International Journal of Endocrinology

Огляд літератури
Literature Review

UDC 618.11-007.1 DOI: https://doi.org/10.22141/2224-0721.19.2.2023.1259

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Association of polycystic ovary syndrome with multiple health factors and adverse pregnancy outcomes

For citation: Mìžnarodnij endokrinologìčnij žurnal. 2023;19(2):137-142. doi: 10.22141/2224-0721.19.2.2023.1259

Abstract. *Polycystic ovary syndrome (PCOS), an endocrine and metabolic disorder in women of reproductive age, is characterized by high androgen levels, irregular periods, and small cysts in the ovaries. PCOS affects approximately 10 % of reproductive age women of all races and ethnicities. PCOS has been recognized to affect women of reproductive age since antiquity and in the 21st century, it emerges as the most widespread and serious reproductive metabolic disorder in the world. PCOS is a multifactorial disorder that affects both the reproductive and metabolic health of women. In addition, PCOS is a leading symptom of infertility in women. Nevertheless, women with PCOS who become pregnant unfortunately have an increased risk of complications, such as gestational diabetes mellitus (GDM), preterm birth. Many people believe GDM disappears after childbirth, despite the fact that GDM is a warning symptom of type 2 diabetes mellitus, metabolic syndrome, and cardiovascular disease. According to growing evidence, GDM complicates 40 % of PCOS pregnancies, suggesting that PCOS is a risk factor for GDM. Hence, PCOS is a lifelong disorder that can eventually lead to various long-term health complications, including chronic menstrual irregularity, infertility, endometrial hyperplasia, and endometrial cancer. Thus, it's a scientific fact that both PCOS and GDM are significantly associated with each other. However, most studies on the risk of GDM in PCOS patients are retrospective. Therefore, there is no strong evidence whether PCOS is a risk factor for GDM or any other related factor. PCOS, a polygenic endocrinopathy, is in a true sense a set of diseases that worsen the state of the body. Reproductive and metabolic disorders associated with PCOS cause several clinical symptoms, such as irregular and painful periods, hirsutism, acanthosis nigricans, acne, psoriasis, anxiety, mood swings, patterned baldness, cardiovascular problems, type 2 diabetes, infertility, pelvic pain, low libido, low self-esteem, etc. Further studies are needed to understand the genetic and epigenetic contributions of PCOS, PCOS-related comorbidities, the role of placenta in nutrient availability, and influence of medications that may affect the long-term offspring health.*

Keywords: *polycystic ovary syndrome; pregnancy complications; gestational diabetes mellitus; PCOS-related comorbidities; review*

Polycystic ovary syndrome (PCOS) affects approximately 10 % reproductive age women of all races and ethnicities [1, 2]. PCOS has been recognized to affect women of reproductive age since antiquity and in the 21st century, it emerges as the most widespread and serious reproductive-metabolic disorder in the world [3]. PCOS is a multifactorial disorder that affects the female reproductive system and is characterized by hyperandrogenism, ovarian dysfunction, and polycystic ovarian morphology [4].

However, the phenotypic heterogeneity among women with PCOS variably affect pregnancy outcomes. Women with PCOS may have challenges conceiving secondary to the effects of obesity, metabolic dysfunction including insulin resistance (IR), inflammation, or endocrine abnormalities. These conditions influence ovulatory function, endometrial receptivity, and oocyte quality [5]. The phenotypic variability of PCOS and differences in diagnostic criteria from adolescence to adulthood have contributed to the research, intervention, and clinical management challenges for this condition [6].

Pregnant women with PCOS have increased risks for adverse pregnancy outcomes, independent of subfertility and use of assisted reproductive technology [7]. Adverse peri-

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natal outcomes include early pregnancy loss, gestational diabetes mellitus (GDM), hypertensive spectrum disorder (i.e., gestational hypertension and preeclampsia), small- and large-for-gestational-age infants (SGA, LGA), preterm birth, and cesarean deliveries [8, 9].

The pathobiology of these adverse perinatal outcomes among women with PCOS is debated. The metabolic, genetic, clinical, and biochemical characteristics of PCOS contribute to an altered intrauterine environment, increased risks for pregnancy complications, and long-term fetal developmental programming risks observed in this higher risk population. Despite the higher rates of adverse pregnancy outcomes associated with PCOS, there is no consensus on perinatal guidelines specific to the management of PCOS in pregnancy. Increased surveillance and clinical management strategies during pregnancy have been directed from PCOS-related conditions and characteristics [10, 11].

PCOS is complicated by phenotypic heterogeneity, different diagnostic criteria, and variable chronic health conditions that an individual may have entering pregnancy, which challenges the development of evidenced-based strategies to improve pregnancy outcomes. PCOS-related comorbidities include overweight/obesity, IR, dyslipidemia, low-grade chronic inflammation, and mental health disorders [12]. PCOS is associated with an increased risk of adverse perinatal outcomes, but the effect of the different PCOS phenotypes on these adverse outcomes are conflicting [13].

