

INVITED REVIEW

Clinical management of pregnancy in women with polycystic ovary syndrome: An expert opinion

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Abstract

Polycystic ovary syndrome (PCOS) is associated with a higher risk for pregnancy and birth complications according to the specific features associated with PCOS. The features include obesity before and during pregnancy, hyperandrogenism, insulin resistance, infertility, cardiometabolic risk factors, and poor mental health. PCOS is not often recognized as a risk factor for poor pregnancy and birth outcomes in pregnancy care guidelines, while its associated features are. Pregnancy-related risk profile should ideally be assessed for modifiable risk factors (e.g., lifestyle and weight management) at preconception in women with PCOS. Hyperglycaemia should be screened using a 75-g oral glucose tolerance test at preconception or within the first 20 weeks of pregnancy if it has not been performed at preconception and should be repeated at 24–28 weeks of pregnancy. In the absence of evidence of benefit for strategies specific to women with PCOS, the international evidence-based guidelines for the assessment and management of PCOS recommend screening, optimizing, and monitoring risk profile in women with PCOS (at preconception, during and postpregnancy) consistent with the recommendations for the general population. Recommended factors include blood glucose, weight, blood pressure, smoking, alcohol, diet, exercise, sleep and mental health, emotional, and sexual health among women with PCOS. The guidelines recommend Metformin in addition to lifestyle for assisting with weight management and improving cardiometabolic risk factors, particularly in those with overweight or obesity. Letrozole is considered the first-line pharmacological treatment for anovulatory infertility in PCOS. Individualized approach should be considered in the management of pregnancy in PCOS.

KEYWORDS

antenatal care, gestational weight gain, guideline, lifestyle, polycystic ovary syndrome, pregnancy, screening, treatment

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1 | INTRODUCTION

Polycystic ovary syndrome (PCOS) is a common endocrine disorder affecting up to 8%–13% of reproductive-aged women.¹ According to the Rotterdam criteria, PCOS in adults is diagnosed based on a minimum of two of the following: oligo/anovulation, clinical and/or biochemical hyperandrogenism, and PCO morphology on ultrasound, after ruling out differential diagnoses.² These criteria result in four phenotypes of PCOS including phenotype A with oligo/anovulation, hyperandrogenism, and PCO morphology; phenotype B with oligo/anovulation and hyperandrogenism; phenotype C with hyperandrogenism and PCO morphology; and phenotype D with oligo/anovulation and PCO morphology. PCOS is associated with metabolic, reproductive, and psychological features.³ Aetiology is complex including genetic, in-utero, potential epigenetic factors, exacerbated by adverse lifestyle and excess adiposity. Hyperandrogenism, insulin resistance, and resulting hyperinsulinemia are common underpinnings in PCOS.

PCOS and excess adiposity have a bidirectional relationship with excess weight exacerbating the underpinning hormonal imbalance and PCOS itself appearing to predispose to excess weight and weight gain.⁴ The prevalence of PCOS in women with obesity is up to 37%.⁵ Women with PCOS may also be more likely to gain weight longitudinally⁴ and at a greater pace.⁶ This may be attributable to impairments in appetite-regulating hormones and hyperinsulinemia,⁷ and a more sedentary lifestyle,⁸ and may be inter-related to the psychological features of PCOS such as anxiety, depression, and poor quality of life.⁹ Obesity further exacerbates hyperandrogenism and hyperinsulinemia and plays a key independent role in increasing cardiometabolic risks in women with PCOS.^{10,11}

Women with PCOS commonly have oligo/anovulation, with or without irregular menstrual cycles,^{12,13} with PCOS the most common cause of anovulatory infertility.¹⁴ Infertility and a longer time to pregnancy may confer a higher risk for pregnancy and birth complications.^{15,16} Additionally, the type and intensity of treatment used to manage infertility, may further complicate pregnancy and birth independent of multiple pregnancies.^{15,17} Infertility is exacerbated by obesity.

