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Review

Polycystic ovary syndrome and pregnancy – From a clinical perspective

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Summary

For decades, infertility and metabolic health challenges have been the main concerns for women diagnosed with polycystic ovary syndrome (PCOS). Poorer pregnancy outcomes and obstetric complications have only recently been recognized as concerns for women with PCOS. Women diagnosed with PCOS are more often overweight and obese, and the prevalence of pregnancy complications in PCOS is influenced by several co-factors such as body mass index, co-morbidities, and ethnicity. The most frequently reported pregnancy complications in PCOS are gestational diabetes, miscarriage and preterm delivery, hypertension, and preeclampsia. This narrative review focuses on existing evidence and clinical practice for prepregnancy screening, antenatal care, and postpartum follow-up of women with PCOS. We also briefly review treatment options, neonatal outcomes, and breastfeeding. Our aim is to increase awareness about obstetric challenges in PCOS.

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Introduction

Until quite recently, polycystic ovary syndrome (PCOS) was a condition mainly dealt with by endocrinologists and gynecologists in the field of reproductive medicine with the ultimate goal to achieve pregnancy. During antenatal care, the PCOS diagnosis as medical history was (often still is) out of scope and forgotten. Its relevance was uncertain, and there were no guidelines to lean on. The general knowledge about PCOS is low and varies among professionals [1], and recognition of the consequences of PCOS for the course of pregnancy and pregnancy outcome is even less. During the last decades, however, numerous epidemiologic and clinical studies have contributed to increased knowledge about pregnancy with PCOS. Four meta-analyses have concluded on increased complication rates in PCOS pregnancies [2–5], and the newly developed International Evidence Based Guideline on PCOS 2018 is a milestone [6] (see Table 1).

It is important to bear in mind that most studies on PCOS pregnancies have been carried out on a *referred* PCOS population that may have more pronounced symptoms and represent more severe conditions than unselected birth cohort–based PCOS populations [7].

This review is based on a search of recent literature on pregnancies of women with PCOS.

We performed a search in PubMed that AND-combined MeSH and title words for PCOS with MeSH and title words for pregnancy and NOT-combined the result with a group of title words indicative of irrelevant aspects.

The aim of this narrative report is to review existing evidence and clinical knowledge on prepregnancy screening, antenatal care, and postpartum follow-up of women with PCOS. We believe that increased awareness of this complex condition will improve pregnancy outcomes.

Prepregnancy conditions

Co-morbidities

There is increasing understanding that women with a known PCOS diagnosis have a higher prevalence of different co-morbidities already in their twenties and thirties, which of course may have impact on both maternal and fetal pregnancy outcomes [8]. In a Nordic multicenter study on 487 women with PCOS, more than 50% reported one or more co-morbidities diagnosed *before* pregnancy. Depression, migraine, asthma, thyroid disorders, and bulimia were the conditions most often reported [9]. It is important to be aware of the co-

Table 1

Summary of pre-pregnancy, antenatal, and post-partum recommendations for women with PCOS.

	Conditions	Check/control
Prepregnancy	Overweight/obesity	Consider weight reduction/optimization
	Type 2 diabetes	Screening with OGTT/HbA_1c
	Hypertension	Optimize blood pressure—adjust medication
In pregnancy	General health	Prior medical history of great importance Increased prevalence of co-morbidities
	Weight gain	Encourage adherence to weight-gain recommendations in pregnancy
	Gestational diabetes	Screening in the 1st trimester, if negative, repeat screening in gest. week 24–28 with OGTT
	Hypertensive disorders	Check-ups according to local guidelines
	Preterm delivery	Attention to signs of cervical ripening, preterm labor
Postpartum	General postpartum	Consider need of follow-up • Weight reduction • Rule out type 2 diabetes • Persistent hypertension • Breastfeeding difficulties
	Post-partum depression	Consider screening with validated tools—EPDS

PCOS, polycystic ovary syndrome.

morbidities and to optimize treatment and adjust medication before pregnancy.

Body mass index

Women with a known PCOS diagnosis report a higher average prepregnancy and early pregnancy body mass index (BMI) than control women and reference populations [10]. The extent of overweight and obesity among PCOS varies, depending on ethnicity and the society they live in Ref. [11]. As high BMI is an independent risk factor for most pregnancy complications and inferior pregnancy outcome, it is often debated whether PCOS *per se* has a negative impact on pregnancy or if the increased complication rate in PCOS is related to obesity. Recently, large meta-analyses have provided information that PCOS *per se* is a risk factor for complications in pregnancy that are not entirely attributable to obesity [5].

Women with PCOS have a higher gestational weight gain compared with women without the diagnosis [12]. This also contributes to their increased risk for pregnancy complications.