Women with PCOS who undergo *in vitro* fertilization (IVF) have similar clinical pregnancy rates as other women who undergo IVF for other infertility causes. In a recent meta-analysis, among women who underwent IVF, PCOS was associated with higher rates of miscarriage (odds ratio (OR) 1.52; 95% confidence interval (CI) 1.04–2.22), ovarian hyperstimulation syndrome (OR 4.62; 95% CI 3.20–6.68), GDM (OR 2.67; 95% CI 1.43–4.98), gestational hypertension (OR 2.06; 95% CI 1.45–2.91), LGA (OR 2.10; 95% CI 1.01–4.37), and preterm birth (PTB) (OR 1.60; 95% CI 1.25–2.04) compared with IVF performed for other causes of infertility [7]. The review was limited by varying degrees of heterogeneity between the studies and the limited number of prospective studies included in the analysis but underscore the significant risks associated with PCOS among this higher risk IVF population.

The most common pregnancy complications reported among women with PCOS are GDM (OR 2.78–3.58) and hypertensive spectrum disorder (OR 2.46–3.43), which are significantly increased, independent of age, fertility treatment, obesity status, or other confounding demographic factors [8, 13, 14].

A significant number of these women meet criteria for metabolic syndrome; research models have suggested preconception or early pregnancy measures of sex-hormone binding globulin, afamin, androstenedione, fasting glucose and triglycerides, and IR as potential predictors of GDM among the PCOS population. These metabolic markers are in addition to known risk factors such as age, obesity, prediabetes, family history of diabetes, and history of GDM [15, 16].

Prospective studies are needed to determine the efficacy of these markers in predicting GDM among women with PCOS. The association of PCOS with adverse neonatal outcomes is inconsistent. In the most recent meta-analyses, PCOS was associated with an increase in the risk for PTB (OR 1.52–1.93) [7, 14].

Studies have reported an increased risk for both SGA and LGA among women with PCOS but only when considering prospective studies and within specific populations [8]. Opposite growth outcomes may suggest different underlying comorbidities known to affect growth, including IR, prediabetes, dyslipidemia, hypertensive disorders, obesity, obstructive sleep apnea, and over-/undernutrition. Neonates born to mothers with PCOS have higher rates of neonatal intensive care unit admissions (OR 1.74–2.31) and perinatal mortality (OR 1.83–3.07) [8, 17].

The placenta is the largest endocrine organ during pregnancy, communicating with both the fetus and the mother to ensure normal fetal development and growth. The placenta serves as a mediator of pregnancy complications, neonatal outcomes, and developmental programming of the offspring [18]. Human studies suggest higher prevalence of placental infarctions, villitis, and villous immaturity even after adjusting for significant demographic and pregnancy complications associated with PCOS during pregnancy [19]. The variable PCOS phenotype and the significant maternal and neonatal morbidities associated with PCOS have contributed to the challenges and paucity of studies focused on placental dysfunction and contributions to adverse outcomes.

Offspring born to women with PCOS are associated with increased risks for higher childhood body mass index (BMI), abnormal cardiometabolic markers, and neurodevelopmental disorders [20]. The genetic and epigenetic contributions of PCOS, PCOS-related comorbidities, and adverse pregnancy conditions (GDM, SGA, LGA, and preeclampsia) affect the intrauterine environment and long-term offspring health.

Periconception individuals with PCOS have multiple factors that are associated with increased perinatal complications [21]. Pregnancy is often a motivating period for individuals and families. Optimizing health before pregnancy may improve pregnancy outcomes and maternal lifelong health. The preconception period provides a window of opportunity where pregnancy-related complications can be discussed, preventative screening and safe treatments during pregnancy can be initiated, and nutritional and lifestyle behaviors can be optimized to improve oocyte quality and potentially pregnancy outcomes [22].

Pre-pregnancy BMI is strongly associated with adverse perinatal outcomes and incrementally increases the risk for preeclampsia, GDM, indicated preterm delivery, and macrosomia [23, 24]. Lifestyle interventions incorporating high-quality nutrition, physical activity, and behavioral strategies should be advised before pregnancy as the primary approach to aid in losing weight and improving health [25]. Studies have demonstrated improved fecundity and live birth rates among modest weight-loss (5–10 % of initial body weight) and healthy lifestyle interventions in the subfertile PCOS population, but trials showing a benefit from a weight-loss intervention pre-pregnancy to reduce pregnancy-related complications are currently lacking [26].