Women with PCOS are generally at higher risk of pregnancy and birth complications including gestational diabetes (GDM), gestational hypertension, pre-eclampsia, induction of labour, caesarean section, preterm birth, and large for gestational age babies. The association of PCOS with pregnancy and birth complications varies by PCOS phenotype, target population, ethnic background, self or family history of metabolic, reproductive, and potentially psychological complications during or outside pregnancy, and women's lifestyle.^{10,18–20} In pregnancy, obesity is an independent risk factor for complications, as is excess gestational weight gain.^{10,18,21} Both obesity and increased gestational weight gain are documented in PCOS although whether there is an additional adverse impact of gestational weight gain on pregnancy and birth complications in women with PCOS is not still well understood.^{10,18}

While common features of PCOS are recognized as risk factors for pregnancy and birth complications by pregnancy care guidelines,²²

PCOS per se is not consistently perceived as a risk factor for complications in pregnant women with PCOS. Delayed and missed diagnosis is common in the general population²³ and recognition of PCOS as a risk factor in pregnancy and birth complications is even poorer.²⁴ In this context, we aimed to review the relationships between PCOS and pregnancy and birth complications, the intersecting impact of obesity and excess gestational weight gain, the need to enhance recognition of PCOS before and during pregnancy, and to provide maternity care that meets the needs of this high-risk group. Here, we seek to reflect the evidence assembled for the International evidence-based guidelines for the assessment and management of PCOS and the multidisciplinary recommendations for clinical management of pregnancy in PCOS from the guidelines including risks, screening, pregnancy care, lifestyle, healthy gestational weight gain, and lifestyle in pregnancy.

2 | PCOS, PREGNANCY, AND BIRTH COMPLICATIONS

Increased body mass index (BMI) at conception is associated with adverse pregnancy outcomes such as GDM, pregnancy hypertensive disorders, and macrosomia. Similarly, risks are increased with excess gestational weight gain in pregnancy.²¹ Additionally, women with a BMI in the overweight or obese category are more likely to exceed gestational weight gain recommendations.²⁵ Selected populations of women with PCOS who were referred for infertility treatments conceived with a higher BMI,^{10,18,26} and in nonpregnant women with PCOS the prevalence of overweight and obesity is higher.²⁷ However, there is no evidence about preconception BMI in unselected populations of women with PCOS. Two systematic reviews of pregnancy and birth complications in women with and without PCOS confirmed that women with PCOS have higher total gestational weight gain compared with women without PCOS.^{10,18} However, it was unclear whether this higher gestational weight gain results in a higher proportion of women with PCOS exceeding the internationally recognized National Academy of Medicine (NAM, formally Institute of Medicine [IOM])²⁸ recommendations for a healthy gestational weight gain (Table 1).²⁹

Women with PCOS are at increased risk for ectopic pregnancy,³⁰ hydatidiform molar pregnancy,³¹ and miscarriage,^{10,32,33} mainly

TABLE 1 National Academy of Medicine (NAM, formally Institute of Medicine [IOM]) recommendations for a healthy gestational weight gain in singleton pregnancies

Preconception BMI category	Total weight gain (kg)
Underweight (<18.5 kg/m ²)	12.5–18.0
Normal (18.5–24.9 kg/m ²)	11.5–16.0
Overweight (25.0–29.9 kg/m ²)	7.0–11.5
Obese (≥30 kg/m ²)	5.0–9.0

Abbreviations: BMI, body mass index; OGTT, oral glucose tolerance test.

following fertility treatments. Given that fertility treatments are known risk factors for the outcomes, it is hard to disentangle the association of PCOS per se with these adverse outcomes.¹⁰ Age, increased BMI, insulin resistance and hyperandrogenic phenotypes have all been reported to contribute to the risk of miscarriage in women with PCOS. Advanced maternal age,¹⁰ was the main factor increasing the risk of miscarriage in a systematic review of PCOS and pregnancy (spontaneous or after fertility treatment). A study has recently demonstrated that following assisted reproductive treatment (ART), the odds of miscarriage was higher in women with PCOS after 13 weeks of pregnancy³⁴ but not after adjustment for BMI.³⁵ A systematic review of pregnancy after ART reported that overweight or obesity and insulin resistance are likely main risk factors for higher miscarriage in PCOS.³⁶ Women with hyperandrogenic phenotypes of PCOS are at increased risk for miscarriage and women with nonhyperandrogenic PCOS have reported similar risk of miscarriage to those without PCOS. One proposed mechanism for increased miscarriage and hyperandrogenic phenotype is reported increased endometrial abnormalities.^{10,37} Initiating antiandrogenic treatments at a younger age may help with improving fecundability and live birth in affected women³⁸; but is yet to be proven in randomized clinical trials.

