Comparing the risk of adverse pregnancy outcomes of Chinese patients with polycystic ovary syndrome with and without antiandrogenic pretreatment

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Objective: To evaluate the prevalence of adverse pregnancy outcomes in healthy Chinese women and to investigate whether these outcomes could be decreased in patients with polycystic ovary syndrome (PCOS) by ethinylestradiol/cyproterone acetate (EE/CPA) pretreatment.
Design: Retrospective study.
Setting: Medical university.
Patient(s): Six thousand healthy women (group A) were selected from 24,566 pregnant women by randomized sampling. Four hundred forty-eight patients with PCOS without EE/CPA pretreatment were assigned to group B, and 222 patients with PCOS with 3 months of pretreatment to group C. All patients with PCOS had biochemical and/or clinical hyperandrogenism and conceived within 3 monthly ovulation inductions using clomiphene.
Intervention(s): None.
Main Outcome Measure(s): Gestational diabetes mellitus (GDM), pregnancy-induced hypertension (PIH), premature delivery (PD), and neonatal birth weight.
Result(s): The prevalence of GDM, PIH, and PD was higher in group B than in groups A and C (A vs. B vs. C: GDM, 21.2% vs. 35.0% vs. 22.5%; PIH, 6.5% vs. 14.1% vs. 7.7%; PD, 5.4% vs. 8.6% vs. 6.8%). No significant difference was found in neonatal birth weight. After adjusting for age, pregestational body mass index, education level, and employment status, PCOS without pretreatment increased the risk of GDM (adjusted odds ratio [aOR] = 1.666; 95% confidence interval [CI], 1.340–2.072), PIH (aOR = 1.487; 95% CI, 1.093–2.023), and PD (aOR = 1.522; 95% CI 1.051–2.205), compared with healthy women. No increased risk was found in group C.
Conclusion(s): In our highly selected study population, patients with PCOS are more likely to develop GDM, PIH, and PD. Pretreatment with EE/CPA was associated with a lower risk of GDM, PIH, and PD. (Fertil Steril® 2018;109:720–7. ©2017 by American Society for Reproductive Medicine.)
Key Words: Polycystic ovary syndrome, gestational diabetes mellitus, pregnancy-induced hypertension, premature delivery, neonatal birth weight

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Polycystic ovary syndrome (PCOS) is one of the most common endocrine and metabolic disorders, affecting 6%–15% women of reproductive age (1). PCOS is characterized by oligoanovulation, clinical or biochemical indicators of androgen access, polycystic ovarian morphology, insulin resistance, obesity, hirsutism, and acne (2). Long-term risks of PCOS include infertility, cardiovascular disease, type II diabetes, dyslipidemia, metabolic syndrome, and endometrial cancer (3). It is believed that insulin resistance, hyperandrogenism, and obesity are mostly responsible for the pathogenic process (4, 5).

Only a few reports have been published about spontaneous ovulation among women with PCOS. In a placebo-controlled trial, spontaneous ovulation occurred in only 32% of cycles (6). Most patients with PCOS have to undergo ovulation stimulation (7). Even if they become pregnant, they often suffer from disadvantageous conditions like miscarriage, gestational diabetes mellitus (GDM), pregnancy-induced hypertension (PIH), and premature delivery (PD) (8, 9). PCOS may also have a negative impact on neonatal birth weight, manifested as low birth weight (LBW) or macrosomia (9). The adverse outcomes could be attributed to hyperandrogenism and hyperinsulinemia and/or endocrine and paracrine dysregulation of growth factors, disordered follicular environment, and dysfunctional endometrial receptivity (10–12).

Hyperandrogenism in women with PCOS plays an important role in preterm delivery and preeclampsia (13). Therefore, antiandrogenic treatment combined with weight management before pregnancy might be beneficial for patients with PCOS to improve pregnancy outcomes. Combined oral contraception (COC) has been considered for patients with PCOS who do not want pregnancy to improve menstrual cycle stability and to treat hyperandrogenism (14, 15). However, whether this could improve pregnancy outcomes in PCOS remains controversial. One study concluded that COC pretreatment increased implantation and pregnancy rates (16), while another study did not find any benefit regarding pregnancy outcomes and the risk of miscarriage (17). To our knowledge, our study is the largest study that aims to identify the prevalence of adverse pregnancy outcomes in a large cohort of healthy women and the first study to investigate whether pretreatment using ethinylestradiol/cyproterone acetate (EE/CPA) is associated with a lower risk of adverse pregnancy outcomes in women with PCOS.

MATERIALS AND METHODS

Study Population

All subjects met the inclusion criteria: age 20–40 years, spontaneous pregnancy, and singleton pregnancy. The exclusion criteria were age less than 20 or older than 40 years, multiple pregnancy, preexisting diabetes or impaired glucose tolerance and/or preexisting hypertension before pregnancy, use of antidiabetic agents such as metformin or myo-inositol before pregnancy, and a history of recurrent miscarriage and gynecological malignant tumors, neonatal malformation, cervical malfunction, thyroid dysfunction, systemic lupus erythematosus, smoking, excessive alcohol consumption, congenital malformations, intrauterine infection, or missing delivery information.

The diagnosis of PCOS was established according to the 2003 European Society of Human Reproduction and Embryology/American Society for Reproduction Medicine Rotterdam consensus criteria (18). The diagnosis could be made if at least two out of the three criteria were met: [1] oligo- and/or anovulation, [2] clinical and/or biochemical signs of hyperandrogenism, or [3] polycystic ovaries and exclusion of other etiologies (congenital adrenal hyperplasia, androgen-secreting tumors, Cushing's syndrome). We only selected patients with PCOS with biochemical and/or clinical hyperandrogenism who could conceive by ovulation induction with clomiphene within 3 months. Biochemical hyperandrogenism was diagnosed if T exceeded 55.07 ng/dL according to the reference value of our laboratory. Clinical hyperandrogenism was indicated by hirsutism, acne, androgenic alopecia, and so on.

Study Cohort

In this retrospective study, we screened the electronic medical records of 65,008 women who attended for standard antenatal examinations and delivered in Beijing Obstetrics and Gynecology Hospital, Capital Medical University, People's Republic of China, from January 2013 to June 2016. A total of 24,566 pregnant women were selected. All women strictly met the inclusion and exclusion criteria; 24,118 women without PCOS were defined as healthy women. After one in four healthy women was selected by systematic randomized sampling, 6,000 women were chosen as the background population (group A). Another 448 patients with PCOS who conceived within 3 months of ovulation induction without antiandrogenic pretreatment were selected from our medical records and assigned to group B. Since all patients in this group wished to conceive, they immediately started ovulation induction without antiandrogenic pretreatment.

Another 222 PCOS women were treated with EE/CPA for 3 months. They also met the criteria above and were allocated into group C. We used EE/CPA if it was indicated according to the product license, that is, patients with biochemical and/or clinical signs of hyperandrogenism. After EE/CPA pretreatment, ovulation induction was started with clomiphene at once without a break. The patients were followed up until they gave birth in our hospital from June 2015 to June 2016. They took EE/CPA every day, starting from day 5 of the menstrual cycle for 21 days, followed by a 7-day pill-free interval. Each tablet contains 35 μg EE and 2,000 μg CPA.

In our study the comparable preconditions are most important for groups B and C to meet the main aim of the study, which is to ascertain whether 3 monthly antiandrogenic pretreatments can improve adverse pregnancy outcomes.

The enrollment data are presented in Figure 1.

Data Collection

Demographics and menstrual characteristics. All information including birthplace, employment information, level of education, age, age at menarche, length of menstrual cycle, length of menstrual period, height, and pregestational weight