Antiobesity medications are not recommended during pregnancy, and women should be advised to discontinue and implement other strategies before pregnancy [27]. Although bariatric surgery has been shown to decrease rates of GDM, hypertensive disorders, and macrosomia, it has associated risks with potential postsurgical complications, fetal growth restriction, and nutritional challenges that need to be considered [28]. Among women who undergo bariatric surgery, pregnancy should be avoided within 1 year of the operation or weight stabilization. Bariatric surgery often improves IR, impaired glucose tolerance, hyperlipidemia, and sleep-disordered breathing, but as an intervention to improve conception rates or pregnancy-related complications among women with PCOS is considered investigational.

PCOS is also associated with an increased risk of depression, anxiety, bipolar disorder, eating disorders, and obsessive-compulsive disorder, particularly among individuals with weight concerns or subfertility [29]. Routine screening for depression, anxiety, and other mental health disorders are recommended upon diagnosis of PCOS and if negative to screen again among those with high-risk factors such as obesity, diabetes, pregnancy, postpartum, or family history of mental health disorders [29].

IR, hyperinsulinemia, and impaired glucose tolerance are common features observed among individuals with PCOS that may present even during adolescence. Because of the increased risk for GDM, women are recommended to be screened for diabetes and cardiovascular risk factors (obesity, dyslipidemia, and nicotine use) before conception.

International guidelines have recommended a 75-g oral glucose tolerance test to be offered in all women with PCOS when planning pregnancy or seeking fertility treatment [30]. Women taking metformin should discontinue the medication for at least 3 to 5 days before oral glucose tolerance test.

IR and obesity are strongly associated with sleep-breathing disorders. Obstructive sleep apnea increases the risk for GDM and preeclampsia 2–3-fold in addition to more rare maternal outcomes such as cardiomyopathy, pulmonary edema, and mortality [31]. Therefore, women with PCOS should be screened for symptoms related to sleep-breathing disorders preconception and throughout pregnancy [32].

Women with PCOS have higher risks for adverse pregnancy outcomes and are recommended to have closer surveillance during the prenatal and postpartum period. Even after adjusting for significant confounders, individuals with PCOS have up to a 2-fold higher risk for hypertensive spectrum disorder and GDM [4]. However, there are no specific guidelines for antenatal fetal surveillance or ultrasound assessments for PCOS. Recommendations for this population is driven by the high-risk characteristics that women with PCOS commonly have. Therefore, individualized fetal surveillance and perinatal management is recommended.

Metformin use during pregnancy among women with polycystic ovary syndrome Metformin has been widely used in women with PCOS for induction ovulation, to improve insulin sensitivity and treat prediabetes in women planning to conceive. It readily crosses the placenta, but studies do not demonstrate an associated teratogenic risk with short-term use of metformin during pregnancy [33]. Metformin has not been shown by most of the randomized controlled trials (RCTs) to improve pregnancy outcomes, including miscarriage, PTB, excess gestational weight gain, GDM, or preeclampsia [34]. Although some observational trials and meta-analyses have suggested that metformin may decrease early pregnancy loss and preterm delivery the American Society for Reproductive Medicine published guidelines on the role of metformin for ovulation induction in PCOS and concluded insufficient evidence that metformin alone increases live birth rates or decreases miscarriage [35]. The Preg-Met study was an RCT among women with PCOS (Rotterdam criteria) who were randomized to 1700 to 2000 mg metformin versus placebo at 5 to 12 weeks of pregnancy in 11 centers in Norway [36]. In both Preg-Met and Preg-Met 2, metformin did not statistically reduce GDM, preeclampsia, preterm birth, cesarean delivery, birthweight, or macrosomia (defined as > 4500 g) [37]. Similarly, a Cochrane review and meta-analysis, which included RCTs of high-risk women with PCOS, obesity, or IR who were treated with metformin periconception or before 20 weeks gestation, did not improve GDM risk (risk ratio 1.03; 95% CI 0.85–1.24) compared with placebo [38]. The available data are insufficient to support metformin use to prevent miscarriage or PTB. Long-term use of metformin seems to be effective at reducing b-cell demand and progression of GDM to type 2 diabetes mellitus (T2DM) [39]. However, it is unlikely that the short-term, marked IR of pregnancy, and the demand for a 2-fold increase in insulin secretion can be significantly mitigated by metformin.

The PCOS and GDM offspring studies were limited by relatively small follow-up populations from the original cohorts. A systematic review and meta-analysis of GDM or PCOS RCTs (778 children) of mothers randomized to metformin versus insulin or placebo concluded that prenatal metformin was associated with increased offspring weight but not height or BMI during childhood [40]. Recently, the Metformin in Type 2 Diabetes RCT (MiTY) was completed, which randomized 502 women with T2DM on insulin to metformin or placebo in 25 centers in Canada and 4 in Australia and included 17 % of women with PCOS (MiTy) [41].

