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# **Polycystic ovary syndrome and pregnancy - review**

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Summary of review

Introduction and purpose

Polycystic Ovary Syndrome(PCOS) is one of the most common endocrinological disorders, and it affects 7-8 % of women globally. It is very heterogenous disease, which pathogenesis is complex and composed of many factors like genetics, hormonal changes, environmental factors and insulin resistance. PCOS has many symptoms, which appearance is dependent on comorbidities like obesity, diabetes mellitus, hypercholesterolemia. Due to complexity of the pathogenesis of PCOS it may have four phenotypes: A,B,C,D. The pregnancy pathologies connected to PCOS are mainly gestational diabetes mellitus, pregnancy induced hypertension. Pregnant women with PCOS have 3-4 times a higher risk of developing pregnancy induced hypertension (PIH) and preeclampsia and a three times higher risk of gestational diabetes mellitus (GDM). More than 64% of pregnancies in women with PCOS were terminated via caesarean section. Metformin, although still controversial may be a good option for the treatment of PCOS before and during pregnancy as a second-line therapy.

PCOS is a disease which affects the women in childbearing age and may have negative impact on its course. Pathologies connected to PCOS during pregnancy affect not only mothers, but foetus and according to new researches also children and adults from mothers with PCOS. It is very essential to extract women with PCOS to implement treatment and prevent its complications. Moreover, due to its common association with obesity patients should be under cardiologists care due to higher cardiovascular risk.

### Introduction and purpose

Polycystic Ovary Syndrome (PCOS) is one of the most common endocrinological disorders, and it affects 7-8 % of women globally. [1] PCOS is a heterogeneous disease and many factors have an impact on its development. It is affected by genetic, hormonal and environmental factors. [2] The main symptoms of PCOS are hirsutism, anovulation, menstrual dysregulation, 50% of patients are obese and suffer from lipid and carbohydrate metabolism disorders. PCOS is often associated with insulin resistance, causing hyperinsulinemia, which can lead to development of diabetes mellitus type 2. Moreover, in PCOS, there are incorrect levels of lipoproteins: total cholesterol, triglycerides, low-density lipoprotein are elevated, whereas the level of high-density lipoprotein is decreased. [3] Lipid levels change and obesity leads to an increase of cardiovascular risk. [3] According to data, PCOS is also associated with adverse pregnancy outcomes concerning mother and infant.

PCOS during pregnancy can induce a greater risk of gestational diabetes mellitus (GDM), preeclampsia, pregnancy induced hypertension, preterm delivery, caesarean delivery, hypoglycaemia and perinatal death. [4] PCOS complications can affect not only the mother but also the foetus and later children and lead to severe conditions. The aim of this work is to raise the awareness of the pathologies in pregnancy due to PCOS and to approximate the data about PCOS pathogenesis.

## PATHOGENESIS

The exact mechanism of pathogenesis of PCOS is not fully known now but it is multifactorial and modified by the coexistence of diseases such as obesity and diabetes mellitus.

In PCOS the excessive release of androgens in ovaries and adrenal glands is observed. In PCOS follicles grow fast from primordial to growing, moreover due to hormonal changes maturation of follicles is disturbed. (increased: luteinizing hormone (LH), insulin, androgen, and Anti-Müllerian Hormone (AMH) concentrations and inadequate follicle-stimulating hormone (FSH) concentrations).

The disorders of hypothalamic- pituitary axis

In women with PCOS, the increased frequency of gonadotropin-releasing hormone (GnRH) pulses is described and as a result increases LH pulse amplitude, and increased LH/FSH ratios occur. [5] Increased LH levels stimulate folliculogenesis and oocyte development. Cyclically repeated disorders of folliculogenesis can be a reason of infertility.

### Insulin resistance and obesity

Among the main risk factors of PCOS development it is essential to highlight obesity. Excess body weight has a negative effect on carbohydrate metabolism by enhancing insulin resistance and hormonal changes. The mechanism of the insulin resistance is very complex. The activity of aromatase and  $17\beta$ -Hydroxysteroid dehydrogenase is increased in adipose tissue and peripheral aromatization increases with body weight. [6] The efficiency of conversion of androstenedione to estrone is elevated in obese patients, additionally level of plasma sex hormone binding globulin (SHBG) is decreased resulting in a higher level of active hormones. [7] The result of all these changes is hyperestrogenism, without sustainability of progesterone. According to analysis, hyperandrogenemia is related to insulin action even in nonobese PCOS women. [8]

## Genetics

PCOS development has many risk factors and genetics remain one of them, although studies failed to find a fully penetrant variant. PCOS as a very heterogeneous disease with complex patomechanism it is unrealistic to extract one gene responsible for its development. [9]

### Endothelial disfunction

Guanylate cyclase (GC) pathway is one of the most important regulatory pathways. The key

mediators are nitric oxide and carbon monoxide and of course cyclic guanosine 3',5'monophosphate [10]. There are several possible direct pharmacological interventions modifying its action [11]. This pathway is responsible for the regulation in blood flow in circulation. It was confirmed that women with PCOS exhibit microvascular endothelial dysfunction, indicated by an inhibited vasodilatory response to Ach [12]. Results of experimental animal studies suggest that pharmacological intervention on this level is possible [13]. In that condition important is to consider dual actions of aspirin. A low dose is used in PCOS patients [14], but increase in dose may additionally decrease depleted endothelial function [15]. Dietary intervention in these systems may be responsible for inadequate response to therapy [16,17].

