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OBESITY REPRESENTS A STRONG PATHOGENETIC LINK WITH THE PATHOLOGY OF PREGNANCY AND CHILDBIRTH

© D.S. Seryogina[1], I.P. Nikolayenkov[1], T.U. Kuzminykh[2]

[1] The Research Institute of Obstetrics, Gynecology, and Reproductology named after D.O. Ott, Saint Petersburg, Russia;
[2] Saint Petersburg State University, Saint Petersburg, Russia

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▪ Obesity is a significant health and social problem that is the scale of the growing worldwide epidemic. Over the past 10 years, the number of obese pregnant women has doubled. There are multiple risk factors associated with obesity, which includes poor nutrition, foods that are high in easily digestible carbohydrates and fats, frequent snacks, and widespread fast food consumption. Metabolic changes, especially in women with the genetic predisposition, are manifested by insulin resistance, hyperinsulinemia, arterial hypertension, and hypercoagulation syndrome. The course of pregnancy and childbirth in obese women is associated with a series of successive pathological conditions, such as miscarriage, the occurrence of gestational diabetes mellitus, preeclampsia and eclampsia, infectious complications, prolonged pregnancy, the occurrence of bleeding and much more. We have analyzed modern ideas about women's reproductive health and the course of pregnancy and childbirth in obesity.

▪ **Keywords:** obesity; insulin resistance; diabetes mellitus; placental insufficiency; preeclampsia; childbirth.

ОЖИРЕНИЕ — ВЕДУЩЕЕ ПАТОГЕНЕТИЧЕСКОЕ ЗВЕНО ПАТОЛОГИЧЕСКОГО ТЕЧЕНИЯ БЕРЕМЕННОСТИ И РОДОВ

© Д.С. Серегина[1], И.П. Николаенков[1], Т.У. Кузьминых[2]

[1] Федеральное государственное бюджетное научное учреждение «Научно-исследовательский институт акушерства, гинекологии и репродуктологии им. Д.О. Отта», Санкт-Петербург;
[2] Федеральное государственное бюджетное образовательное учреждение высшего образования «Санкт-Петербургский государственный университет», Санкт-Петербург

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▪ Ожирение — значимая медико-социальная проблема, достигающая масштабов эпидемии. За последние 10 лет число беременных с ожирением увеличилось вдвое. Ключевыми звеньями патогенеза ожирения являются неправильное питание, использование продуктов, богатых легкоусвояемыми углеводами и жирами, частые перекусы, широкое распространение фастфудов. Метаболические изменения, особенно у женщин с генетической предрасположенностью, проявляются инсулинорезистентностью, гиперинсулинемией, артериальной гипертензией, синдромом гиперкоагуляции. Течение беременности и родов у женщин с ожирением сопряжено с целым каскадом сменяющих друг друга патологических состояний, таких как невынашивание беременности, гестационный сахарный диабет, преэклампсия и эклампсия, инфекционные осложнения, перенашивание беременности, кровотечения и многое другое. В статье проанализированы современные представления о репродуктивном здоровье женщин, а также о течении беременности и родов при ожирении.

▪ **Ключевые слова:** ожирение; инсулинорезистентность; сахарный диабет; плацентарная недостаточность; преэклампсия; роды.

Obesity is a serious medical, social, and economic problem in modern society. According to the World Health Organization, obesity reaches the epidemic in its prevalence [1], and it is called the new noninfectious epidemic of the 21st century. The relevance of obesity is determined by the

high prevalence since 25% of the population of developed countries of the world have a body weight exceeding the normal by 15% [2]. In Russia, obesity and overweight are registered in 25%–37% of the female population [3, 4]. The occurrence of obesity in childhood and adolescence results in a significant increase in the proportion of overweight, and its occurrence in obese women of reproductive age is a particularly alarming fact. Over the past 10 years, the number of pregnant women with obesity has doubled. Thus, maternal obesity has become a significant risk factor in obstetric practice.

Metabolic changes in obesity in the nonpregnant state

Adipose tissue is conventionally referred by several researchers as an "endocrine organ" [5]. It virtually produces all the proteins of the renin–angiotensin–aldosterone system (RAAS), namely, renin, angiotensin I, angiotensin II, angiotensinogen, some other enzymes, and receptor proteins for angiotensin I and II types, although this is not the main source of their synthesis. An increase in adipose tissue volume, in turn, contributes to an increase in the formation of RAAS proteins, which activate additionally its effects. In adipose tissue, cortisol is formed from cortisone, a glucocorticosteroid that does not have the active properties of RAAS. Thus, the cortisol content in the body partially depends on the adipose tissue volume. As a result, as the degree of visceral obesity increases, disorders in glucose homeostasis are aggravated [5].

