Considerations and Challenges for Pregnancy in Polycystic Ovary Syndrome

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Key Points

- PCOS is associated with an increased risk of gestational diabetes, hypertensive diseases of pregnancy, fetal growth abnormalities, preterm birth, and operative delivery.
- PCOS diagnosis is associated with an increased risk for perinatal mortality.
- Some studies suggest an increased risk of sporadic miscarriage in women with PCOS.
- PCOS does not appear to affect rates of congenital anomalies.
- Given an increased risk of adverse pregnancy outcomes, preconceptional and antenatal counseling and stringent antenatal surveillance of pregnant women with PCOS are warranted.
- Postpartum counseling and care should focus on improving the long-term health of patients with PCOS by encouraging and supporting lifestyle modifications that diminish longterm risks of diabetes, hypertension, and cardiovascular outcomes.
- Breastfeeding is associated with greater postpartum weight loss, offers a physiological approach to metabolic wellness, and should be prioritized for mothers diagnosed with PCOS.
- Well-designed prospective studies using standardized definitions are necessary to elucidate the true effects of PCOS on adverse outcomes in pregnancy.

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Scope of the Problem

Although the relationship of polycystic ovarian syndrome (PCOS) with subfertility is well established, postconception effects of PCOS on pregnancy remain debated. Obstetrical complications associated with PCOS may include miscarriage, gestational diabetes mellitus (GDM), hypertensive diseases of pregnancy, preterm birth, birth-weight alterations, perinatal mortality, and increased risk of operative delivery (Table 16.1) [1]. Unfortunately, the heterogeneity of the syndrome and the paucity of large randomized controlled trials studying pregnancy in PCOS limit our understanding of causal relationships between PCOS and adverse pregnancy outcomes. This chapter reviews the pathophysiology of PCOS in pregnancy, updated literature regarding the association with adverse pregnancy outcomes, and the effect of PCOS treatments on pregnancy outcomes.

Effects of PCOS on Pregnancy

Early Pregnancy Loss

The prevalence of early pregnancy loss, defined as miscarriage during the first trimester, has been reported in women with PCOS to be as high as 30–50% [2]. This rate is approximately threefold higher than reported rates of 10–15% for women without PCOS [2]. Conversely, in women who have a history of prior miscarriages, polycystic ovaries (PCO) were identified on ultrasound imaging in up to 40–82% of the subjects, compared to 23% of unselected women [3, 4]. However, the presence of morphologically abnormal ovaries on imaging may not translate to an increased risk of miscarriage in a subsequent pregnancy [4].

Although the association of PCOS with early pregnancy loss has been repeatedly reported in earlier studies, the relevance of PCOS for recurrent pregnancy loss remains contested. The broad variance in reported rates of ovarian findings in these studies can be attributed to the use of non-standardized diagnostic criteria, discrepant modes of imaging (transabdominal vs. transvaginal), and variable subject selection criteria [5].Furthermore, it is important to note that these studies reported only the findings of PCO and not the presence or the absence of other clinical and biochemical alterations that define the syndrome [6].

Table 16.1 Possible obstetrical complications associated with PCOS

Early pregnancy loss
Gestational diabetes mellitus
Hypertensive disorders of pregnancy
Alterations in birth weight
Preterm birth
Increased risk for operative (cesarean) delivery
Perinatal morbidity and mortality

The pathophysiology of early pregnancy loss in PCOS has been attributed to the various metabolic and endocrinologic abnormalities commonly encountered in women with PCOS, including obesity, hyperinsulinemia, hyperandrogenemia, abnormal pituitary gonadotropin profile with elevated luteinizing hormone (LH) concentrations, and endometrial dysfunction [1, 5]. We will evaluate the roles of each of these putative mechanisms in pathophysiology of early pregnancy loss and potential management directed at each metabolic perturbation.