## Recognition of PCOS

Currently, applicable rules of PCOS diagnostic criteria are made by the *European Society for Human Reproduction and Embryology/ American Society for Reproductive Medicine* and include: 1) hyperandrogenism (detected by clinical and/or biochemical testing) 2) ovulation abnormalities, and/or 3) 12 or more cysts on one ovary and/or ovarian volume > 10 mL. [18]

Based on the signs of the disease there are four phenotypes of PCOS. [Table 1] [9]

Phenotype	А	В	С	D
Menstrual disorders (oligomenorrea)	+	+		+
Clinical and/or biochemical hyperandrogenism	+	+	+	
Policystic ovaries	+		+	+

Table 1: Phenotypes of patients with PCOS.

Phenotype-A is more common in subjects identified in clinical populations, whereas phenotype-C is more common in unselected populations. [19]

Women with PCOS have higher risk of pregnancy complications such as a pregnancy induced hypertension, preeclampsia, gestational diabetes mellitus. According to Tingting Wang et al. 26% of pregnant women participating in the meta-analysis have GDM and 94% of patients present pregnancy induced hypertension (PIH). Pregnant women with PCOS have 3-4 times a higher risk of developing PIH and preeclampsia and a three times higher risk of GDM. More than 64% of pregnancies in women with PCOS were terminated via caesarean section. [20,21,22]

According to Akramsadat Dehghani Firoozabad et al. in an analysis where 200 women with PCOS during pregnancy were categorised into groups depending on the phenotype of PCOS and the prevalence of diabetes mellitus, pregnancy induced hypertension and other diseases were checked. In the analysis the most common was phenotype D. The risk of diabetes mellitus was the highest in phenotype A and the prevalence of pregnancy induced hypertension in phenotype B. There was not any difference in neonatal outcomes noted. In group A the history of abortion and infertility was higher than in another groups, there was no difference in the rate of miscarriage. [23]

In other studies also phenotype A and B have more than the other phenotype pregnancy pathologies, preeclampsia rate was higher. In the meta-analysis made by Jun Z Qui the risk of lower birth weight and risk of admission to neonatal intensive care unit (NICU) was higher for the neonates born by mothers with PCOS. [16] This result however has not been confirmed in another analysis [24,25].

Children born from mothers with PCOS have a higher risk of being obese in adulthood. [26]

#### Metformin treatment

Metformin is an oral administered drug, which improves insulin sensitivity in the liver and the peripheral tissues, where it inhibits hepatic glucose production and increases glucose uptake and use in muscle. [27] As the effect, it decreases the insulin resistance. Metformin use during pregnancy raised doubts due to reports about its teratogenic effect on foetus. The latest analysis shows however, that metformin use in pregnancy is beneficial in women with type 2 diabetes mellitus or PCOS as second-line therapy. During analysis of metformin vs placebo,

the metformin group had fewer miscarriages, fewer cases of GDM, lower birth weight and lower incidence of pregnancy induced hypertension. [28]

The limitations of metformin usage in pregnant women are uncertain long-term effects of the treatment. Children of mothers with GDM or PCOS treated with metformin in some studies showed higher body mass, waist-hip ratio (WHR), arm and hip circumference than children from the insulin group. [29] Another study shows no difference between insulin and metformin group. [30] According to guidelines insulin remains the first-line therapy in diabetes mellitus during pregnancy, apart from the guidelines of the British National Institute for Health and Care Excellence, where metformin is recommended as first-line treatment.

### Summary

PCOS and its components can be harmful during pregnancy and cause severe complications not only to pregnant woman and foetus but also results in diseases development in children from a woman with PCOS. Therefore, it is essential to detect PCOS before pregnancy and implement therapy. First and the most important is weight control and a diabetic diet with a low glycaemic index. Hormone disorders associated with overweight and obesity lead to pregnancy pathologies. Metformin reduces the risk connected with PCOS during pregnancy and is beneficial for a pregnant woman with this disorder. Further analysis is required to check the long-term effects of metformin treatment on children, but at this moment it seems to be a reasonable and beneficial treatment of PCOS during pregnancy. Due to the endothelial disorders in PCOS and related to this higher risk of cardiovascular diseases it is essential to make regular cardiological examinations.

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