Infertilty and Pregnancy Complications in PCOS*

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Polycystic Ovary Syndrome (PCOS), one of the most common endocrine disorders occurring during reproductive age, is characterized by ovulatory dysfunction, biochemical or clinical hyperandrogenism, and polycystic ovaries.[1] Its prevalence ranges from 5% to 10% based on population studies, and largely depends on the diagnostic criteria used, and ethnicity of the population being investigated. PCOS is currently considered a syndrome with metabolic and reproductive consequences that could affect women's health during different stages of reproductive age. There is increasing body of evidence suggesting a negative effect of PCOS on fertility and pregnancy outcomes.[1,2,3]

Pregnancy Complications

Several studies have highlighted that the risk for maternal, neonatal, and obstetric complications

Table 1. Main data synthesis from three published meta-analyses on pregnancy complications in women with PCOS. (adapted from Palomba, et al. 20153)

Outcome	Boomsma *et al.* (2006)	Kjerulff *et al.* (2011)	Qin *et al.* (2013)
Maternal			
PIH	3.67 (1.98–6.81)	4.07 (2.75–6.02)	3.07 (1.82–5.18)
PE	3.47 (1.95–6.17)	4.23 (2.77–6.46)	3.28 (2.06–5.22)
GDM	2.94 (1.70–5.08)	2.82 (1.94–4.11)	2.81 (1.99–3.98)
Preterm delivery	1.75 (1.16–2.62)	2.20 (1.59–3.04)	1.34 (0.56–3.23)
Neonatal			
SGA	1.16 (0.31–5.12)	2.62 (1.35–5.10)	—
LGA	—	1.56 (0.92–2.64)	—
Macrosomia	1.13 (0.73–1.75)	—	—

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may be increased in women with PCOS. 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, a summary of which is shown in the table.[4]

These meta-analyses, which were largely based on retrospective studies, consistently demonstrated 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 in women with PCOS.

The meta analyses likewise showed that women with PCOS had statistically significantly more small for gestational age (SGA) babies. A possible explanation for this could be the good glycemic control, which was achieved by treating the women who developed GDM with diet (51%) or insulin (30%) Another cause of the high rate of SGA could be aberrant placentation. Placentas of women with PCOS show more often signs of thrombosis and infarction.[4]

The meta-analysis by Boomsma, et al. showed no difference in multiple pregnancy rates between women with PCOS and controls, but comparison of outcomes from multiple pregnancies in women PCOS with controls was not possible because of the lack of stratification in the studies included.[2]

It is still debated whether women with PCOS have an increased risk of miscarriage compared with women without a fertility disorder. According to the PCOS consensus of 2012, miscarriage rates are suggested to be comparable, although available data show conflicting results. Two meta-analyses of studies concerning women with and without PCOS demonstrated no difference in miscarriage rates.[3,5] None of the nine studies included in this meta-analysis showed any difference in miscarriage rates. Recently, a large Australian study demonstrated that the miscarriage rate was more frequent in women with PCOS than in controls (20 versus 15%, respectively, P = 0.003), although PCOS was not an independent risk factor for pregnancy loss but the miscarriage rate was strongly influenced by BMI.

Hyperandrogenic women with PCOS have a 4-fold increased risk of adverse pregnancy outcomes compared to nonhyperandrogenic women.[3] This statement is supported by a prospective, multicenter cohort study by de Wilde, et al.[4] which showed that women with hyperandrogenic PCOS demonstrated a threefold to fourfold increased risk of maternal complications compared with the reference group after adjusting for BMI. Women with hyperandrogenic PCOS also exhibited an evidently increased rate of induced preterm delivery and delivery of a SGA infant. This suggests that hyperandrogenism per se may play an important role in generating pregnancy complications. Another retrospective study observed a more than twofold increased rate of preeclampsia and preterm delivery in hyperandrogenic PCOS.[7]

Hyperandrogenism is closely related to the incidence and extension of microscopic alterations in early trophoblast invasion and placentation. The alterations in endovascular trophoblast invasion and placentation may be the result of a suboptimal implantation process due to the direct effect of androgens on the endometrium and/or to a specific tissue susceptibility. In animal models, excess maternal androgens decrease placental size, affect the ability of the placenta to deliver nutrients to the fetus, alter placental steroidogenesis and lead to dysregulation of lipid metabolism in the adult female offspring.. Androgens can likewise increase the incidence of adverse pregnancy outcomes by acting on cervical remodelling and myometrial function.[8]

Infertility

Infertility among women with PCOS may be explained by the effects of obesity and/or metabolic, inflammatory, and endocrine abnormalities on ovulatory function, oocyte quality, and endometrial receptivity.[5]

Women with PCOS may exhibit reduced developmental competence (defined as the ability of the oocyte to complete meiosis, achieve fertilization, and develop into a normal embryo) of the oocyte. Ovarian hyperandrogenism and hyperinsulinemia may promote premature granulosa cell luteinization, and paracrine dysregulation of growth factors may disrupt the intrafollicular environment and impair cytoplasmic and/or nuclear maturation of oocytes. Endometrial abnormalities may also potentially affect implantation.[5]

Prevention and Management of Pregnancy Complications

Assessment of a woman with PCOS for infertility involves evaluating for preconceptional issues that may affect response to therapy or lead to adverse pregnancy outcomes.

Health should be optimized before conception, with advice about smoking cessation, lifestyle, diet, and appropriate vitamin supplementation (e.g., folic acid).[8] These women should be screened and treated for hypertension and diabetes prior to attempting conception and should be counseled about weight loss prior to attempting conception.[9]

At present, there are no recommended guidelines for a specific management of pregnant women with PCOS. But testing for type 2 Diabetes Mellitus is highly recommended at the first prenatal visit. Women with PCOS commonly showed more abnormal uterine artery Doppler indices during the early phases of pregnancy suggesting a potential role of ultrasonography in selecting PCOS patients at high risk of adverse pregnancy and perinatal outcomes.[3]

Different pharmacological measures have been proposed in women with PCOS during pregnancy in order to reduce the obstetric and neonatal risks. Most of the available studies use metformin, and different reviews largely show conflicting results. Metformin has a good safety profile and is effective and safe for the treatment of GDM particularly for overweight and obese women. Potential advantages for the use of metformin over insulin in GDM were suggested regarding maternal weight gain during pregnancy, neonatal outcomes (including less visceral fat) and patient compliance.[3] Data regarding the potential effect of metformin on the prevention of preeclampsia (PE) and pregnancy-induced hypertension (PIH) are scarce. At present, clinical data seem to show a limited effect of metformin in preventing PIH and PE.[3] ESHRE/ASRM PCOS Consensus 2012 stipulates that there is no evidence for improved live-birth rates or decreased pregnancy complications with the use of metformin either before conception or during pregnancy.

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