Body mass excess is commonly encountered with more than one-third of PCOS patients having body mass index (BMI) greater than 30 kg/m^2 [7]. In a retrospective study evaluating women with PCOS who conceived on ovulation induction therapy utilizing low-dose gonadotropins, overweight body habitus (BMI between 25 and 27.9 kg/m^2), compared to individuals of normal BMI, was associated with an increased risk in miscarriage at or below 8 weeks gestation (60% vs. 27%, $p < 0.05$) [7]. The negative impact of obesity on maintenance of pregnancy in the PCOS population was also described in a prospective observational cohort study of 270 women with PCOS and infertility from Kuwait with 121 pregnancies [8]. Live birth was noted in 97.2% of women with BMI 18–24 kg/m^2, compared to approximately 60% for BMI >30 kg/m^2. A large cohort study further argues that obesity may be the primary mechanism underlying early pregnancy loss in women with PCOS; the authors observed that the risk of pregnancy loss in PCOS fades after adjusting for obesity [9]. Additional meta-analyses have demonstrated a higher risk of early pregnancy loss in women with POCS after spontaneous conceptions (RR = 2.87; 95%CI:1.65–4.98) and in pregnancies conceived with in vitro fertilization (IVF) (OR = 1.41, 95%CI:1.04–1.91) [10–12].

This association of BMI with adverse pregnancy outcomes in both PCOS and non-PCOS patients results in the empiric recommendation of pre-conception weight reduction and lifestyle modifications. Although a 2011 Cochrane review found insufficient well-designed literature on the effect of lifestyle interventions on reproductive outcomes, newer data have shown potential benefits. A randomized controlled trial in a PCOS population demonstrated improved ovulation and live birth rates with delayed fertility treatment with clomiphene citrate when preceded by lifestyle modification with weight loss compared with immediate treatment. In non-PCOS populations, however, a randomized trial showed that women who successfully lost weight prior to pregnancy were more likely to have greater weight gain later in pregnancy [13]. Further research is needed on the impact of prepregnancy weight optimization in PCOS patients on adverse pregnancy outcome other than miscarriage.

Hyperinsulinemia is common to PCOS and has been proposed as an independent risk factor for miscarriage, irrespective of BMI [14]. Proposed mechanisms of hyperinsulinemia-induced early pregnancy loss include excess transplacental transport of glucose to the fetus [15], and alterations in levels of serum glycodelin [16], insulin growth factor-binding protein-1 (IGFBP-1) [16], and plasminogen activator inhibitor 1 (PAI-1) [17]. Glycodelin and IGFBP-1 are major endometrial secretory proteins that may play important roles in endometrial receptivity during the implantation period and in the maintenance of pregnancy [16]. PAI-1 activity is the major

determinant of hypofibrinolysis, and overexpression may result in higher rates of venous thromboembolism and adverse pregnancy outcomes, including recurrent miscarriage, intrauterine growth restriction, placental abruption, preeclampsia, and intrauterine fetal demise. Treatment with metformin may reverse the thrombophilic state induced by PAI-1 overexpression, thereby preventing adverse pregnancy outcomes resulting from thrombosis-induced placental insufficiency [18]. Despite the putative mechanistic contributions, it is important to note that there is no current role for screening for levels of these proteins in pregnancies with or without PCOS.

Hyperandrogenemia has been described in subjects experiencing recurrent early pregnancy loss, both with and without PCOS [5]. Comparison between studies is difficult due to measurements of different androgens, including total testosterone, free testosterone, and calculated free-androgen index [6]. Abnormal endometrial development [19], reduced expression of endometrial protein PP14 [19], and detrimental effects on oocyte quality [20] are proposed as mechanisms relating androgen excess to early pregnancy loss. Endometrial protein PP14 correlates well with luteal phase endometrial dysfunction [19]. Negative correlation between plasma androgen concentrations and uterine PP14 concentrations in the women with recurrent miscarriages suggests that high androgen concentrations may result in an abnormal secretory endometrium and hence a suboptimal milieu for successful implantation. In a small study of women with PCOS who were treated with ethinylestradiol/cyproterone acetate (EE/CPA) for 3 months prior to conception, lower rates of preterm delivery, GDM, and gestational hypertension were noted than women with PCOS who did not undergo pretreatment, further supporting the association of hyperandrogenism with poor pregnancy outcomes [21]. The rate of miscarriage remains higher in women with PCOS and a hyperandrogenic phenotype when controlling for obesity as demonstrated in a recent meta-analysis [22].