While acknowledging that there are inconsistent diagnostic criteria for GDM,³² women with PCOS are at two to four folds higher risk for GDM.^{10,33,39–41} The higher risk for GDM was recently confirmed in a large unselected population of American women with and without PCOS.⁴² The higher risk in PCOS does not appear to apply to the nonhyperandrogenic phenotype and the magnitude of risk may differ by PCOS phenotypes and ethnicity,^{10,43} possibly due to differences in degrees of hyperandrogenism, obesity, and insulin resistance across these groups.^{27,44,45} The higher risk of GDM is independent of, yet exacerbated by obesity in PCOS related to insulin resistance.³² This is consistent with the finding that there is a higher risk for GDM in BMI-matched and nonobese populations with PCOS.¹⁰ Excessive early gestational weight gain has also been reported to be associated with a higher risk of developing GDM.^{46,47} In a large unselected population of women with and without PCOS, the risk of GDM was similar where women with PCOS had a higher BMI at week 15 of pregnancy but similar early gestational weight gain.¹⁹ Studies reporting GDM in women with and without PCOS do not often report abdominal obesity and insulin resistance status at preconception or at early pregnancy¹⁰ as risk factors for GDM.⁴⁸

The risk of hypertensive disorders of pregnancy including gestational hypertension and pre-eclampsia is also higher in women with PCOS.^{10,33,39–41} Dysregulation in glucose profile and GDM are amongst the risk factors for hypertensive disorders of pregnancy⁴⁹ and the aetiology of hypertensive disorders and GDM might be similar.^{10,50} This was confirmed in a systematic review where (similar to GDM) PCOS was not an independent risk factor for gestational hypertension or pre-eclampsia in nonhyperandrogenic phenotypes of PCOS, for women with a BMI > 30 kg/m,² some ethnic backgrounds or pregnancy post-ART, but PCOS was a risk factor in BMI-matched studies in women without obesity and who spontaneously conceived.¹⁰

Regardless of BMI, women with PCOS are more likely to have a medicalized birth including induction of labour and caesarean section,^{10,33,39,41} but have similar rates of instrumental vaginal birth to women without PCOS.^{39,40} While the higher risk for medicalized birth is probably due to a higher rate of pregnancy and birth complications in women with PCOS,⁵¹ literature is limited with the medical indication for interventions not being reported.¹⁰

Prior research reports that the risk and severity of psychological complications including anxiety, depression, and poor quality of life is higher in women with PCOS, outside pregnancy.⁵² This could potentially increase the risk of antenatal psychological issues,⁵³ however, the most recent meta-analysis found no study looking at antenatal mental health in women with PCOS either as a pregnancy complication or as a risk factor for pregnancy and birth complications.¹⁰ Women with GDM and hypertensive disorders of pregnancy are more likely to experience anxiety and depression.⁵⁴ Two recent studies on unselected populations of women with and without PCOS found that women with PCOS have a higher risk for antenatal depression and anxiety.^{55,56} The association of antenatal psychological complications with PCOS remained significant for women who had oligoanovulation and acne⁵⁶ and also for those who had a history of stillbirth but not for post-ART pregnancies.⁵⁵

Infants born to women with PCOS are more likely to be born premature.^{18,33,39–41} However, most studies do not report whether the onset of preterm birth is spontaneous.¹⁰ The odds of preterm birth in PCOS differ by PCOS phenotypes and ethnic background of the population.¹⁸ However, the likelihood was similar in BMI-matched and post-ART pregnancies in women with and without PCOS.¹⁰ This suggests that the higher odds are to some extent related to more severe phenotypes of PCOS with a higher prevalence of obesity and fertility treatments.⁵⁷ The odds also remained higher in singleton pregnancies.¹⁰

It appears that PCOS does not restrict intrauterine growth of foetuses,^{18,33} however infants born to women with PCOS have lower birth weight compared with infants born to women without PCOS.^{18,39,41} The lower birth weight in PCOS reported is not clinically significant and is probably related to, a higher rate of multiple pregnancies and a higher rate of preterm birth in women with PCOS.^{18,39} The most recent systematic review reported that infants born to women with PCOS are more likely to be large for gestational age,¹⁸ although similar rates for macrosomia were not found.^{18,33,39,40} possibly due to higher rate of preterm birth¹⁸ and medicalized birth.¹⁰

Two systematic reviews reported that infants born to women with PCOS have higher rates of admission to Neonatal Intensive Care Unit (NICU)^{39,41} and higher rates of perinatal mortality.^{35,39} It should be noted that the results were limited to small numbers with only five studies providing data for each of these two outcomes. Given that infants born to women with PCOS have a similar rate of respiratory distress syndrome to infants born to women without PCOS,³³ the higher rate of admission to NICU in infants born to women PCOS is likely due to routine admission of infants born to GDM affected pregnancies.³²

3 | RECOMMENDATIONS FROM GUIDELINES FOR IMPLEMENTATION IN HEALTHCARE

Recommendations from the international evidence-based guidelines for the assessment and management of PCOS for clinical management of women with PCOS at preconception, pregnancy, and postpartum is summarized in Figure 1.

