
Black	94 (5)		
Asian	125 (7)	Endocrine evaluations	
Other	64 (4)	Ferriman-Gallwey Score	3.7 \pm 5.0
First degree family history of DM	142 (9)	FAI	5.3 \pm 4.4
First degree family history of CVD	1423 (92)	SHBG, nmol/L	48 \pm 27
Gravidity		AD, nmol/L	6.0 \pm 2.6
0	1191 (70)	Testosterone, nmol/L	1.9 \pm 0.9
1	312 (18)	DHEAS, umol/L	4.8 \pm 2.4
2	124 (7)	Estrogen, pmol/L	222 \pm 197
3 or more	70 (4)	FSH, U/L	6.1 \pm 2.3
Parity		LH, U/L	10.6 \pm 9.4
0	1352 (79)	Metabolic evaluations	
1	287 (17)	BMI, kg/m ²	26.2 \pm 6.1
2	60 (4)	WHR	0.8 \pm 0.1
3 or more	16 (1)	Systolic BP, mm Hg	119 \pm 13
Cigarettes/d	2.0 \pm 4.9	Diastolic BP, mm Hg	76 \pm 10
Current smoker	296 (21)	Glucose, mmol/L	4.8 \pm 0.8
Current alcohol use	530 (44)	Insulin, pmol/L	60 \pm 56
Drinks/wk	1.5 \pm 2.8	LDL-C, mmol/L	2.9 \pm 1.2
		HDL-C, mmol/L	1.5 \pm 0.4
		Triglycerides, mmol/L	1.0 \pm 0.8
		Total cholesterol, mmol/L	4.8 \pm 1.0

Variables given as mean \pm SD for continuous variables or number (percent) for categorical variables.

Abbreviations: AD, androstenedione; DM, diabetes mellitus; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

1.1 and 52 (3%) children had an Apgar score below 7 (low Apgar) (Table 2).

Frequency of obstetric and perinatal outcomes among women with and without baseline diagnostic criteria for PCOS

Comparing women with and without the individual 2003 Rotterdam diagnostic criterion (2, 3) for PCOS, women with hyperandrogenism had a significantly higher frequency of preeclampsia (5% vs 2%, $P = 0.003$) and preterm deliveries (11% vs 7%, $P = 0.004$) than women without hyperandrogenism. No significant differences were seen between women with and without oligo-amenorrhea or PCOM across all outcomes (significance was determined after Holm-Bonferroni correction for multiple comparisons) (Fig. 1).

Prediction of adverse outcomes

The main outcomes of interest were (i) preeclampsia, (ii) preterm delivery, (iii) SGA, (iv) low Apgar score, and (v) a composite variable of any of the four obstetric or perinatal adverse outcomes analyzed. Factors to include in final multivariable regression analyses were selected using separate GEEs controlling for twin siblings for outcomes using offspring data and separate logistic regression analyses for maternal outcomes. A threshold of $P < 0.1$ was used for inclusion. The following outcomes were predicted by the corresponding baseline features and included in final multivariable models: preeclampsia was predicted by non-Caucasian ethnicity, family history

of CVD, presence of a multiple gestation pregnancy, smoking status, FAI, body mass index (BMI), diastolic BP, fasting insulin, and total cholesterol; preterm delivery was predicted by non-Caucasian ethnicity, presence of a multiple gestation pregnancy, smoking status, testosterone, dehydroepiandrosterone sulfate (DHEAS), estrogen, diastolic BP, and fasting glucose; SGA was predicted by age, non-Caucasian ethnicity, parity, presence of a multiple gestation pregnancy, smoking status, BMI, and fasting glucose; low Apgar was predicted by presence of a multiple gestation pregnancy, drinks/week, oligo-anovulation, FAI, waist-to-hip ratio (WHR), fasting insulin, and low-density lipoprotein cholesterol; any adverse outcome was predicted by age, non-Caucasian ethnicity, presence of a multiple gestation pregnancy, smoking status, testosterone, DHEAS, WHR, diastolic BP, and fasting insulin.