Another common feature of PCOS that has been implicated in early pregnancy loss is the abnormally elevated circulating LH. Elevated LH is a neuroendocrine hallmark of PCOS which results from persistent rapid pulsatile secretion at an exaggerated amplitude [23]. Proposed theories regarding the pathophysiology of early pregnancy loss in PCOS include the premature maturation and aging of oocytes and dysfunctional endometrial development secondary to the abnormally elevated LH. Although early studies suggested a link between LH hypersecretion and miscarriage [24], recent data have been unable to corroborate the earlier findings [5, 25]. Variations in findings can be attributed to the difference in experimental assays and design [25]. Suppression of elevated LH levels before conception in a subset of women with a history of recurrent pregnancy loss and PCO does not appear to improve pregnancy outcomes [26].

Ovulation induction strategies are commonly utilized for the management of ovulatory infertility in women with PCOS and include clomiphene citrate, letrozole, gonadotropin, laparoscopic ovarian drilling (LOD), and use of metformin [5]. Clomiphene citrate, a mixed estrogen agonist-antagonist, until recently has been considered as a first-line strategy to induce ovulation in PCOS with anovulation [27]. However, in patients who experience recurrent miscarriage after successful conception, it is uncertain whether clomiphene offers any protective advantage [5].

Letrozole, an aromatase inhibitor, has become the first-line agent of choice for ovulation induction for women with PCOS given its association with a higher live birth rate (OR 1.64; CI, 1.32–2.04) as well as an increased clinical pregnancy rate (OR, 1.40; CI, 1.18–1.65) [27]. Gonadotropin treatment is commonly utilized to induce ovulation in anovulatory women who are clomiphene resistant. However, there have been no studies evaluating the effects of gonadotropins in the management of recurrent miscarriage. Ovarian drilling, a surgical procedure thought to decrease androgen-producing tissue in the PCOS ovary, is an accepted alternative therapy in clomiphene-resistant patients [28]. Use of LOD has also been shown to decrease testosterone, LH, and the LH/FSH ratio while increasing FSH levels. Ovulation rates and clinical pregnancy in women with PCOS are thereby improved [29]. The ongoing pregnancy rate after LOD, followed by clomiphene citrate or gonadotropin therapy (if anovulation persists), seems equivalent to rates seen with the use of recombinant follicle-stimulating hormone alone, although pregnancies after ovarian drilling carry a lower risk of multiple gestation [28]. Rates of miscarriage at less than 12 weeks gestation were comparable between LOD and gonadotropin therapy arms. Lastly, metformin, an oral anti-hyperglycemic medication, initially held promise in decreasing miscarriage risk and increasing live birth rate in women with PCOS, compared to clomiphene citrate and LOD [30, 31]. However, this latter impression was not confirmed by a meta-analysis that failed to establish an efficacy of metformin in reducing miscarriage rate in women with PCOS [32, 33]. A randomized controlled trial (PregMet2) also failed to demonstrate a benefit to metformin use in preventing late miscarriage [34].

Women who have PCOS and have failed ovulation induction strategies alone may go on to in vitro fertilization (IVF). A multi-center randomized control trial compared frozen embryo transfer to fresh embryo transfer in infertile women with PCOS undergoing IVF cycles. Women with PCOS who underwent frozen embryo transfer had a higher rate of live birth after the first transfer (49.3% vs 42.0%) giving a rate ratio of 1.17 (95% CI: 1.05–1.31; $p = 0.004$). The rate of early pregnancy loss was also lower in women with frozen embryo transfer (22.0% vs 32.7%) with a rate ratio of 0.67 (95% CI: 0.54–0.83; $p < 0.001$) [35]. This finding of decreased rates of early pregnancy loss was further seen in a secondary analysis of a randomized control trial looking at women with PCOS undergoing IVF with frozen vs fresh embryos [36].

