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FEATURES OF THE COURSE OF PREGNANCY IN WOMEN WITH POLYCYSTIC OVARY SYNDROME

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▪ Polycystic ovary syndrome is one of the most common pathologies in the practice of an obstetrician-gynecologist. Overcoming infertility characteristic of this syndrome is an important problem of endocrinology, gynecology, and reproductive medicine. Innovative therapeutic and surgical methods of treatment can correct hormonal and metabolic disorders, induce ovulation and achieve a long-awaited pregnancy. Early gestation periods in patients with polycystic ovary syndrome often occur with miscarriage, and the risks of developing gestational diabetes mellitus, cervical insufficiency, gestational arterial hypertension, preeclampsia, and placental insufficiency increase. We have analyzed modern ideas about the effect of various pathogenetic links of polycystic ovary syndrome on the course of pregnancy.

▪ **Keywords:** polycystic ovary syndrome; insulin resistance; hyperandrogenemia; obesity; gestational diabetes mellitus; cervical insufficiency; placental insufficiency; preeclampsia.

ОСОБЕННОСТИ ТЕЧЕНИЯ БЕРЕМЕННОСТИ У ПАЦИЕНТОК С СИНДРОМОМ ПОЛИКИСТОЗНЫХ ЯИЧНИКОВ

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▪ Синдром поликистозных яичников является одной из самых распространенных патологий в практике врача — акушера-гинеколога. Преодоление характерного для этого синдрома бесплодия находится в области внимания эндокринологии, гинекологии, репродуктологии. Современные терапевтические и хирургические методы лечения позволяют скорректировать гормональные и метаболические нарушения, провести индукцию овуляции и добиться наступления долгожданной беременности. Ранние сроки гестации у пациентов с синдромом поликистозных яичников зачастую протекают с угрозой прерывания, в дальнейшем возрастают риски развития гестационного сахарного диабета, истмико-цервикальной недостаточности, гестационной артериальной гипертензии, преэклампсии, плацентарной недостаточности. В статье изложены современные представления о влиянии различных патогенетических звеньев синдрома поликистозных яичников на течение беременности.

▪ **Ключевые слова:** синдром поликистозных яичников; инсулинорезистентность; гиперандрогенемия; ожирение; гестационный сахарный диабет; истмико-цервикальная недостаточность; плацентарная недостаточность; преэклампсия.

Polycystic ovary syndrome (PCOS) occurs in 6%–8% of women of reproductive age and is a key factor leading to anovulatory infertility [1, 2]. This disorder is characterized by impaired folliculogenesis, delayed development of small and large antral follicles with the remaining number of primordial follicles, lack of initiation of the dominant follicle, and consequently, impaired ovulation which is clinically manifested by opsomenorrhea and amenorrhoea, hirsutism, acne, and changes in ovarian size, shape, and structure in the form of polycystic transformation [3]. There are three main pathogenetic pathways in PCOS development such as impaired pulsatile luteinizing hormone secretion, insulin resistance and hyperinsulinemia, and ovarian aromatase deficiency. Ovarian aromatase deficiency [4, 5] and the hyperproduction of anti-Mullerian hormone play a significant role in the disease development [5, 6]. Metabolic disorders in PCOS are manifested by insulin resistance, hyperinsulinemia, impaired glucose tolerance, excess body weight, and obesity. Impaired glucose tolerance or diabetes mellitus is found in 40% of patients over 40 years of age, and obesity is found in 40%–60% of patients [7, 8]. Changes in fat metabolism manifested by hyperlipidemia lead to vascular endothelial damages [9]. Vascular endothelial growth factor is increased in the blood of patients with PCOS, and its levels correlate positively with the number of antral follicles and severity of the clinical manifestations of the disease [10]. Metabolic disorders impair both the quality and duration of life and must be promptly corrected using medications [11].

The rapid development of reproductive endocrinology technologies has enabled to combat the clinical manifestations of PCOS as well as to effectively overcome infertility that is specific to women suffering from this syndrome. The use of drugs such as insulin sensitizers, anti-androgens, hormonal contraceptives, and ovulation inducers, and techniques such as laparoscopic ovarian cauterization along with the introduction of various *in vitro* fertilization (IVF) programs has contributed to the onset of pregnancies. However, from the earliest stages of pregnancy, there are various obstetric pathologies associated with difficulties in carrying a pregnancy, such as spontaneous miscarriages in the early stages, cervical insufficiency (CI), and premature labor in the later stages. Gestational diabetes mellitus (GDM), preeclampsia, and placental insufficiency are also more common. This review presents current data on the complications of pregnancy associated with PCOS.