These factors were then entered into separate multivariable regression analyses. A backward elimination technique with a threshold of $P < 0.1$ was used to develop the final prediction models. All baseline features meeting this predefined threshold in the final iteration of the models are presented in Fig. 2. Preeclampsia was independently predicted by presence of a multiple gestation pregnancy [OR (95% CI); 2.9 (1.2 to 7.3), $P = 0.020$], FAI [1.1 (1.0 to 1.1), $P = 0.020$], and diastolic BP [1.1 (1.0 to 1.1), $P < 0.001$] [Fig. 2(A)]. Preterm delivery was independently predicted by presence of a multiple gestation pregnancy [13.2 (7.8 to 22.2), $P < 0.001$], Caucasian ethnicity [0.6 (0.4 to 0.9), $P = 0.023$], testosterone [1.5 (1.2 to 1.7), $P = 0.001$], estrogen [1.001 (1.000 to 1.002), $P = 0.007$], and fasting glucose [1.4 (1.2 to 1.7), $P = 0.001$] [Fig. 2(B)]. SGA was independently predicted by Caucasian ethnicity [0.3 (0.3 to 0.6), $P < 0.001$], smoking status [2.0 (1.3 to 2.9), $P < 0.001$], and BMI [0.96 (0.92 to 0.99), $P = 0.011$] [Fig. 2(C)]. Low Apgar score was independently predicted by presence of a multiple gestation pregnancy [2.6 (1.3 to 5.4), $P = 0.008$] and oligo-amenorrhea [0.2 (0.1 to 0.4), $P < 0.001$] [Fig. 2(D)]. Finally, any adverse outcome was independently predicted by presence of a multiple gestation pregnancy [5.9 (3.6 to 9.8), $P < 0.001$], Caucasian ethnicity [0.5 (0.4 to 0.7), $P < 0.001$], smoking status [1.7 (1.2 to 2.3), $P = 0.002$], testosterone [1.2 (1.1 to 1.4), $P = 0.002$], and fasting insulin [1.003 (1.001 to 1.005), $P = 0.013$] [Fig. 2(E)].

Discussion

A large cohort of 2768 prospectively phenotyped infertile women diagnosed with PCOS before conception was linked with the national Dutch Perinatal registry, including a total of 1715 pregnancies and 1786 offspring.

Table 2. Maternal and Offspring Outcomes of 1715 Infertile Women Diagnosed With PCOS With Recorded Pregnancy After Screening (%)

Maternal Outcomes (n = 1715)	
Multiple gestation pregnancy	70 (4)
Preeclampsia	64 (4)
Delivery term	
Preterm	174 (10)
Term	1522 (88)
Postterm	12 (1)
Gestational age, wk	39.1 ± 2.4
Offspring Outcomes (n = 1786)	
Gender	
Male	932 (52)
Female	850 (48)
Birth weight, g	3268 ± 666
Birth weight percentile, %	51 ± 28
SGA	151 (9)
LGA	172 (10)
5-min Apgar	9.4 ± 1.1
Low Apgar	52 (3)

Variables given as mean ± SD for continuous variables or number (percent) for categorical variables.
Abbreviations: DM, diabetes mellitus; LGA, large for gestational age.