Gestational Diabetes Mellitus

Gestational diabetes mellitus (GDM) is defined by the American Congress of Obstetrics and Gynecologists as carbohydrate intolerance that begins or is first recognized during pregnancy [37]. Rates of GDM in pregnancies in the general US population are currently reported to be 3–9%, although this number is expected to continue to escalate secondary to the parallel obesity epidemic, sedentary lifestyles, urbanization, and older maternal ages at conception [38]. Complications of GDM in pregnancy include fetal macrosomia, polyhydramnios, birth trauma, instrumental

vaginal delivery, cesarean section, and higher perinatal mortality. Although universal screening for GDM at the beginning of the third trimester is standard protocol for most institutions within the United States, screening for GDM early in pregnancy is recommended in women with PCOS who are overweight or obese, if not performed prior to conception [37]. A recent large randomized clinical trial evaluating the efficacy of GDM treatment showed that dietary counseling, home blood glucose monitoring, and insulin therapy effectively reduce serious perinatal morbidity and may also improve the woman's health-related quality of life [39].

More than 50% of nonpregnant patients with PCOS exhibit resistance to the action of insulin [40]. Up to 40% of all women with PCOS will develop type 2 diabetes mellitus or impaired glucose tolerance during their reproductive years or by the age of 40 [41]. During gestation, the inherent insulin resistance of PCOS is further compounded by physiologic changes of pregnancy designed to accommodate and prepare for the nutritional requirements of the developing fetus, especially in the third trimester. Placental hormones, such as human placental lactogen, cortisol, progesterone, and estrogen, all alter maternal glucose homeostasis by inducing peripheral insulin resistance [42].

Women with PCOS demonstrated a significantly higher chance of developing GDM (OR 2.94, 95% CI 1.70–4.08) in a meta-analysis [43]. A subgroup analysis of five higher validity studies from the same meta-analysis further reinforced the increased risk (OR 3.66, 95% CI 1.20–11.16) [43]. Conversely, in a study comparing women with a previous history of GDM with those without such a history, a higher prevalence of PCO by ultrasound (41% vs. 3%, $p < 0.0001$) and other clinical and endocrinologic stigmata of PCOS (hirsutism, $p < 0.01$; irregular menstrual cycles, $p < 0.01$; higher BMI, $p < 0.001$; and higher concentrations of androstenedione, $p < 0.01$; testosterone, $p < 0.01$; and LH/FSH ratio, $p < 0.01$) were apparent in women with a history of GDM [44].

As with early pregnancy loss, a potential confounder in studies relating GDM to PCOS is obesity [45]. In a population-based retrospective study in the United States, pregnant women with PCOS were more likely to be obese (22.3% vs 3.5%, $p < 0.001$) than women without PCOS and more likely to have pregestational diabetes (4.1% vs 0.9%, $p < 0.001$) [46]. In a meta-analysis of studies evaluating the effect of BMI on development of GDM, the risk of carbohydrate intolerance is significantly positively correlated with prepregnancy BMI [47]. A later meta-analysis of pregnancy complications in women with PCOS in China demonstrated that when controlling for BMI, the rates of GDM were significantly higher in women with PCOS who were overweight/obese prior to pregnancy. Women with PCOS who had insulin resistance prior to pregnancy were also shown to have higher risks of GDM [48]. Likelihood for developing GDM in the overweight, moderately obese, and morbidly obese women was observed to be linear with odds ratio for developing GDM of 1.97 (95% CI 1.77–2.19), 3.01 (95% CI 2.34–3.87), and 5.55 (95% CI 4.27–7.21), respectively. Nonetheless, even after controlling for BMI, the increased risk of developing GDM remained evident in women with PCOS [43]. Obese women with PCOS who develop GDM have also been found to have lower homeostasis models assessment of ß-cell function (HOMA-ß) at preconception than those

without GDM, and measurement of this at preconception has been proposed as a predictor of the development of GDM in women with PCOS [49].

Metformin, an insulin sensitizer and an inhibitor of gluconeogenesis, is a commonly used pharmacotherapy in nonpregnant patients with PCOS as a strategy for improving insulin resistance and hyperandrogenemia of PCOS; addition of metformin to ovulation induction strategy is suggested to improve treatment success with clomiphene citrate, especially in women with PCOS who are also obese [27, 45, 50].

The frequent use of metformin in the patients with diabetes and PCOS, and its favorable safety profile, therefore led to a hypothesis that metformin may decrease the risk of GDM in patients with PCOS [14]. Metformin treatment in early pregnancy, however, has not been shown to reduce incident GDM rates compared to placebo controls (17.6% vs. 16.9%, $p = 0.87$) [51]. This lack of improvement was further confirmed in two more recent studies [34, 52]. It is recommended that women with PCOS should continue metformin until the end of the first trimester if they were taking it prior to pregnancy, but studies regarding this recommendation are limited [37]. Metformin has been used as a management strategy for GDM and has demonstrated a reassuring safety profile with perinatal complication rates comparable to those treated with the gold standard, insulin [37].