The distribution of adipose tissue is mainly determined by hormones of the gonads and adrenal cortex, and the conversion of androgens to estrogens in adipocytes plays an important role. Adipose tissue, mainly visceral, has high hormonal and metabolic activity, contains a large number of adrenergic receptors, corticosteroids, and androgen receptors, and can also accumulate various steroids, such as testosterone, androstenedione, and cortisol because of their lipophilicity [6].

The main synthesis of sex hormones occurs in the ovaries, and extragonadal synthesis of estrogen from androgens occurs in adipocytes by aromatization and conversion of androstenedione and testosterone to estrone and estradiol, respectively. With obesity, the peripheral aromatization of androgens to estrogens increases, resulting in the metabolism disorder of androgens and estrogens [7, 8].

Adipose tissue is well supplied with blood and is most metabolically active, and adipocytes have a high density of beta-adrenergic receptors (which stimulation leads to lipolysis) with a relatively low density of alpha-adrenergic and insulin receptors (their stimulation inhibits lipolysis). Adipose metabolism in the thighs and buttocks is mainly regulated by lipoprotein lipase enzymes. Lipogenesis occurs mainly here, and lipolysis activity is low, due to which peripheral obesity, as a rule, only affects the appearance of women and not their health. Intensive lipolysis in the adipose tissue of the abdominal-visceral region increases the level of free fatty acids in the systemic blood circulation, which causes metabolic disorder characteristic of abdominal obesity, namely, insulin resistance, increased glucose, insulin, and cholesterol, and very low density lipoproteins and triglycerides. Fat cells (adipocytes) produce leptin, which is an integrator of neuroendocrine functions and promotes energy use. Metabolic process disorders may be associated with leptin deficiency, including a dysregulation of its secretion or resistance to its action. Leptin is a reliable marker of general obesity, which correlates significantly with other markers of adipose tissue. In obese individuals, serum leptin levels are significantly increased, which results in suppression of insulin secretion and causes insulin resistance [9, 10]. The role of leptin in the regulation of the reproductive system function has been proven. A significant reduction in adipose tissue impedes normal reproductive function. Some researchers have suggested that leptin evolved less as a satiety hormone and more as a signal to the reproductive system about an adequate energy supply. Animal observations revealed that leptin levels increase only before puberty and that puberty can be accelerated by the administration of exogenous leptin [2].

Many studies have demonstrated the significant role of melatonin secretion disorders in the development of obesity and metabolic syndrome, due to the effect of melatonin on the suprachiasmatic nucleus and receptors located in peripheral tissues, such as adipose tissue, muscles, pancreatic beta cells, and reproductive organs [11–14].

To date, it has not been established which of the factors are leading in the progression of obesity and

how they affect the reproductive system function. Obesity has been shown to be a risk factor for the hyperplastic processes [15].

Arterial hypertension

Obesity is often accompanied by arterial hypertension already in childhood. In most adolescents with obesity, a pathological reaction of the vessels is detected. In pediatric patients with stable arterial hypertension, vascular endothelial dysfunction occurs 1.5 times more often than in children with normal vascular endothelial function. A direct relationship was also revealed between the functional state of vascular endothelium and the degree of obesity. In adolescents with endothelial dysfunction, the fat content in the body is significantly higher than in children with normal endothelial function. There is often an increase in the blood levels of glucose, insulin, cholesterol, and triglycerides, which indicates fat and carbohydrate metabolism disorder, and the content of blood insulin correlates significantly with the adipose tissue mass [16].

Reproductive health problems in obese women

It has been established that obesity adversely affects the reproductive health of adolescent girls, thereby creating a premorbid background. Obesity progression after puberty is accompanied by the formation of ovarian failure.

Amenorrhea type menstrual disorder or opsomenorrhea is often associated with obesity [17, 18]. In the vast majority of obese women, regardless of the pathology form, the possibility of subsequent pregnancies is reduced because of the abnormal functioning of the brain diencephalic structures [19].