3.1 | Preconception care

To improve fertility and promote healthy pregnancy, optimizing health at preconception is of great importance for women with PCOS. It is recommended that all women see their health practitioner for common preconception risk assessments with enough time before conception to intervene. These assessments are particularly important where the risk for infertility may be higher such as for increased BMI and diabetes in women with PCOS. Recommendations for preconceptional care are presented in Table 2.

In the international evidence-based guidelines for the assessment and management of PCOS,³ lifestyle and weight management are recommended as an initial treatment strategy in PCOS. Lifestyle interventions can be defined as interventions aimed at improving dietary intake or physical activity through behavioural strategies and support. Weight management can be defined as prevention of weight

gain, achieving modest weight loss, and maintaining this reduced weight. The PCOS guidelines recommend for women with excess weight to achieve modest weight loss, an energy deficit of 30% or 500–750 kcal/day (1200–1500 kcal/day) tailored to individual energy requirements, body weight, food preferences, physical activity levels, and preferred approach could be considered. This could be achieved with a lower energy intake through diet, with a higher energy expenditure through increased physical activity level, or a combination of these two lifestyle components. Dietary recommendations are for a range of balanced dietary approaches as per the general population guidelines.³ There is not one recommended type or composition of diet specific to women with PCOS, due to limited evidence of benefit.

The physical activity recommendations are also consistent with the general population guidelines and recommend a minimum of 150 min/week moderate or 75 min/week vigorous intensity exercise for prevention of weight gain and general health and that women minimize sedentary time and include muscle-strengthening exercises on two nonconsecutive days/week.³ A range of behavioural components can also be incorporated into lifestyle interventions to optimize weight management, healthy lifestyle, and emotional wellbeing in women with PCOS including using strategies such as SMART (specific, measurement, achievable, realistic, and timely) goals, goal setting, self-monitoring, stimulus control, problem solving, assertiveness training, slower eating, reinforcing changes, and relapse prevention.³ With regard to preconception and lifestyle in women

Preconception
<ul style="list-style-type: none"> • As per the general population guidelines PLUS • Assessment of impaired glucose tolerance and type 2 diabetes with a 75 g OGTT. • Lifestyle modifications and weight management <ul style="list-style-type: none"> • Weight loss of 5% for those with a BMI > 25 kg/m² • Pharmacological treatment with or without lifestyle modifications for weight loss in those with a BMI > 25 kg/m² plus contraception whilst they are on medications • If bariatric surgery for those with a BMI ≥ 35 kg/m² considered appropriate, undertake at least for one year prior to conception and seek nutritional advice.
Pregnancy
<ul style="list-style-type: none"> • As per the general population guidelines PLUS • Consider as a high risk pregnancy • Assessment of impaired glucose tolerance and type 2 diabetes with a 75 g OGTT before 20 weeks of pregnancy
Postpartum
<ul style="list-style-type: none"> • As per the general population guidelines PLUS • Assessment of impaired glucose tolerance and type 2 diabetes with a 75 g OGTT every one to three years, depending on risk factors • Assessment of blood pressure every year • Contraception and family planning

FIGURE 1 Recommendations for clinical management of women with PCOS, preconception, pregnancy, and postpartum. BMI, body mass index; OGTT, oral glucose tolerance test; PCOS, polycystic ovary syndrome