Additionally, women with GDM managed on metformin demonstrated less weight gain from enrollment to term compared to term (0.4 ± 2.9 vs. 2.0 ± 3.3, $p < 0.001$) [53]. In a randomized trial, women treated with metformin had lower mean glucose levels and neonates with lower rates of hypoglycemia than those randomized to insulin [54]. A recent meta-analysis also demonstrated that women treated with metformin had a higher rate of preterm birth (risk ratio 1.5), but had a lower rate of gestational hypertension (risk ratio 0.53) when compared to women treated with insulin [55]. Metformin does cross the placenta and as such is not recommended as a first-line treatment. When considering its use in pregnancy, it is recommended that women be counseled about the increased rate of preterm birth, placental transfer, and the lack of long-term safety data [37].

Hypertensive Disorders of Pregnancy

Hypertensive disorders during pregnancy are the second leading cause of maternal mortality in the United States (after thromboembolism). Accounting for almost 15% of maternal deaths [56], these disorders are estimated to affect 2–8% of all pregnancies [57]. Hypertensive disorders in pregnancy are categorized into chronic hypertension, preeclampsia/eclampsia, preeclampsia superimposed on chronic hypertension, and gestational hypertension [57]. Some known risk factors for hypertensive disorders of pregnancy include diabetes, autoimmune disease, renal disease, and obesity [58].

Women with PCOS demonstrated a significantly higher chance of developing a hypertensive disorder of pregnancy in a meta-analysis (OR 3.67, 95% CI 1.98–6.81) [43]. A subgroup analysis of two higher validity studies also revealed a significant increased risk of any hypertensive disorder of pregnancy (OR 3.71, 95% CI

1.72–17.49) and preeclampsia (OR 3.47, 95% CI 1.95–6.17). However, many earlier studies in which preeclampsia was an endpoint reported a lower parity, higher BMI, or more multiple pregnancies among women with PCOS versus controls [58]. A recent retrospective cohort study comparing a diverse group of pregnant women with PCOS to women without PCOS demonstrated that women with PCOS were at higher risk of gestational hypertension, but this was not independent of weight status. The same study demonstrated that nulliparity and higher prepregnancy BMI was associated with increased risk of gestational hypertension, with or without PCOS [59]. A more recent cross-sectional analysis showed an increased risk of hypertensive disorders in women with PCOS who were underweight or obese, but this was not seen in women with PCOS who were of normal weight or overweight [60]. A meta-analysis performed in 2016 demonstrated that women with PCOS have higher rates of hypertensive disorders of pregnancy (RR = 2.46; 95% CI:1.95–3.09, $p < 0.001$) as well as preeclampsia (RR = 2.79, 95% CI 2.29–3.38, $p < 0.001$) even after controlling for age and BMI [10]. Additional risk factors contributing to hypertensive disorders include nulliparity, obesity, gestational diabetes, multiple gestations, hyperandrogenism, and IVF [61].

Preterm Birth

There are approximately 12% of births in the United States that are preterm, defined as occurring at less than 37 weeks gestation [62]. A recent meta-analysis demonstrated a moderate association between PCOS and preterm birth (RR = 1.52; 95% CI:1.22–1.9, $p < 0.001$), but the studies were heterogenous and a subgroup analysis controlling for BMI did not show an association of PCOS and preterm birth when the prepregnancy BMI is >25 kg/m^2 [10]. Prior meta-analysis also showed a twofold increased risk of preterm birth, but the studies did not differentiate between spontaneous preterm birth and iatrogenic preterm birth related to medically indicated deliveries [1, 43]. In 2014, a cohort study showed an increased risk of preterm birth in women with PCOS, but was confined to those with hyperandrogenism [61].