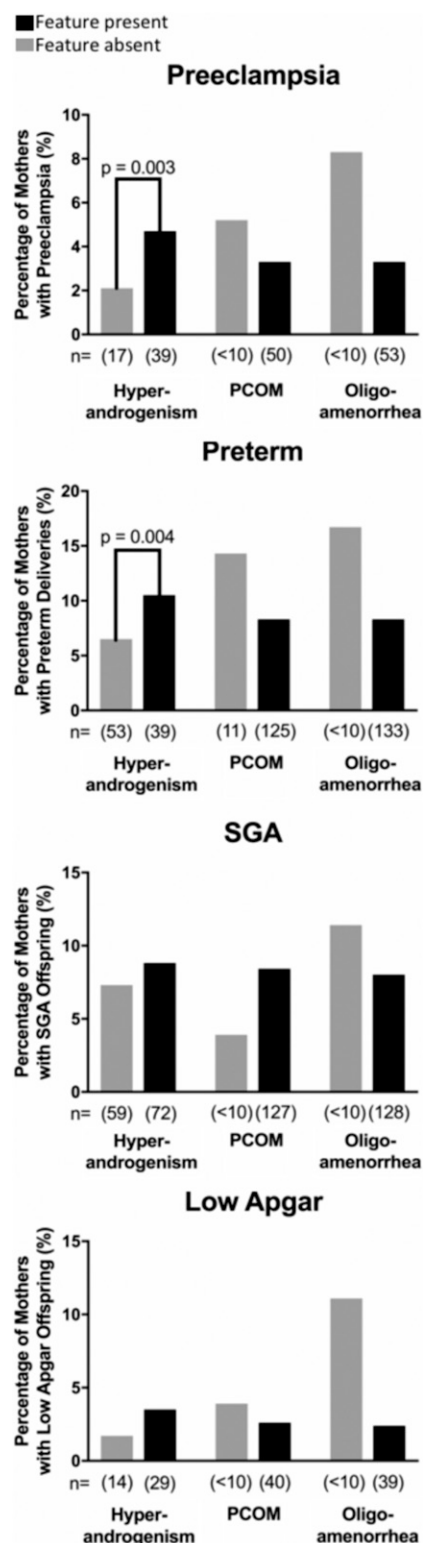


Figure 1. Percentage of women with PCOS (total $n = 1645$) and singleton pregnancies that developed obstetric and perinatal complications compared among women with and without individual 2003 Rotterdam diagnostic criterion for PCOS (2, 3). Comparisons are made among the main diagnostic criterion for PCOS. Analyses include women with single gestation pregnancies only. P values determined by χ^2 tests or Fisher's exact tests. P values are listed for significant comparisons after Holm-Bonferroni correction. The following definitions were used for baseline features: Hyperandrogenism = $\text{FAI} \geq 4.5$ or a Ferriman-Gallwey score of ≥ 9 ; PCOM = ≥ 12 follicles

The current study provides convincing evidence that preconception hyperandrogenism and impaired glucose tolerance, among women with PCOS, predict multiple obstetric and perinatal complications believed to affect both maternal wellbeing and the future health of offspring.

In the present cohort of women with PCOS, androgen levels independently predicted development of preeclampsia, preterm deliveries, and any adverse obstetric or perinatal outcome. Previous reports have observed comparable results among women with single gestation pregnancies (15, 23) and utilizing either nonadjusted analyses (23) or minimally adjusted models controlling for PCOS nonspecific features such as age, BMI, and parity (15). The current study has observed these results in fully adjusted models controlling for an extensive array of potentially confounding features, such as markers of metabolic and CVD, while including women with multiple gestation pregnancies (31–33) and controlling for this factor in multivariable modeling. Furthermore, unlike previous studies, the current results were found within a large population of women with PCOS. This suggests women with PCOS and hyperandrogenism are at increased risk of obstetric and perinatal disease compared not only to non-PCOS women, but also to women with PCOS without hyperandrogenism.

Hyperandrogenism may have a direct role in disease development. Androgens may contribute to abnormal placental morphology (34), alterations in early trophoblast invasion and placentation, and altered cervical remodeling and myometrial function (35–38). Risk of disease may also be partially due to the link between hyperandrogenism and more severe metabolic dysfunction, including obesity and insulin resistance, among women with PCOS (6, 25). The present results, however, were observed after controlling for any relevant baseline marker of cardio-metabolic disease available thus suggesting an independent effect of androgens on disease risk. Overall, it appears that, prior to pregnancy, hyperandrogenism is a potential indicator of increased likelihood of obstetric and perinatal disease among women with PCOS.

Few have evaluated the possible influence of metabolic dysfunction on obstetric and perinatal complications in women with PCOS. The current data indicate that fasting glucose concentrations before conception predict preterm delivery and fasting insulin is associated with the

Figure 1. (Continued). per ovary or an ovarian volume ≥ 10 mL. Black bars represent presence of a feature and gray bars indicate absence of a feature. Groups with less than 10 people are indicated by " $n < 10$ " to protect individual citizen's privacy per Dutch CBS protocol.