Early pregnancy loss

Spontaneous miscarriages occur in 15.5%–24.7% of patients with PCOS [12]; after overcoming infertility, some authors have reported a miscarriage rate of over 80%, with a rate of 87% for pregnancies occurring after IVF techniques [13]. Several studies have reported a 30% miscarriages rate in the first trimester due to PCOS, followed by ovulation stimulation with clomiphene citrate or letrozole, but there were no significant differences when using anti-estrogens (31.8%) and aromatase inhibitors (29.1%) [14]. The multifactorial pathogenetic mechanisms of this syndrome leads to different ways of affecting pregnancy development. PCOS is known to be the most common form of hyperandrogenemia, accounting for 90% of all diseases associated with increased blood androgen levels [15]. In our own studies, hirsutism occurs in 81.4% of non-pregnant patients with PCOS, and hyperandrogenemia occurs in 65.9% of these patients [16]. Hyperandrogenemia predominantly contributes to the development of microcirculatory disorders. Microcirculatory changes resulting from hyperandrogenemia can also affect uterine vessels, leading to impaired uterine circulation and myometrial sclerosis and contributing to various pregnancy complications, including early termination in 36% of women [17].

Chronic anovulation in PCOS is manifested by both the inadequacy of the secretory endometrial transformation and hyperplastic processes, with their frequency reaching 82.1%, endometrial hyperplasia occurring in 76.9%, and endometrial polyps occurring in 10.3% of cases [16]. Endometrial hyperplasia is associated with impaired fetal implantation and placenta formation, leading to an increased incidence of early pregnancy loss in PCOS.

Multiple pregnancy

In multiple pregnancies, compared with singleton pregnancies, the course of many physiological processes has several characteristic features.

The increase in the area and weight of the placental tissue, marked increase in the extent of the vascular system, increased significant hormonal changes in the body, overstretching of the uterus, greater increase of intra-abdominal pressure compared with a singleton pregnancy, and effect on the abdominal and pelvic organs lead to an increased frequency and severity of various pregnancy and labor complications. These complications include anemia, CI, preeclampsia, placental insufficiency, single and multiple fetal growth retardation, and premature labor. The incidence of multiple pregnancies in Russia and Europe is 0.7%–1.5%, and it increases steadily every year. At the D.O. Ott Research Institute of Obstetrics and Gynecology, the incidence rates of multiple pregnancies in 2017, 2018, and 2019 were 2.6%, 2.7%, and 2.8%, respectively. PCOS is not directly responsible for multiple pregnancies, but the infertility characteristic of this syndrome is associated with a high frequency of various ovulation induction methods, as well as IVF, which significantly increases the incidence of multiple pregnancies in PCOS. Moreover, ovulation induction with gonadotropins or anti-estrogens is significantly more likely to result in multiple pregnancies compared with single embryo transfer in IVF [18]. Thus, twins in PCOS are associated with a ten-fold increase in the frequency of low birth weight fetuses in relation to gestational age and a six-fold increase in premature labor [19]. Despite the obvious potential complications of multiple pregnancies with PCOS, some researchers have not found statistically significant differences in the occurrence of these complications when adjusting for the age of a pregnant woman and her concomitant obesity [20].

Hypertensive disorders during pregnancy

Endothelial dysfunction is an important factor that leads to vascular disorders in patients with PCOS. Abnormal brachial artery diameter (basal and after reactive hyperthermia), abnormal flow-mediated dilatation, and intima-media thickening of the common carotid arteries are known to be common in PCOS women [21]. The changes in the functional activity of various mechanisms and links of leukocyte adhesion regulation, vascular tone, and thrombogenicity of the vascular wall are predominantly associated with PCOS. Thus, blood levels of intercellular adhesion molecules, vascular adhesion molecules, endothelin-1, and plasminogen activator inhibitor (PAI-1) are significantly higher in these patients compared with women randomized by age, body mass index, and comorbid somatic pathology without signs of this syndrome [22, 23].