Alterations in Birth Weight

The increased risks of gestational diabetes and preeclampsia for women with PCOS have led to hypotheses that the offspring in this population may be at an enhanced risk for a spectrum of growth aberrations that range from small-for-gestational age to large-for-gestational age [1]. Existing literature however is equivocal, and a lack of consistency in observed relationships can in part be attributed to differing definitions of macrosomia and SGA utilized across published studies. In a meta-analysis, pooled results from 12 studies showed statistically, albeit not clinically, significantly lower neonatal birth weight among infants of women with PCOS (mean weight difference, −38.4 g; 95% CI −62.2 to −14.6) [43]. Subgroup analysis of four studies in which controls were matched for confounders showed no significant difference in neonatal birth weight. PCOS babies also showed no significant increase in the

incidence of macrosomia or growth restriction. In a more recent meta-analysis, there was again no association between PCOS and large for gestational age (LGA), fetal growth restriction, fetal macrosomia, or congenital malformations [10]. However, in a subgroup analysis with prepregnancy BMI, there was an association between small for gestational age (SGA) and PCOS when the prepregnancy BMI was >25 kg/m^2.

Perinatal Morbidity and Mortality

In a meta-analysis of 5 studies with 162 pregnancies with PCOS and 725 control pregnancies, a statistically and clinically significant increase in perinatal mortality was observed in the offspring of women with PCOS compared to controls (OR 3.07; 95% CI 1.03–9.21) [43]. Reported causes for perinatal mortality in offspring of pregnancies affected by PCOS include lethal malformations, cervical insufficiency, sepsis, and placental abruption. However, as with many other pregnancy complications, most studies showed a higher BMI in women with PCOS compared to controls, which is a recognized independent risk factor for perinatal mortality [63].

A large Swedish study utilizing the national birth registry, published after the previous meta-analysis, reported that women with polycystic ovary syndrome are at increased risk of adverse pregnancy and birth outcomes that cannot be explained by the increased use of assisted reproductive technologies in this population. Infants born to mothers with PCOS were more prone to be large for gestational age (aOR 1.39; 95% CI 1.19–1.62), meconium aspiration (aOR 2.02; 95% CI 1.13–3.61), extreme prematurity (aOR 2.21; 95% CI 1.69–2.90), and Apgar scores <7 at 5 min (aOR 1.41; 95% CI 1.09–1.83) [64].

The exposure of the offspring of women with PCOS to insulin resistance and hyperandrogenism may be associated with increased risk of developmental disorders. In a recent population-based prospective study, the diagnosis of PCOS was associated with an increased risk of the offspring failing the fine motor domain area of the Ages and Stages Questionnaire (ASQ) assessed at 4,8, 12, 18, 24, 30, and 36 months of age [65]. Women who did not receive treatment for their PCOS had a stronger association with failing ASQ than among the offspring of women who reported receiving treatment for their PCOS.

Mode of Delivery

In some meta-analyses, women with PCOS were noted to have a higher incidence of delivery by cesarean section compared to controls (OR 1.56; 95% CI 1.20–2.02) [43], but this was contradicted by more recent meta-analyses showing no association [58]. The total number of deliveries, proportion of cesarean delivery, and indications for cesarean delivery were not reported in the meta-analysis. However, when a subgroup analysis was performed on three higher validity studies, no significant increased risk of cesarean delivery was observed (OR 0.92; 95% CI 0.54–1.58). This increased risk in surgical delivery in some studies was attributable to the

differences in body habitus between PCOS and control groups. There were no differences between rates of spontaneous vaginal and forceps or vacuum-assisted vaginal deliveries (OR 1.37; 95% CI 0.80–2.35).

Breastfeeding

Breastfeeding is a major focus of global strategies to improve infant nutrition and is considered to be the most effective single factor influencing the worldwide infant death rate [66]. The health benefits of breastfeeding are well established in the neonate, but there are maternal benefits as well [67]. Breastfeeding is associated with greater postpartum weight loss which can contribute to an increase in metabolic rate which can extend to 24 months after delivery [68]. This is especially important in women with PCOS who are also obese or overweight. Additionally, breastfeeding has shown to decrease the risk of type 2 diabetes and cardiovascular disease [69].