The work of Shakirova showed that among menstrual irregularities in obese patients, menstrual disorders predominate. According to most researchers, menstrual disorders are secondary and develop because of obesity [20]. With alimentary obesity, menstrual dysfunction is noted six times more often, which often leads to primary infertility. There is a direct correlation between body weight gain and ovarian failure severity, which is manifested by anovulation, insufficiency of the second phase of the menstrual cycle, and infertility [2].

Polycystic ovary syndrome (PCOS) is diagnosed in 35%–60% of obese women, and the pathogenetic mechanism of its development is a dysfunction of the hypothalamic-pituitary system, accompanied by overproduction of androgens in the adrenal glands and ovaries [7, 8]. PCOS occurs in 6%–8% of women of reproductive age [21]. The proportion of PCOS patients with obesity in Russia significantly differs in various studies (10%–42%) [22]. According to several authors, the highest incidence of obesity in PCOS patients has been recorded in the USA and Australia, reaching 61%–76%. The presence of severe abdominal obesity is associated with higher insulin resistance [23]. Pregnancy in PCOS patients is accompanied by the development of gestational diabetes mellitus (DM) in 16.1% of cases [24], and concomitant insulin resistance increases the incidence of gestational DM to 46% [25]. In 6.5% of PCOS patients, pregnancy ends with premature birth [26].

The risk of developing diseases concomitant with obesity is largely determined by the characteristics of adipose tissue deposition in the body. The most unfavorable is the abdominal type of obesity, combined, as a rule, with a complex of hormonal and metabolic risk factors. According to the literature, for patients with obesity and endometrial hyperplastic processes, compared with obese women without endometrial pathology, significantly higher body mass index values are predominant, as well as mainly the abdominal distribution of adipose tissue, a high frequency of pathological conditions—thyroid gland and hepatobiliary system diseases, DM, essential hypertension, inflammatory genital organ diseases, and uterine myoma—and a greater frequency and duration of infertility [19, 27].

Aspects of the course of pregnancy, childbirth, and the postpartum period with obesity

During pregnancy, favorable conditions are formed for the development of fatty tissues, which biological purpose consists of metabolic protection of the fetus. From the first days of pregnancy, hormonal changes in the woman's body begin, including an increase in the synthesis of progesterone, chorionic gonadotropin, prolactin, and placental lactogen, which stimulate adipose tissue deposition in the body.

One of the main mechanisms influencing sex hormones on adipose tissue is direct stimulation by estrogen of lipoprotein lipase activity, which is the enzyme that regulates the accumulation of triglycerides in adipocytes and causes the deposition of adipose tissue mainly in the thighs and buttocks, where the activity of this enzyme is higher than in the adipose tissue of the abdominal region. As a result, lipids accumulate to provide adequate energy reserves during pregnancy and lactation. Progesterone is also involved in the regulation of adipose tissue deposition, and its level increases during pregnancy. Progesterone competes with glucocorticoids for their receptors in adipocytes, thereby preventing the lipolytic effect of glucocorticoids on adipose tissue [28].

As a result of the increased activity of the hypothalamus-pituitary-adrenal system during pregnancy, the production of tropic hormones increases, namely, somatotropic hormone, prolactin, and adrenocorticotropic hormone (ACTH). Because of the increased ACTH formation, the hormonal activity of the adrenal glands and the synthesis of glucocorticoids (cortisol) and mineralocorticoids (aldosterone) increase; as a result of these changes, the female body adapts to the necessary activation of vital processes to meet the requirements of the developing fetus. The ACTH level during pregnancy increases almost twice, partly due to placental ACTH, which is not suppressed by glucocorticoids but maintains a normal circadian rhythm. Because of the increased ACTH production during pregnancy, the total amount of cortisol increases two to three times. The binding of cortisol to protein (corticosteroid-binding globulin or transcortin) also increases because of the increased estrogen synthesis; as a result, the level of free biologically active cortisol remains normal [29, 30].

An excess of cortisol in adipocytes has a local lipolytic effect, stimulates adipogenesis in visceral depots, and reduces the sensitivity of peripheral tissues to insulin and the development of insulin resistance. Because of changes in the RAAS during pregnancy, the level aldosterone rises, and this increases the volume of circulating blood and facilitates the maintenance of a normal sodium and potassium balance. Serum aldosterone levels increase starting from week 8 of pregnancy and increase up to 10 times by birth [30].