Hyperandrogenemia has been shown to contribute to various cardiovascular diseases, including hypertension and ischemic heart disease [24, 25]. There are many studies indicating the important role of endothelial dysfunction in the formation of gestational arterial hypertension and preeclampsia [26, 27]. Several studies have reported that the serum levels of total and free testosterone were significantly higher in pregnant women with preeclampsia compared to pregnant women without preeclampsia. Blood levels of steroid-binding globulin, dehydroepiandrosterone, and estradiol did not differ significantly in the studied groups [28]. Hyperandrogenemia inherent in PCOS is a significant factor of endothelial dysfunction and can occur with or without obesity. Obesity is a common PCOS symptom, with hyperandrogenemia manifesting in a form of metabolic disorders that are characteristic of an increased adipose tissue [29].

During physiological pregnancy, significant metabolic changes occur in the woman's body due to the formation of a temporary endocrine organ, i.e., the placenta, which produces protein hormones (placental lactogen and chorionic gonadotropin) and sex steroid hormones (progesterone, estriol, estrone, and estradiol). Physiological insulin resistance develops, with the aim of preserving glucose for the fetus, which serves as the main source of energy. In genetically predisposed women, insulin resistance leads to the development of GDM. Hyperinsulinemia is found in 60%–70% of patients with PCOS who may or may not have obesity, whereas insulin resistance reaches 80% [30, 31]. Insulin resistance and ovarian aromatase deficiency are central factors of the PCOS pathogenesis [16]. In patients with PCOS, insulin resistance underlies carbohydrate and lipid metabolism disorders. Compensatory hyperinsulinemia contributes to the development of hypertension and atherosclerosis. More severe insulin resistance is to be expected in cases where the pregnancy develops with obesity. It is

supported by the fact that pregnancy is predominantly complicated by GDM in obesity [32, 33]. Various types of diabetes mellitus are associated with endothelial dysfunction and preeclampsia [26]. Insulin resistance manifests by decreasing nitric oxide synthesis, increasing endothelin-1 production, and enhancing PAI-1 expression [34].

A group of researchers studied the activity of several steroidogenic enzymes in the placenta of full-term pregnant women with and without PCOS. The activity of 3-beta-hydroxysteroid dehydrogenase, steroid sulfatase, and P450 aromatase was determined, and it was shown that P450 aromatase activity was reduced and 3-beta-hydroxysteroid dehydrogenase activity was increased in the placenta of patients with PCOS [35]. Earlier studies have shown that a 1% decrease in the placental aromatase activity leads to marked virilization in female fetuses [36]. Insulin and insulin-like growth factor are known to inhibit placental aromatase activity and activate 3-beta-hydroxysteroid dehydrogenase activity [37, 38]. The development of preeclampsia is closely related to a deficiency of catechol-O-methyltransferase, an enzyme involved in catecholamine metabolism, contributing to its inactivation during synaptic transmission. Deficiency of this enzyme is observed in PCOS, obesity, and diabetes mellitus, leading to sympatho-adrenal activation, vasoconstriction, and arterial hypertension [39, 40]. Thus, PCOS can lead to endothelial dysfunction and subsequently, the development of hypertensive pregnancy complications through both hyperandrogenemia and obesity, insulin resistance, and hyperinsulinemia.

GGDM

Numerous multicenter studies have reported a high incidence of GDM, which is the most common pregnancy complication in patients with PCOS [41]. Early diagnosis of carbohydrate metabolism disorders, timely and adequate administration of dietary therapy, and strict glycemic control significantly reduce the risks of complications for both the pregnant woman and the newborn [41, 42]. According to various studies, the risks of developing GDM in PCOS vary widely, from 4.9% versus 12.1% among patients in the control group [43] to 28.8% versus 1% in the control group [44]. In a large prospective study in 2014, the incidence of GDM was reported to be threefold higher compared with the general population, and accounted for 14.7% [45]. Such significant discrepancies were due both to the selection criteria for the studied groups and the heterogeneity of PCOS, which requires phenotypic and clinical clarifications when included in the study.

There are many opinions regarding the efficiency of insulin sensitizers that are used during the preconception period. In a multicenter study aimed at assessing the effectiveness of metformin in reducing the incidence and severity of pregnancy complications in patients with PCOS, it was shown that the incidence of GDM in the metformin and placebo groups was 17.6% and 16.9%, respectively [46]. According to other studies, the incidence of GDM was significantly lower in patients with PCOS and obesity treated with metformin compared with pregnant women stratified by body mass index and age without appropriate preconception treatment [47]. Diabetes mellitus in patients with PCOS affects the vascular wall, mainly due to hyperglycemia, leading to the development of oxidative stress and the formation or aggravation of pre-existing endothelial dysfunction [48].