PCOS is a high-risk condition, but studies are inconclusive on whether the prevalence of postpartum depression is increased in this population [42]. However, screening for depression and anxiety should be performed through the first year postpartum [43].

Although PCOS is commonly associated with biologically plausible physiologic and psychological causes of breastfeeding challenges, such as IR, hyperandrogenism effects on prolactin, and breast tissue transformation; higher BMI is a stronger risk factor for lower breastfeeding rates than PCOS alone [44]. Women who develop GDM and breastfeed for at least 6 months reduce their risk for T2DM and the long-term risk to their offspring for childhood obesity [45]. One of the strongest risk factors for later obesity, metabolic disease, and T2DM is postpartum weight retention [46]. Encouraging the continuation of healthy lifestyle interventions and resuming or initiating metformin in the postpartum period are important for preventing the progression of metabolic dysfunction and T2DM. Metformin can be immediately resumed postpartum.

PCOS is associated with multiple health factors and adverse pregnancy outcomes that can challenge the transition from pregnancy to parenthood and long-term chronic health disease management.

Conclusions

Women with PCOS should be informed of their increased pregnancy risks, including early pregnancy loss, GDM, hypertensive spectrum disorder, and cesarean deliveries. Preconception health optimization to screen for mood disorders, diabetes, and cardiopulmonary risk factors with the implementation of lifestyle interventions or specific therapies is strongly recommended. Prospective, preconception intervention studies are needed to determine efficacy of reducing adverse pregnancy outcomes. Offspring of women with PCOS have higher rates of increased BMI, abnormal cardiometabolic markers, and neurodevelopmental disorders. Further studies are needed to understand the genetic and epigenetic contributions of PCOS, PCOS-related comorbidities, placenta's role in nutrient availability, and influence of medications that may affect the long-term offspring health. Metformin is not recommended to be continued beyond the first trimester to improve perinatal outcomes, but it can be immediately restarted after delivery.

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Received 09.01.2023
Revised 24.02.2023
Accepted 07.03.2023

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Conflicts of interests. Authors declare the absence of any conflicts of interests and own financial interest that might be construed to influence the results or interpretation of the manuscript.

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Взаємозв'язок синдрому полікістозних яєчників із певними чинниками та несприятливим перебігом вагітності

Резюме. Синдром полікістозних яєчників (СПКЯ) — ендокринний і метаболічний розлад у жінок репродуктивного віку, характеризується підвищеним рівнем андрогенів, нерегулярними менструаціями та появою кіст в яєчниках. СПКЯ вражає приблизно 10 % жінок репродуктивного віку будь-якої раси та етнічної групи. У XXI столітті СПКЯ розглядається як найпоширеніший серйозний репродуктивний і метаболічний розлад. СПКЯ — це багатофакторна патологія, що впливає на репродуктивне здоров'я жінок, провідний симптом безпліддя. На тлі вагітності жінки із СПКЯ мають підвищений ризик ускладнень, таких як гестаційний цукровий діабет (ГЦД), передчасні пологи. Попри думку, що ГЦД зникає після пологів, такий розлад є провісником цукрового діабету 2-го типу, метаболічного синдрому та серцево-судинних захворювань. Згідно з дедалі більшою кількістю доказів, ГЦД ускладнює 40 % вагітностей при СПКЯ, що свідчить про те, що СПКЯ є фактором ризику розвитку ГЦД. Отже, СПКЯ є тривалим розладом, який може призвести до різноманітних ускладнень, включаючи порушення менструального циклу, безпліддя, гіперплазію та рак ендометрія. В оглядовій статті підкреслюється, що СПКЯ та ГЦД значною мірою пов'язані один з одним. Однак більшість досліджень щодо ризику розвитку ГЦД у пацієнток із СПКЯ є ретроспективними. Тому відсутні переконливі докази стосовно того, чи є СПКЯ фактором ризику ГЦД і будь-якого іншого пов'язаного чинника. СПКЯ, полігенна ендокринопатія, у реальному розумінні розглядається як сукупність захворювань, що погіршують стан організму. Репродуктивні й метаболічні розлади, пов'язані з СПКЯ, спричиняють такі клінічні симптоми, як гірсутизм, акне, псоріаз, тривожність, перепади настрою, облисіння, серцево-судинні проблеми, цукровий діабет 2-го типу, зниження лібідо, низьку самооцінку тощо. Необхідні подальші дослідження для розуміння генетичного та епігенетичного внеску СПКЯ, супутніх захворювань, пов'язаних із СПКЯ, ролі плаценти і ліків, що можуть вплинути на перебіг вагітності і здоров'я нащадків.

Ключові слова: синдром полікістозних яєчників; ускладнення вагітності; гестаційний цукровий діабет; супутні захворювання, пов'язані із СПКЯ; огляд