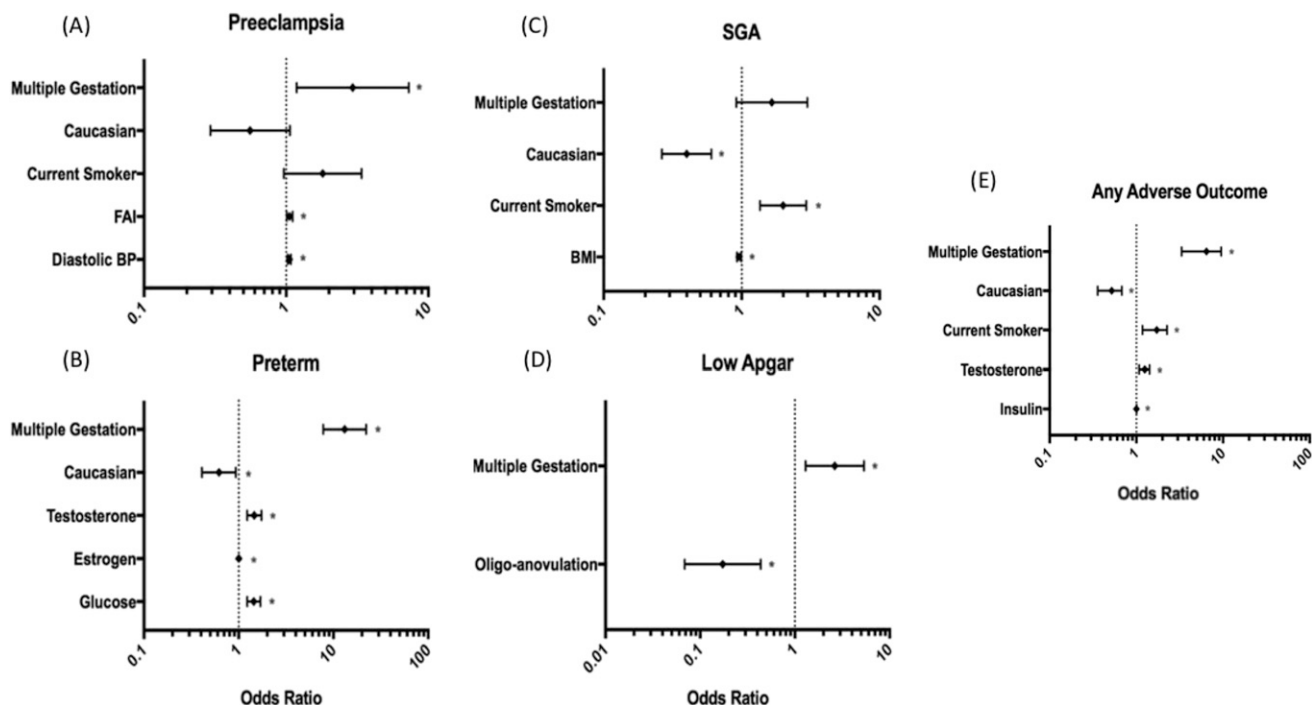


Figure 2. Odds of developing perinatal and obstetric complications among 1715 infertile women diagnosed with PCOS. ORs are presented for all factors retained in the final multivariable logistic regression models for (A) preeclampsia and (B) preterm delivery and final multivariable GEE models for (C) SGA, (D) low Apgar, and (E) any adverse outcome. A P value threshold of $P < 0.1$ was used to determine which factors were retained in each model and in turn presented in this figure. Each model controls for the presented factors as well as other features that did not meet the threshold for inclusion in the final model, but predicted each outcome in separate baseline analyses at the $P < 0.1$ level including: family history of CVD, BMI, fasting insulin, and total cholesterol for preeclampsia; smoking status, dehydroepiandrosterone-sulfate, and diastolic BP for preterm delivery; age, parity, and fasting glucose for SGA; drinks/wk, FAI, WHR, insulin, and low density lipoprotein cholesterol for low Apgar score; age, oligo-anovulation, WHR, diastolic BP, and dehydroepiandrosterone-sulfate for any adverse outcome. ORs using continuous variables are given for a 1-unit increase. Significant ORs are indicated with an asterisk ($P < 0.05$).

odds of any adverse outcome in multivariable analyses. Impaired glucose regulation is associated with endothelial dysfunction, inflammation, and may exacerbate adverse effects of hyperandrogenism, which may explain the observed relationship with these outcomes (39, 40). Thus, increased fasting glucose and insulin prior to pregnancy may be linked to worsening hyperandrogenism and predict obstetric disease among women with PCOS.