During pregnancy, both production and inactivation of androgens are enhanced because of an increase in the metabolic clearance rate, which ensures the maintenance of a normal ratio of circulating androgen levels. However, 20%–50% of obese pregnant women can experience a significant increase in androgen level (testosterone, dehydroepiandrosterone, and dehydroepiandrosterone sulfate), and hyperandrogenism develops, which can lead to miscarriage [19].

Complications of the gestational process in obese women develop in 45%–85% of cases [1]. In pregnant women with excess body weight, the frequency of obesity-associated diseases increases 1.5 to 2 times compared with women with normal body weight; the risk of the pathological course of pregnancy, childbirth, and the postpartum period increases; and the frequency of birth of children with congenital malformations increases, which increases perinatal morbidity and mortality [31]. Most often, pregnant women have cardiovascular diseases (17%–44%), infectious complications due to a decrease in the immunological body resistance (52%–60%), and diseases of the digestive system (4%–8%), urinary system (5%–10%), and respiratory organs (7%) [1]. The course of concomitant somatic diseases during pregnancy aggravates significantly.

Obesity in pregnant women is considered as a risk factor for severe forms of arterial hypertension, preeclampsia, and eclampsia, which are the most common complications during pregnancy. The frequency of preeclampsia in obese women is about three times higher than in women with normal body weight and reaches 78%, according to various sources [32–34]. The development of preeclampsia in pregnant women with obesity is associated with metabolic changes, such as endothelial dysfunction and systemic inflammation, especially pronounced in women with an abdominal type of obesity before pregnancy, as well as hemodynamic disorders in the second half of pregnancy. Pregnancy, complicated by preeclampsia, increases the risk of cardiovascular diseases in mothers by seven times [1].

Risk factors for neonatal asphyxia in obese women have been studied. It turned out that the most significant risk factor for asphyxia in newborns of women with obesity is its severity with previous arterial hypertension and impaired

thyroid and reproductive functions, which subsequently probably serve as a background for the development of pregnancy complications [1].

In obese women, the risk of urinary tract infection is increased by 1.2–1.9 times [35].

The third trimester of pregnancy is known to be accompanied by physiological hypercoagulation as a result of decreased natural antithrombotic protection and increased activation of antithrombotic mechanisms, which increase the level of blood coagulation factors, tumor necrosis factor-α (TNF-α), plasminogen, and plasminogen activator inhibitor. In pregnant women with obesity, due to insulin resistance, these changes are more pronounced, and the incidence of cardiovascular and thrombotic complications increases. Increased levels of TNF-α and plasminogen activator inhibitor are known to be independent factors of thrombophilia and thrombosis development during pregnancy [36].

Gestational DM

During pregnancy, for the first time, various disorders of carbohydrate metabolism are often diagnosed, such as impaired glucose tolerance and DM. With a normal pregnancy in trimester I, insulin sensitivity increases as a result of exposure to the placental complex. Subsequently, with an increase in gestational age, insulin production increases, peripheral tissue sensitivity to insulin decreases, and physiological insulin resistance develops. These changes occur because of the action of counter-insulin hormones, namely, placental lactogen, placental growth hormone, estrogen, progesterone, and cortisol, which ensure the energy needs of the fetoplacental system by enhancing lipolysis and ketogenesis. After birth, peripheral insulin sensitivity is quickly restored [37, 38]. In the presence of obesity before pregnancy, especially abdominal obesity, which is associated in most cases with insulin resistance development, hyperinsulinemia manifests itself in various disorders of carbohydrate metabolism, and insulin concentration increases significantly compared with women of normal weight. Therefore, the risk of carbohydrate metabolism disorders, including gestational diabetes, increases [40]. The risk of gestational diabetes in the general population is 2%–6%, and in the presence of obesity before pregnancy, it rises to 17% [4]. In turn, gestational diabetes increases the risk of type 2 diabetes, which develops in more than a third of women with obesity within 15 years after childbirth [37, 38]. Obesity before pregnancy, polyhydramnios, age over 30 years, type 2 DM in first-degree relatives, and fast and pathological weight gain during real pregnancy are risk factors for developing gestational diabetes.

The risk of complications of gestational diabetes for the mother and fetus depends on its compensation. It has been established that one of the main factors of impaired fetal development during DM-burdened pregnancy is the excessive transplacental transfer of glucose [40]. The inadequate compensation for gestational diabetes leads to fetal hyperglycemia, which can result in pregnancy malformations of the heart, spine, gastrointestinal tract, and spinal cord in the first trimester. In the second trimester, hyperplasia and hyperfunction of cells of the fetal pancreas develop in response to hyperglycemia, followed by hyperinsulinemia in the fetus, which can lead to macrosomia, severe and prolonged hypoglycemia in newborn, and central nervous system malformations.