Hyperandrogenicity

While hyperandrogenicity is abundantly documented in nonpregnant women with PCOS, androgen status in pregnancy is less well documented. A Chilean study found that second trimester androstenedione, testosterone, dehydroandrostenedione, and free testosterone indexes were higher in women with PCOS compared with controls [13]. Higher androgen levels in midpregnancy [14] and in the third trimester of pregnancy were reported in women with PCOS compared with pregnant controls [15]. Recent longitudinal data show that pregnant women with PCOS have significantly higher levels of androstenedione, testosterone, and free testosterone index compared with healthy control women, in the first and second trimester of pregnancy (Andræ F submitted). The impact of maternal serum androgen levels on pregnancy and offspring outcome is uncertain. Testosterone levels are increased 1.5–2.4 fold in pregnancies with preeclampsia, and women with hyperandrogenic PCOS phenotype are at increased risk of developing preeclampsia [16,17]. High maternal androgen levels have been shown to correlate to the shortening of the cervix [18].

Complications in pregnancy

PCOS is linked to several pregnancy complications [19–21]. The risk of pregnancy complications varies with ethnicity, socioeconomic status, and the level of health care provided in the general population. Thus, the risk of pregnancy complications among women with PCOS will vary with their background risk. PCOS phenotype may also have impact on pregnancy outcome. Some studies report higher pregnancy complications in the full-blown PCOS (phenotype A) [22,23], while others find no difference [24].

Miscarriages and preterm births

Increased risk of miscarriage is well known in PCOS. A large meta-analysis by Yu *et al.* published in 2016 demonstrated a relative risk of 2.9 (95% confidence interval [CI]:1.7–5.0) of miscarriage in women with PCOS compared with non-PCOS [5]. These findings vary with study design. A cross-sectional analysis of an Australian longitudinal cohort study demonstrated more miscarriages among women with self-reported PCOS compared with those without PCOS [25]. In this study,

PCOS was not independently associated with miscarriage, but obesity and need of fertility treatment were individually linked to pregnancy loss.

Yu *et al.* also reported an association between PCOS in pregnancy and the risk of preterm delivery, with a relative risk of 1.52 ($p \leq 0.001$) [5]. This is in accordance with other studies. For example, Roos *et al.* found an increased risk of especially very-preterm birth (delivery < week 32 in pregnancy) among women with PCOS who conceived spontaneously, adjusted odds ratio: 2.21 ($p < 0.0001$) [19]. Also, moderately preterm birth showed the same tendency with an adjusted odds ratio of 1.31 ($p = 0.004$). The analyses were adjusted for BMI, maternal age, smoking, years of education, assisted reproductive technology, and year of delivery.

Hypertensive disorders in pregnancy

Women with PCOS have an increased risk of both pregnancy-induced hypertension and preeclampsia. A large Swedish population-based cohort study compared 3787 women with PCOS to 1 191 336 women without PCOS and found an increased risk of preeclampsia among women with PCOS after adjusting for BMI and use of assisted reproductive technology with an odds ratio of 1.45 (95% CI: 1.24–1.69) [19]. A meta-analysis from 2013 found an odds ratio of 3.43 (95% CI: 2.49–4.74) of hypertensive disorder in pregnancy, and an odds ratio of 2.17 (95% CI: 1.96–2.46) of preeclampsia, after adjusting for heterogeneity, and excluding studies of borderline eligibility [4]. The studies included in this meta-analysis reported BMI, differences in parity, and multiple pregnancies as possible confounders. A Danish study published in 2014 compared 459 pregnant women with PCOS, recruited from an IVF clinic, to a background population of 5409 pregnant women; they found no significant difference in the overall risk of preeclampsia with an odds ratio of 1.69 (95% CI: 0.99–2.88, $p = 0.05$). The risk was significantly increased in only the hyperandrogenic subgroup of their PCOS population, odds ratio 2.41 (95% CI: 1.26–4.58, $p < 0.01$) [17].

Gestational diabetes mellitus

According to meta-analyses, the risk of gestational diabetes mellitus (GDM) is about three-fold higher in women with PCOS with a relative risk of 2.78 ($p < 0.001$) compared with non-PCOS women [5]. The previously mentioned Danish cohort study confirmed an increased risk of GDM among women with hyperandrogenic PCOS phenotype [17].

A pooled analysis of three randomized, controlled multicenter trials (RCTs) on pregnant women with known PCOS demonstrated a 25% incidence of GDM according to the WHO 1999 criteria and 40% according to WHO 2013 criteria [9]. There are, however few prospective, age and BMI matched studies on pregnancy outcomes in PCOS versus non-PCOS women. One prospective Danish study with BMI matched controls concluded that in a normal-weight, European cohort, PCOS diagnosis was not associated with increased rate of gestational diabetes [26]. One could speculate that when women with PCOS are of normal weight, their risk for GDM (and maybe other pregnancy complications) is fairly low or similar to non-PCOS. However, when they gain weight and become overweight or obese, they present more often and more severe complications than age and weight matched non-PCOS controls.