Although key features of PCOS are associated with obstetrical complications, SGA was only predicted by factors well known to affect pregnancy outcomes in the general population including a multiple gestation pregnancy, ethnicity, smoking, and BMI (41). Previous reports are conflicting with regards to risk of SGA among PCOS women (8). The prevalence of SGA in the Netherlands as of 2013 is 6.3%, lower than that of the reported 9% in the current data set (42). The present findings, however, may suggest that this increased rate is mainly secondary to modifiable risk factors such as BMI and smoking as well as demographic information such as ethnicity.

The presented study has several strengths. The current data analysis represents the largest systematic evaluation

of prepregnancy features in PCOS linked to obstetric and perinatal outcomes as registered nationally. Previous studies of this kind have included less than 500 participants with PCOS (15, 17, 21–23, 26, 43, 44). Utilizing a national database also circumvented issues such as lost to follow-up, often faced in other prospective cohort studies. Data collected from multiple centers in the Netherlands and across several years were included, improving generalizability of the results. Additionally, after initial screening, all women were included regardless of method of conception [spontaneous, ovulation induction—the anticipated vast majority (45), or in-vitro fertilization] increasing applicability of results across treatment strategies. Women were extensively phenotyped in a standardized fashion and the reliability of outcome variables obtained from the Dutch Perinatal database were validated ensuring good accuracy of our baseline and outcome variables. Furthermore, an extensive number of preconception features were available for analysis allowing for a comprehensive evaluation of obstetric and perinatal disease. To accomplish this systematic assessment multiple tests were required increasing the likelihood of a type I error. To mitigate this risk, the Holm-Bonferroni correction method was used

for two-sample comparisons. Finally, these results appear to be highly relevant. The value of the Rotterdam criteria to guide treatments for women with PCOS has recently been called into question (46). However, the present findings suggest that the Rotterdam criteria (chiefly hyperandrogenism and oligo-anovulation), in addition to having utility for predicting reproductive outcomes, appear to be useful for identifying risk of obstetric and perinatal disease (46).

Some limitations of the current study should also be mentioned. Recruitment was primarily of infertile women presenting with menstrual cycle irregularities and few women with regular cycles were included. Analyses of oligo-anovulation were thus restricted and our ability to draw conclusions regarding causality between this feature and perinatal outcomes was limited. Baseline variables and outcomes used for analyses were restricted to those already collected in our prospective cohort study or reliably available from the Dutch Perinatal registry. As such, we were unable to include analyses on pregnancy induced hypertension and gestational diabetes mellitus: two major obstetric complications in PCOS. Limited data were also available concerning paternal features, method of conception, or monitoring and interventions during pregnancy, which are known to impact obstetric outcomes and thus may have confounded observed results (47–50). Finally, of the 38% of women who did not have an identified pregnancy after screening the percentage of women who attempted to achieve pregnancy but were unsuccessful, had miscarriage, or terminated a pregnancy is not known as only live births were recorded in our data set. External validation is also required to ensure applicability of these results to populations outside of the Netherlands.

Taken together, the present analyses represent the largest assessments of a possible association between baseline characteristics in women with PCOS and major obstetric and perinatal complications. The current results suggest that primary disease characteristics of PCOS, chiefly hyperandrogenism and changes in blood glucose regulation, have relevance in predicting obstetric complications among PCOS women. Based on these findings it appears that women with PCOS and these features should be the focus of increased surveillance during pregnancy to help mitigate these women's and their children's increased risk of disease.

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