During pregnancy, under conditions of diabetes, the placenta and fetus undergo various metabolic changes. The degree of these changes depends on the glycemic level of not only the mother but also the fetus. Other important alternating factors are fetal hyperinsulinemia and impaired transporter functioning of various substances. Most structural changes occur in the fetal part of the placenta. This is manifested by the thickening of the basement membrane, a decrease in the number of syncytiotrophoblast microvilli, impaired activity of various transporter proteins, and, as a consequence, a cascade change of all metabolic reactions.

It has been proven that abnormalities in the fetoplacental complex develop in women with various types of DM, causing not only placental dysmorphogenesis but also various fetal body changes [41].

In combination with obesity, gestational diabetes increases the incidence of gestational arterial hypertension.

Thus, maintaining a woman's normal blood glucose during pregnancy and adequately compensating gestational diabetes represent important conditions for a favorable pregnancy.

The labor dominant in obese women is not completely formed by the end of pregnancy, which leads to pregnancy overbearing and poor uterine contraction strength development in 10%–15% of pregnant women, whereas the severity of the disorders increases in proportion to the degree of obesity [42]. Childbirth occurs with complications in 59%–89% of cases, and the risk of various obstetric complications increases, such as premature (11%) and delayed (6%) delivery, anomalies of activity (30%), birth injury (46%), development of newborn macrosomia (18%), and intrauterine hypoxia of the fetus (60%) [31, 39]. The high frequency of obstetric complications is explained by the violation of adaptive and compensatory-adaptive mechanisms, abnormality of regulatory systems, development of dysmetabolic disorders, and immunological dysfunction syndrome [21, 43]. Complications, such as poor uterine contraction strength, dystocia, and untimely amniotic fluid discharge, increase the duration of the act of delivery, development of fetal hypoxia symptoms, frequency and severity of birth injuries of the mother and newborn, and frequency of surgical interventions in childbirth. In addition, overweight women are two to three times more likely to have pregnancy overbearing than healthy women since the excretion of progesterone before childbirth does not decrease because of its accumulation in adipose tissue [44–46].

The frequency of cesarean section in women with excess body weight averages 13%–17%, and according to some reports, it reaches 50% [34]. A high level of surgical interventions in overweight women is due to the presence of severe extragenital pathology, obstetric complications, in particular, clinical mismatch of the fetal head and woman's pelvis size, pre-eclampsia, poor uterine contraction strength, and chronic intrauterine hypoxia of the fetus [47]. In turn, surgery (cesarean section) in pregnant women with obesity is also associated with a risk of thrombotic complications and worsening of postoperative wound healing. The frequency of operative delivery due to complicated delivery in obese women is two to four times higher than in pregnant women with normal weight.

The obesity of the mother significantly increases the risk of chronic fetal hypoxia and newborn asphyxiation due to the formation of placental insufficiency. Endocrine disorders typical of obesity affect fetal-placental circulation, contributing to the development of placental pathology (cyst formation, small focal infiltrates, calcifications, etc.). Moreover, the frequency of adaptation disorders in newborns reaches 68% [48–50].

In 32% of cases, overweight women have a large fetus with an average weight of 376 g more than children born by women with normal body weight. This is of significant importance since at the birth of a large fetus, the aggravated course and adverse outcome of childbirth are most often registered. Thus, birth injury in newborns with macrosomia is noted two times more often than in newborns with normal weight. The immune system of large-weight newborns is characterized by dysfunction of lymphocytopoiesis processes and disproportion in the concentration of immunoglobulins A, M, and G in the umbilical cord blood and by pronounced metabolic disorders in the adaptation period [51].

Untimely amniotic fluid discharge and poor uterine contraction strength are noted most often in obese pregnant women (10%–35% of cases) since the contractility of the myometrium is impaired due to the disorder of the ratio of endogenous estrogens and progesterone and changes in uteroplacental hemodynamics, which is manifested by a slowdown of blood flow, dyslipidemia, and fatty fiber degeneration of the myometrium and abdominal muscles.