Pregnancy outcomes

Newborn anthropometry

Several studies report on somewhat lower or comparable birth weight and birth length in offspring of women with PCOS compared with women without PCOS [4,5]. However, most studies are not matched for maternal BMI, gestational weight gain, and gestational age at birth. As overweight, obesity, gestational weight gain, and GDM prevalence are all causal pathways to large for gestational age babies, it is surprising that the newborns are not heavier. We can only speculate whether there is a hidden growth restriction among offspring of PCOS women. In a Norwegian study, PCOS-newborns had altered anthropometrics compared with a national reference population matched for gestational age and gender; the newborns were both shorter and 'fatter' [27]. There is also evidence that female offspring of women with PCOS may be exposed to excess androgens in utero, demonstrated by increased anogenital distance and seborrhea [28]. Higher perinatal mortality [2,5,29], more congenital anomalies, lower Apgar scores [29,30], and more frequent admission to neonatal intensive care unit [2,4,29] are found in PCOS offspring.

Twin pregnancy

One Swedish population-based cohort study showed increased risk of preterm delivery of twins when the mother had a PCOS diagnosis [18], while a Danish study did not demonstrate increased obstetrical complications because of PCOS status in twin pregnancies [31].

Recommendations/treatments

With few exceptions, large RCTs lack evidence-based recommendations on prepregnancy and antenatal screening. There are no guidelines on antenatal care that specifically target women with PCOS. Most recommendations are indirect and on the basis of the evidence that pregnancy complications such as GDM, hypertension, preeclampsia, and preterm deliveries are more frequent among women with PCOS [3–5,20]. Optimally, antenatal care should aim to detect and, if possible, modify risk factors before and during pregnancy (Table 1).

Preconception and antenatal screening

Screening for hypertension and type 2 diabetes should be offered preconception to women with PCOS, either

by oral glucose tolerance test (OGTT) or HbA1c, depending on local guidelines and availability [6]. If screening is not performed before pregnancy, an OGTT should be carried out in the first trimester and repeated at gestational week 24–28 [6]. Detection of hypertension and PE is part of all antenatal care programs.

Weight gain goals

Women with PCOS gain more weight in pregnancy than women without PCOS [12]. Excess weight gain in pregnancy is associated with poorer outcomes. Close monitoring of weight according to general weight-gain recommendation based on prepregnancy BMI is advisable to prevent excess weight gain [32].

Diet

There is no evidence-based, PCOS-specific diet to be recommended in pregnancy. As for all pregnant women, general recommendations on healthy food intake with minimalized intake of refined sugar and saturated fats are advised.

Metformin

During the last four decades, metformin has been used in pregnancy for different indications without solid evidence. The main purpose for metformin-use in PCOS pregnancy was to reduce miscarriage and gestational diabetes. On the basis of 'individual pooled data' analyses from three RCTs, metformin compared with placebo, reduced *late* miscarriage, preterm birth, and resulted in less gestational weight gain. It had, however, no effect on gestational hypertension or preeclampsia. Most surprisingly, metformin treatment from the late 1st trimester to delivery did not have any effect, whatsoever, on the incidence of gestational diabetes, the time point of debut of gestational diabetes, insulin need, or any parameters of glucose homeostasis. Follow-up of the metformin versus placebo-exposed offspring showed increased overweight and central adiposity in the metformin-exposed offspring at the mean age of 8 years [34]. This insight calls for limited and cautious use in selected, well-informed patients with increased risk for miscarriage and preterm birth. Routine use of metformin in pregnancy to prevent or treat gestational diabetes is not supported by evidence [35].

Inositol

There is not enough evidence in the literature to support the use of inositol in pregnancy.

Emotional/psychological wellbeing

While there are abundant reports on increased prevalence of depression, anxiety, decreased quality of life among nonpregnant women with PCOS [36,37], there is essentially no information on their emotional and psychological health during pregnancy and postpartum.

Breastfeeding

Both case reports, clinical and epidemiological studies report on less breastfeeding among women with PCOS compared with women without PCOS, also after adjusting for socioeconomic status [38–41]. However, increased BMI seems decisive for breastfeeding ability as the difference disappeared when adjusting for BMI [41]. Women with PCOS who experienced no breast increment in pregnancy (and had decreased breastfeeding ability) had a poorer metabolic profile already in early pregnancy [42]. This indicates that inferior metabolic health precedes poor breastfeeding ability in PCOS and is not a *consequence* of it. It also implicates that modifying, optimizing metabolic health *before* pregnancy may have positive effect on breastfeeding ability.

Conclusions

There is evidence that women with PCOS, especially those with overweight and obesity, run an increased risk for gestational weight gain and common pregnancy complications. It is, however, important to keep in mind that most women with PCOS have uneventful pregnancies. Diet and lifestyle modifications to optimize weight-control before pregnancy and adjusting treatment for co-morbidities is of importance. Both preconception and antenatal screening for diabetes and hypertension is recommended. Metformin should not be used routinely in pregnancy. Decreased breastfeeding ability in mothers with PCOS is probably linked to preexisting overweight and obesity. Longitudinal studies on age and BMI matched women with PCOS and controls are needed. Studies on emotional and psychological wellbeing during pregnancy and postpartum is essentially lacking and urgently needed.

Conflict of interests

There is no conflict of interests.

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