CCI

The incidence of CI in PCOS is statistically higher compared to the population average, that is, 2.9% *versus* 0.5%, and there is ethnic heterogeneity in the CI distribution, with 1% in the Caucasian race and 7.8% and 17.5% in the South Asian and African American races, respectively [49]. Among the factors leading to premature labor in PCOS, CI accounts for up to 28% [50]. The pathogenetic pathways of CI during pregnancy in patients with PCOS are varied. Insulin resistance and hyperandrogenemia are associated with chronic inflammation through an increased production of proinflammatory cytokines, such as tumor necrosis factor-alpha, interleukin-1, and interleukin-6, leading to an increased uterine activity, cervical shortening, and, consequently, formation of CI [51]. Altered uterine-placental circulation and uterine vascular sclerosis in hyperandrogenemia are associated with CI in 31% of pregnant women in the second trimester [17]. Another mechanism of CI formation, in addition to hormonal and metabolic mechanisms, is a mechanical

one, associated with an increase in intra-abdominal pressure, overstretching of the uterine walls, and distortion of the uterine ligamentous apparatus, which is particularly manifested in multiple pregnancies that frequently occur in PCOS.

Placental insufficiency

Pregnancies occurring after overcoming PCOS-associated infertility are associated with chronic placental insufficiency in 23.1%–24.1% of cases [13]. The probable factors leading to its formation are hypertensive disorders, GDM, infections, and endometrial hyperplastic processes. Impaired trophoblast invasion may occur as a result of hyperandrogenemia. Androgens are known to affect both the endometrium directly and the sensitivity of its receptors to various factors. Androgens stimulate cytoskeleton organization and increase cell motility and the rate of cell division through their own receptors. Dihydrotestosterone leads to cytoplasmic expansion, accelerates the formation of lipid droplets and the extracellular matrix, and increases the number of gap junctions [52]. Hyperandrogenemia due to overstimulation can lead to a decrease in the sensitivity of androgen receptors, and following acceleration, to a delay in placental processes. Hyperandrogenemia leads to the subsequent impaired synthesis and production of placental hormones, placental metabolic disorders, and lipid metabolic changes in the intrauterine fetus. With its lipophilicity, testosterone is able to pass through the placental barrier and affect energy and metabolic processes in the fetus. It has been shown in animals that hyperandrogenemia decreased placental weight, fetal weight, and length. At the receptor level, placental tissue has a 3.2-fold increase in estrogen receptor alpha, 2.5-fold increase in estrogen receptor beta, and 2.3-fold increase in 17-beta-hydroxysteroid dehydrogenase [53]. Trophoblast invasion and placentation are affected by several adverse factors including hyperandrogenemia, insulin resistance, ovarian insufficiency, opsomenorrhea, endometrial hyperplasia, infertility, ovulation inducers, multiple pregnancies, hyperlipidemia, chronic low-grade inflammation, obesity, GDM, and preeclampsia. This pathogenetic network of multiple elements leads to the development and progression of placental insufficiency and the increased frequency and degree of perinatal and neonatal complications in PCOS. Thus, the incidence of low birth-weight babies in PCOS is high and, according to some researchers, is 4.5-fold higher compared to the population average [54].

Currently, sufficient data on the clinical picture and pathogenetic mechanisms of PCOS have been obtained, mechanisms to overcome anovulatory infertility in patients with this syndrome have been developed, and the pathological nature of the pregnancy course has been studied. The disconnection of gynecological and obstetric care for patients with PCOS leads to an obstetric view of a pregnancy achieved with reproductive and gynecological endocrinology techniques as a "clean slate" pregnancy that is initially wrong. This leads to the underestimation and delayed diagnosis of serious pregnancy complications. A pathological network with its links, manifested by insulin resistance, hyperandrogenemia, enzymopathy, hyperlipidemia, obesity, and endothelial dysfunction in various proportions and degrees of severity, aggravating and complementing each other in the mother and intrauterine fetus, has become the cornerstone of the obstetric and perinatal complications in patients with PCOS. No studies have demonstrated the association of phenotypic PCOS variants with obstetric complications such as preeclampsia, GDM, and placental insufficiency. The course of pregnancy in patients with PCOS after IVF, laparoscopic cauterization, and drug ovulation induction by various methods has not been fully investigated. Algorithms for the preconception period have not been developed, and the management of pregnancy and labor in patients with PCOS has not been determined. Studies aiming to elucidate the associations between the pathogenetic PCOS links and certain obstetric complications in such patients should be conducted to meet these challenges.

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