TABLE 2 Preconception care in women with and without PCOS

Preconception care	Special considerations in women with PCOS
Assessment of immunization status such as rubella and determining if boosters are required	<ul style="list-style-type: none"> • Women with PCOS are at higher risk for COVID-19 infection.
Assessment of teratogenicity of any current medications and change in type or dosage of the medications if required.	<ul style="list-style-type: none"> • Metformin is considered safe to continue whilst trying for pregnancy.
Assessment of any relevant family history of congenital anomalies or relevant inherited illnesses such as trisomy 21 and considering whether carrier screening is applicable	-
Offering reproductive carrier screening (if available) for commonly inherited genetic illnesses such as cystic fibrosis, fragile X, and spinal muscular atrophy.	<ul style="list-style-type: none"> • These are not increased in infants born to women with PCOS.
Recommendation of supplementation with folate to prevent NTD. Daily intake of 400 mcg is generally recommended. A higher dose of 5 mg is considered optimal if a woman has a history of a child with an NTD, has type 1 or 2 diabetes or a BMI in the obese range as these increase the risk of NTD	<ul style="list-style-type: none"> • Women with PCOS are more likely to be overweight or obese and are more likely to have type 2 diabetes. • An assessment for the presence of impaired glucose tolerance and type 2 diabetes should ideally be undertaken before conception • The preferred screening method in PCOS is a 75-g OGTT.
Assessment of alcohol, smoking, and other substance use and offering interventions to assist quitting, if applicable	-
Assessment of any previous pregnancies and any associated complications and whether any additional monitoring or management is required	<ul style="list-style-type: none"> • Women with PCOS are at higher risk for pregnancy and birth complications.
Assessment of any current or past mental health disorders.	<ul style="list-style-type: none"> • Women with PCOS are at higher risk for psychological complications. • All women with PCOS should be routinely screen for anxiety and depression upon diagnosis and repeat screening based on risk factors
Measurement of weight and height to estimate preconception BMI, assessment of women's lifestyle including diet and physical activity offering interventions to assist lifestyle optimization, if applicable.	<ul style="list-style-type: none"> • In women with an anovulatory phenotype of PCOS and BMI > 25 kg/m² a modest weight loss of 5% can be sufficient to support the return of cycle regularity and ovulation. • After lifestyle modifications, antiobesity medications or bariatric surgery could be considered in women with obesity and those with a BMI ≥ 35 kg/m² respectively. • Achieving a modest weight loss and healthy lifestyle before ovulation induction is associated with a higher live birth rate compared to immediate treatment. • Pregnancy needs to be avoided during pharmacological treatment and until one year after bariatric surgery due to the associated adverse fertility and pregnancy outcomes.

Abbreviations: BMI, body mass index; NTD, neural tube defects; OGTT, oral glucose tolerance test; PCOS, polycystic ovary syndrome.

with PCOS, these guidelines also state that factors including weight, diet, exercise and other lifestyle factors such as sleep and mental and emotional health need to be optimized in women with PCOS to improve reproductive and obstetric outcomes aligned with recommendations in the general population (Clinical Practice Point 5.1.1).

3.2 | Identification of PCOS and screening

Given the normal physiological changes that occur during pregnancy, diagnostic criteria for PCOS are not applicable and a diagnosis of PCOS is not possible in pregnancy. However, women, particularly those who have a BMI in the overweight or obesity categories at the booking visit of pregnancy, can be validly screened for a PCOS diagnosis through self-reported symptoms of PCOS.^{58,59} This helps

with capturing PCOS as a risk factor for pregnancy and birth complications and following the recommendations for screening and management. Women's height and weight should be measured and BMI calculated at the first antenatal appointment. At every antenatal visit, women should be offered the opportunity to be weighed and be provided with nonstigmatizing advice about optimal weight gain during pregnancy based on their BMI.²² Self-monitoring of weight (ideally once per week) should also be encouraged.

Given the substantial risks of hyperglycaemia and the associated complications for the pregnancy and the foetus, the recent International evidence-based guideline for the assessment and management of polycystic ovary syndrome 2018 recommends that a 75-g oral glucose tolerance test (OGTT) should be offered to all women with PCOS at antenatal booking or before the 20th week of pregnancy, if an OGTT has not been performed at preconception.

If an early pregnancy OGTT is normal, then all women with PCOS should be offered a repeat OGTT at 24–28 weeks gestation.³

Routine measurement of blood pressure is recommended at the first antenatal visit and throughout pregnancy for all pregnant women by antenatal care guidelines.²² Hypertension detected before 20 weeks of gestation is considered chronic hypertension, whilst new hypertension after 20 weeks of gestation is considered to be gestational hypertension. Any woman presenting with gestational hypertension should be assessed for signs and symptoms of pre-eclampsia.²²

In the absence of evidence on pregnancy-related psychological complications in women with PCOS, the International evidence-based guideline for the assessment and management of polycystic ovary syndrome 2018³ was unable to make a recommendations specific to women with PCOS. Therefore, antenatal healthcare providers should be aware of the higher risk for psychological complications in women with PCOS and follow screening recommendations for the general population to assess pregnant women with PCOS routinely for anxiety and depression. The Australian *Clinical Practice Guidelines: Pregnancy Care* recommends using the Edinburgh Postnatal Depression Scale (EPDS) with cultural adaptations to screen pregnant women for a possible depressive disorder at booking and repeat if clinically indicated.²² There are no tools to specifically screen anxiety in pregnant women and clinicians may consider using items three, four, and five of the EPDS for screening.

