Increased rates of complications in singleton pregnancies of women previously diagnosed with polycystic ovary syndrome predominantly in the hyperandrogenic phenotype

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Objective: To study the presence of several maternal and neonatal complications in a cohort of women with hyperandrogenic as well as normoandrogenic polycystic ovary syndrome (PCOS) and women with PCOS who received different fertility treatments.
Design: Prospective multicenter cohort study.
Setting: Hospitals and midwifery practices.
Patient(s): One hundred and eighty-eight women with PCOS and singleton pregnancies (study group) and 2,889 women with a naturally conceived singleton pregnancy (reference group).
Intervention(s): Observational study.
Main Outcome Measure(s): Maternal and neonatal pregnancy complications.
Result(s): Women with PCOS had a statistically significantly increased risk of developing gestational diabetes (adjusted odds ratio [AOR] 4.15; 95% confidence interval [CI], 2.07–8.33) compared with the reference group, and their infants were more often born small for gestational age (AOR 3.76; 95% CI, 1.69–8.35). In a subgroup analysis, maternal complications were statistically significantly more often present in women with hyperandrogenic (defined as a free androgen index >4.5) PCOS (n = 76; 40% of all PCOS women) compared with those with normoandrogenic PCOS (n = 97; 52% of all PCOS women) (45% vs. 24%; P=.003); no statistically significant differences were observed between these groups regarding neonatal complications.
Conclusion(s): Women with PCOS have an increased risk of maternal and neonatal pregnancy complications, especially women with the hyperandrogenic phenotype.
Clinical Trial Registration Number: NCT00821379. (Fertil Steril® 2017;108:333–40. ©2017 by American Society for Reproductive Medicine.)
Key Words: Hyperandrogenic, PCOS, pregnancy complications

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Polycystic ovary syndrome (PCOS), a common endocrine disorder during reproductive life, occurs in up to 15% of all women (1). According to the Rotterdam consensus criteria, this heterogeneous condition is diagnosed when at least two out of the three of the following features are present: polycystic ovaries, oligo- or anovulation, and clinical or biochemical hyperandrogenism (2). Additional characteristic features associated with PCOS include obesity, insulin resistance, and

metabolic abnormalities including dyslipidemia and type 2 diabetes (3, 4). Women presenting with anovulatory infertility and diagnosed with PCOS usually undergo ovulation induction (5) with reported cumulative live-birth rates close to 80% (6, 7). However, multiple pregnancies and related perinatal morbidity represent an inherent complication of such interventions (8). Even when an ongoing singleton pregnancy is achieved, women with PCOS have an evidently increased risk of pregnancy complications (9–11).

Although the pathophysiology of pregnancy complications in PCOS is not entirely understood, it may be directly related to features associated with PCOS itself, including hyperandrogenism, obesity, insulin resistance, infertility treatment, and placental dysfunction. Three meta-analyses addressed pregnancy complications in PCOS (9–11), and four additional studies have been published since then (12–15). These meta-analyses, which were largely based on retrospective studies, demonstrated that a threefold to fourfold increased risk of pregnancy-induced hypertension (PIH) and preeclampsia, a threefold increased risk of gestational diabetes (GDM) and a twofold increased risk of preterm delivery can be observed in women with PCOS.

A large proportion of the published studies on pregnancy complications in women with PCOS do not distinguish between different PCOS phenotypes (i.e., hyperandrogenic versus normoandrogenic women) nor adjust for other potential confounders, such as body mass index (BMI) or parity. This may diminish the sensitivity to establish causal relations between PCOS and adverse pregnancy outcomes. Our prospective study evaluated the presence of several maternal and neonatal complications in a cohort of women with hyperandrogenic as well as normoandrogenic PCOS, and women with PCOS who received different fertility treatments. These women were observed from before conception until pregnancy and delivery and were compared with a large population-based reference group.

MATERIALS AND METHODS

Study Design

Participants in this study originated from two different cohorts. Women with PCOS were prospectively recruited as part of the CoPPer study (Complication of PCOS Pregnancy: Evaluating Risk), for which detailed information was previously published (16). In short, women diagnosed with PCOS who had a wish to conceive were included before conception between April 2008 and April 2012 in four large hospitals in the Netherlands. Polycystic ovary syndrome was diagnosed according to the Rotterdam consensus criteria when at least two of the following criteria were present: clinical and/or biochemical hyperandrogenism, polycystic ovaries, and oligo- or anovulation (2). The women visited the hospital because of oligo- or anovulatory infertility and underwent standardized screening before conception, consisting of a questionnaire that collected information that included baseline characteristics, lifestyle behaviors, and medical, obstetric, and family history.

Standard anthropometry (height, weight, waist and hip circumference) and blood pressure measurements and a transvaginal ultrasound scan of the uterus and ovaries (including antral follicle count) were performed by trained medical doctors. Metabolic and endocrine measurements were collected and analyzed as described elsewhere (17). All women with PCOS underwent an oral glucose tolerance test (OGTT) according to our standard preconception protocol (75-g glucose load, 2-hour follow-up) to rule out preexisting diabetes. For the current study, women with PCOS were not included in cases of preexisting type 1 or type 2 diabetes, when their age was <18 or >45 years, or when there was a language barrier. Because multiple pregnancies are known to have more complications (18, 19), these pregnancies were excluded as well.

The reference group consisted of women recruited as part of the RESPECT (Risk EStimation for PrEgnancy Complications to provide Tailored care) cohort study, a population-based prospective cohort of pregnant women recruited from December 2012 until December 2013 in 31 midwifery practices and six hospitals in the central region of the Netherlands (20). The women were enrolled at a booking appointment in the first trimester of their pregnancy (up to 14 weeks), and they subsequently received standard obstetric care conforming to current Dutch practices. Only singleton pregnancies of women who conceived naturally were included in our study. Women were excluded in cases of pre-existing type 1 or 2 diabetes, age older than 45 years, or miscarriage or termination of pregnancy before 24 weeks.

Study Assessments

All clinical assessments performed in women with PCOS have been extensively described elsewhere (17, 21). Before conception, the total testosterone and sex hormone-binding globulin (SHBG) levels were assessed in all women with PCOS. Testosterone was measured after diethyl ether extraction by use of an in-house competitive radioimmunoassay and with a polyclonal anti-T-antibody (Dr. Pratt AZG 3290). We used [1,2–3H(N)]-T (NET-387, DuPont NEN Nederland B.V.) as a tracer after chromatographic verification of its purity. The SHBG concentrations were measured using an electrochemiluminescence immunoassay on the Modular E170 (Roche Diagnostics) (22).

The free androgen index (FAI) was calculated (testosterone [nmol/L] $\times$ 100)/SHBG [nmol/L]) to make a distinction within the PCOS group between the hyperandrogenic (FAI >4.5) and normoandrogenic (FAI ≤ 4.5) women with PCOS (23). The homeostatic model assessment insulin resistance (HOMA-IR) (glucose [mmol/L] $\times$ insulin [mIU/L]/22.5) was calculated to distinguish between insulin-resistant women and non-insulin-resistant women with PCOS; women were considered insulin resistant when 1/HOMA-IR < 0.47 (24).

After the preconception visit, most women started fertility treatment, such as ovulation induction (with clomiphene citrate or follicle-stimulating hormone), in vitro fertilization (IVF), or intracytoplasmic sperm injection (ICSI). When a pregnancy was not (yet) achieved, all the aforementioned clinical assessments were performed again every 12 months after the preconception visit. When a pregnancy was achieved, women with PCOS were observed intensively