In the subsequent and early postpartum periods, hemorrhage develops in 6%–30% of puerperae with excessive body weight, which is two to five times higher than similar indicators in puerperae with normal body weight [52]. The causes of hemorrhage are impaired uterine contractility (fatigue of the neuromuscular apparatus of the uterus), significant changes in the hemostatic system, intrauterine embolism with amniotic fluid, neuroendocrine insufficiency, and soft tissue trauma in case of a large fetus [53]. The postpartum period in obese puerperae is often accompanied by infectious complications. Endometritis is registered in 3%–17% of cases, uterine subinvolution in 35% of cases, lochiometra in 12%–14% of cases, and thrombophlebitis in 8%–22% of cases [54].

Prospects for solving problems of pregnancy and childbirth management in obese female patients

One of the causes of obesity in pregnant women is overeating. For this reason, dietary recommendations and a regime of physical activity

are mandatory, which can significantly reduce the risk of complications in the mother and fetus. In a metabolic sense, pregnancy is a condition in which the anabolic processes necessary for the formation of new tissues predominate. Data presented indicate that proper nutrition during pregnancy is an important component of unborn baby health.

It should be noted that pregnancy trimesters are characterized by different energy needs, and because of a decrease in physical activity, despite an increase in physiological needs, ultimately, the required level of energy consumption increases slightly.

An indicator of adequate satisfaction of energy requirements is an increase in the body weight of a pregnant woman. With a balanced rational diet, an increase in energy demand implies a greater consumption of all macronutrients and micronutrients.

With a normal increase in body weight during pregnancy, a 9% increase occurs due to protein in the tissues of the mother (uterus, placenta, and mammary glands) and fetus [55]. The greatest accumulation of protein mass occurs in the second half of pregnancy and is 6–8 g per day [56]. In trimester III, urinary nitrogen excretion decreases, and protein synthesis is enhanced. At this time, the fetus accumulates approximately 3 g of protein per day, and the average daily need for protein in a woman increases to 10 g.

Prevention of overweight before and during pregnancy itself, including control of body weight and various metabolic disorders, properly balanced nutrition, and adequate physical activity will help prevent several negative consequences associated with obesity during pregnancy.

At every stage of a woman's life, an obstetrician-gynecologist is faced with such a complex pathological process as obesity. Currently, there are great opportunities for therapy, but in gynecological practice, they often do not consider that weight loss and insulin resistance correction should be the main or first step in the management of women for treating almost all diseases accompanied by obesity. Despite the simplicity of obesity diagnostics, the results of prevention and treatment at the moment cannot be considered satisfactory. An algorithm for the prevention of gestational DM, preeclampsia, placental insufficiency, anomalies of labor, and obstetric injuries in obese women must be developed and implemented.

Thus, obesity is a global problem that should be considered in not only the medical but also the social aspect in every economically developed state, primarily from the position of a woman's reproductive health.

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Information about the authors *(Информация об авторах)*

Darya S. Seryogina — MD, Postgraduate Student. The Delivery Department, the Research Institute of Obstetrics, Gynecology, and Reproductology named after D.O. Ott, Saint Petersburg, Russia. **E-mail:** d.sereogina2010@yandex.ru.

Дарья Сергеевна Серегина — аспирант родильного отделения. ФГБНУ «НИИ АГиР им. Д.О. Отта», Санкт-Петербург. **E-mail:** d.sereogina2010@yandex.ru.

Igor P. Nikolayenkov — MD, PhD. The Delivery Department, the Research Institute of Obstetrics, Gynecology, and Reproductology named after D.O. Ott, Saint Petersburg, Russia. **E-mail:** nikolaenkovigor@mail.ru.

Игорь Павлович Николаенков — канд. мед. наук, врач — акушер-гинеколог родильного отделения. ФГБНУ «НИИ АГиР им. Д.О. Отта», Санкт-Петербург. **E-mail:** nikolaenkovigor@mail.ru.

Tatyana U. Kuzminykh — MD, PhD, DSci (Medicine), Professor. The Department of Obstetrics, Gynecology, and Reproductive Sciences, Medical Faculty, Saint Petersburg State University, Saint Petersburg, Russia. Scopus Author ID: 56719818800. Researcher ID: U-8950-2017. **E-mail:** 9260@mail.ru.

Татьяна Ульяновна Кузьминых — д-р мед. наук, профессор кафедры акушерства, гинекологии и репродуктологии медицинского факультета. ФГБОУ ВО «Санкт-Петербургский государственный университет», Санкт-Петербург. Scopus Author ID: 56719818800. Researcher ID: U-8950-2017. **E-mail:** 9260@mail.ru.