For all the screenings and monitoring during pregnancy by the guidelines, national recommendations, and available resources should be taken into consideration.

3.3 | Managements in pregnancy

3.3.1 | Lifestyle

There are considerations for optimizing weight, diet, and physical activity during pregnancy that women with PCOS can follow consistent with general population guidelines. For weight, recommendations are to achieve appropriate gestational weight gain to optimize maternal and foetal outcomes. A large study on an unselected population of women with and without PCOS found that a high-risk profile for pregnancy and birth complications in PCOS can possibly be compensated by a healthy lifestyle and similar gestational weight gain before the 20th week of pregnancy.¹⁹ Recommendations for optimizing diet during pregnancy are optimal intake of core food groups (whole grains and cereals, vegetables, fruit, meat and/or alternatives, and dairy or alternatives) and limiting intake of “discretionary” or noncore foods which are typically high in sugar, salt, saturated fat, and energy.^{60,61} While micronutrient recommendations also differ from country to country, these generally focus on achieving sufficiency in key micronutrients and additional supplementation of folate and iodine to reduce the risk of pregnancy and birth complications. There is also the need to ensure appropriate food hygiene practices and avoid certain foods that increase the risks of

methylmercury toxicity, listeriosis, and salmonellosis.^{22,60,62–65} Physical activity recommendations promote regular physical activity (at least 150 min of moderate-intensity aerobic activity/week and additional muscle-strengthening exercises) except for women for whom physical activity is contraindicated^{66,67} and with consideration of safety precautions such as excessive heat, physical contact, high altitudes or scuba diving.⁶⁶ Consistent with the recommendations for the general population, women with PCOS should also be assessed for alcohol, smoking, and other substance use at the booking visit of pregnancy and be offered with appropriate support to assist quitting, if applicable.²²

3.3.2 | Medications

Metformin use was recommended in the international guidelines for use in nonpregnant women and in pre-pregnancy to assist in the management of weight, insulin resistance, anovulation, and hirsutism.³ It is a widely offered, inexpensive, and safe medication.³ The data was, however, too scarce to have a medical recommendation on *Metformin* use continuing during pregnancy both in terms of safety and decreasing risks in pregnancy. Since the guideline launch, there has been further research published on *Metformin* use in pregnancy and with long-term follow-up of children born.

A meta-analysis of women with PCOS has found that *Metformin* intake in pregnancy was associated with decreased risk for preterm birth (risk ratio [RR], 0.45; 95% confidence interval [CI], 0.25–0.80; $p = .007$) and with increased head circumference in the offspring (mean difference [MD], 0.47; 95% CI, 0.20–0.74; $p = .0006$) and was not associated with miscarriage, pre-eclampsia and offspring birth weight.⁶⁸ Similar to non-PCOS-populations, *Metformin* in pregnancy has not been shown to prevent GDM.^{68,69} A placebo-controlled trial of *Metformin* in pregnancy in women with PCOS with over seven years follow-up showed no difference in weight or androgen status for *Metformin* users compared to non-users.^{70,71} Interestingly, in the same study subanalysis when disaggregated by foetal sex, *Metformin* showed a modest decrease in maternal androgen levels during pregnancy for women with female foetuses, although no effect was observed in the androgen levels of the girls subsequently at age 5–10 years.⁷² A recent meta-analysis of children born to women with GDM or PCOS found that *Metformin* intake in pregnancy was associated with higher long-term weight in children.⁷³

Given the positive effects of *Metformin* in systemic level,⁷⁴ it seems rational to use *Metformin* as a pre-pregnancy treatment for weight management although the role of *Metformin* on improving pregnancy rate or live birth rate is still debatable^{75,76} and the benefit seems to be linked to ovulation induction rather than IVF/ICSI.⁷⁷ Nevertheless, the clinical practice should be that when the pregnancy test is positive, *Metformin* intake is stopped unless the woman has been already diagnosed with DM/GDM and *Metformin* is part of her care. It should be noted that treatment initiation with low-dose *Metformin* is more likely to improve adherence to the therapy as many women experience side effects when starting *Metformin*.