In a prospective observational cohort study in Northern California, women who were exclusively breastfeeding and mostly breastfeeding had lower adjusted mean group differences in fasting plasma glucose (mg/dL) of −4.3 (−7.4 to −1.3) and −5.0 (−8.5 to −1.4), fasting insulin (μU/mL) of −6.3 (−10.1 to −2.4) and −7.5 (−11.9 to −3.0), and 2-h insulin of −21.4 (−41.0 to −1.7) and −36.5 (−59.3 to −13.7) (all $p < 0.05$), respectively [69]. Given that women with PCOS have a higher risk of having insulin resistance and of developing diabetes mellitus, breastfeeding is of special importance for optimizing their postpartum long-term health benefits [40, 41]. Unfortunately, the insulin resistance and hyperandrogenism that are often seen in women with PCOS have been proposed to impair successful breastfeeding [67]. Insulin enhances the effect of prolactin on breast tissue during the process of milk synthesis, and maternal androgen levels have been negatively correlated with breastfeeding success in some studies [70, 71].

Summary

PCOS is associated with an increased risk of early pregnancy loss, gestational diabetes, preeclampsia, and preterm birth. Other reported adverse outcomes, such as alterations in birth weight, increased risk of perinatal mortality, and operative delivery, remain debated due to conflicting data between studies. Additional well-designed prospective studies using standardized definitions are necessary to elucidate the effects of PCOS on adverse outcomes in pregnancy and should control for other confounders, such as BMI. Nonetheless, the reported increased risk of adverse pregnancy outcomes warrants preconceptional and antenatal counseling and stringent antenatal surveillance of pregnant women with PCOS. Postpartum counseling and care should focus on improving the long-term health of patients with PCOS by encouraging and supporting lifestyle modifications that diminish the risks of diabetes, hypertension, and cardiovascular outcomes. Practical considerations for management of the patient throughout the reproductive continuum are summarized in Table 16.2.

Table 16.2 Practical pregnancy considerations for the patient with PCOS

Period	Potential risks	Considerations
Trimester zero: preconception [5, 7, 13, 27, 34]	Oligoovulation Hyperandrogenism Infertility Elevated BMI Pregestational diabetes or pre-diabetes	Recommend lifestyle and healthy dietary changes that facilitate weight loss Refer to infertility experts regarding role of ovulation induction or IVF if indicated Refer to endocrinology for optimization of disorder, including discussion of metformin, if indicated Consider combined oral contraceptive if hyperandrogenic, not yet ready for pregnancy, and without contraindications Assess hemoglobin A1c prior to pregnancy, if possible
First trimester [2–36]	Early pregnancy loss Insulin resistance spectrum	Early ultrasound for viability and dating after 5–6 weeks of gestation Assess/reassess hemoglobin A1c or glucose challenge test (unless recent assessment performed); Initiate dietary counseling, home blood glucose monitoring, and insulin therapy, if indicated Start aspirin for preeclampsia prophylaxis at 12–16 weeks GA if the patient has any additional risk factors for hypertensive disorders in pregnancy Apply shared decision-making regarding risks/benefits of metformin in pregnancy
Second and third trimesters [37–65]	Gestational diabetes Hypertension Fetal growth abnormalities Preterm birth Perinatal mortality	Ultrasound surveillance: Anatomical survey at 20 weeks Consider a growth ultrasound in third trimester Antenatal testing as indicated for other comorbidities Monitor maternal blood pressure closely after 20 weeks' gestation Perform glucose challenge testing at 24–28 weeks if no prior evidence of diabetes Management of comorbidities with obstetrician/maternal-fetal medicine, as indicated Apply shared decision-making regarding risks/benefits of metformin in pregnancy
Delivery [58]	Cesarean delivery	Counsel patients regarding potential for increased risk of cesarean delivery to establish appropriate expectations
Postpartum [27, 40, 41, 66–71]	Difficulties with lactation	Shared decision-making via discussion of risks and benefits of breastfeeding Early integration of supportive strategies, including lactation consultant services, if breastfeeding desired Discuss appropriate contraception based on the patient's needs
Interpregnancy interval [27, 72]	Progression of comorbid conditions Unintended pregnancies	Consider bariatric surgery if morbid obesity present in PCOS patient Continuation of care with appropriate healthcare professional for monitoring for insulin resistance, dyslipidemia, weight, cardiovascular disorders, and endometrial cancer

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