It also has to be remembered that in some severe cases of obesity bariatric surgery should be considered instead of Metformin prescription but this is a complex area due to potential nutrient insufficiencies and needs specialist advice.⁷⁸

Myoinositol is the second line medical choice following Metformin, as a modulating glucose tolerance medication. However, the studies on the efficacy of Myoinositol are heterogeneous and lacking placebo-controlled trials. Myoinositol seems to be promising in improving the hormonal and metabolic profile and menstrual cyclicality; thus it possibly has some impact on pregnancy outcomes.^{79,80} Given that myoinositol is an over-the-counter product, without gastrointestinal side-effects that Metformin has, it will be important that future research assesses its effects on pregnancy outcomes in women with PCOS.

Letrozole is considered as the first-line pharmacological treatment for ovulation induction in women with PCOS with anovulatory infertility and without other infertility factors.³ A recent meta-analysis including 10 randomized clinical trials (RCTs) with 948 women with PCOS evaluated the association of low-dose aspirin in combination with letrozole with fertility in women with PCOS.⁸¹ The authors found that adding aspirin to letrozole significantly improves reproductive outcomes, including increased pregnancy rate and decreased miscarriage rate. However, the authors called for further verification in multi-centre, large-sample, high-quality RCTs. A recent study showed that the proteome profile of uncomplicated pregnancies in PCOS is similar to that of pregnancies with pre-eclampsia.⁸² Therefore women with PCOS may benefit from low-dose aspirin intake during pregnancy for prevention of pre-eclampsia and its related neonatal outcomes including intrauterine growth retardation, preterm birth, low birth weight, and perinatal mortality.⁸³ However, the benefit needs to be confirmed in PCOS.

3.4 | Follow-up postpregnancy

The international evidence-based guidelines for the assessment and management of PCOS had a clinical practice recommendation to follow-up blood glucose, weight, blood pressure, smoking, alcohol, diet, exercise, sleep, and mental, emotional and sexual health among women with PCOS postpregnancy, to improve reproductive and obstetric outcomes, aligned with recommendations in the general population.³ An OGTT is recommended to assess glycemic status in women with PCOS every one to three years, depending on existing risk factors and blood pressure should be measured every year.³

After birth, the women should be encouraged to breastfeed and aim to achieve a healthy weight given the high risk for obesity and type 2 diabetes.^{4,27} A higher BMI may be associated with decreased breastfeeding, although studies in women with PCOS are scarce.^{84,85} A study on a large unselected population of American women with and without PCOS showed increased postpartum cardiovascular and psychiatric complications in women with PCOS after adjustment for potential confounders.⁴² In PCOS, the odds for adverse postpartum cardiovascular complications such as pre-eclampsia, eclampsia, hypertensive heart disease, thrombotic disease,

congestive heart failure, cerebrovascular accidents were 1.3-1.5 fold higher, with the odds being higher in black women with PCOS compared with white women with PCOS. The same study also reported a 1.5 fold higher odds for post-partum depression, calling for adequate screening and support for women with PCOS. Contraception and family planning should be discussed postpartum particularly given that the pregnancy hormones may downregulate pituitary pulsatility and facilitate ovulation recovery postpartum. More studies should be performed on postpartum follow-up of women with PCOS.

4 | CONCLUSIONS

PCOS is a common and heterogeneous condition, with affected women at substantively higher risk of infertility and cardiometabolic risks factors, both exacerbated by a greater prevalence of overweight and obesity. During pregnancy, women with PCOS are at higher risk for pregnancy and birth complications, exacerbated by obesity at pre-conception, hyperandrogenism, and possibly higher gestational weight gain. At postpartum, breastfeeding challenges are prevalent and pregnancy complications including cardiovascular and mood disorders may persist through to the longer term in women with PCOS. The international evidence-based guidelines for the assessment and management of PCOS: (1) highlight the lack of high-quality evidence for clinical management of pregnancy and (2) recommend checking blood glucose, weight, blood pressure, smoking, alcohol, diet, exercise, sleep, and mental health, emotional and sexual health among women with PCOS. The guidelines also note the role of engaging with positive health behaviours in the prevention and improvement of long-term cardiometabolic and psychological complications.

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