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Clinical and pathogenetic mechanisms of formation of fetal growth retardation

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Fetal growth retardation (FGR) is a major cause of child morbidity and mortality, and is also an important medical and social problem due to a wide range of pregnancy complications and negative outcomes in the postnatal period. The results of recent studies indicate that chronic arterial hypertension causes a number of pathological changes in a pregnant woman's organism, in particular, it increases the risk of FGR.
The wide knowledge about the pathogenesis of placental dysfunction and FGR allow to establish that the development of these pathologies is primarily caused by the changes in uterine and placental blood circulation, which leads to metabolic disorders. The important etiological reasons for FGR also include social and biological factors, the influence of narcotic substances, insufficient nutrition, alcohol abuse, tobacco smoking, as well as the use of coumarin or derivatives. The mother's older age is also a risk factor for the FGR development.
Over the past decades, both clinical and experimental studies have established that FGR, caused by the influence of the unfavorable environment of the uterus, is a risk factor for the development of hypertension, as well as various diseases in adults. There are a lot of evidences that support the association of FGR with an increased risk of hypertension in adults, but the mechanisms underlying these processes remain unclear. Both clinical and basic scientific studies have confirmed the theory of intrauterine programming of arterial hypertension in adults. That is why many countries have developed programs for the prevention of FGR. Scientific researches indicate a close relationship between social adaptation and the birth of children with low body weight.
The absence of indices decrease in perinatal morbidity and mortality by FGR shows the difficulties caused by polyetiological factors and certain pathogenetic mechanisms of the mentioned complication. Today, the search for an effective pathogenetically based therapy of this pathology continues, which indicates the need for further researches, and the development and implementation of approaches to the prevention of FGR will improve the perinatal putcomes.
Keywords: *pregnancy, fetal growth retardation, risk factors, pathogenesis, obstetric and perinatal complications.*

Клініко-патогенетичні механізми формування затримки росту плода

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Затримка росту плода (ЗРП) посідає вагоме місце серед причин дитячої захворюваності і смертності, а також є важливою медико-соціальною проблемою через широкий спектр ускладнень вагітності та негативні наслідки у постнатальний період. Результати останніх досліджень свідчать, що саме хронічна артеріальна гіпертензія зумовлює цілу низку патологічних змін в організмі вагітної, зокрема підвищує ризик розвитку ЗРП.
Розширення знань про патогенез плацентарної дисфункції та ЗРП дозволило встановити, що їхнє формування передусім зумовлено зміною матково-плацентарного кровообігу, що призводить до метаболічних порушень. До важливих етіологічних причин виникнення ЗРП також належать соціально-біологічні фактори, вплив наркотичних речовин, недостатнє харчування, зловживання алкоголем, тютюнопаління, а також вживання кумарину або дериватів. Фактором ризику виникнення ЗРП також є немолодий вік матері.
За останні десятиліття як клінічні, так й експериментальні дослідження встановили, що ЗРП, спричинена впливом несприятливого середовища матки, є фактором ризику розвитку гіпертензії, а також різноманітних захворювань дорослих. Існує безліч доказів, що підтверджують зв'язок ЗРП із підвищеним ризиком розвитку гіпертензії у дорослих, однак механізми, що лежать в основі цих процесів, залишаються нез'ясованими. Як у клінічних, так і фундаментальних наукових дослідженнях підтверджено теорію внутрішньоутробного програмування артеріальної гіпертензії у дорослих. Тому у багатьох країнах розроблено програми профілактики ЗРП. Наукові дослідження свідчать про тісний взаємозв'язок між соціальною адаптацією і народженням дітей з низькою масою тіла.
Відсутність зниження перинатальної захворюваності та смертності при ЗРП свідчить про труднощі, що зумовлені поліетіологічними чинниками та певними патогенетичними механізмами зазначеного ускладнення. На сьогодні тривають пошуки ефективної патогенетично обґрунтованої терапії цієї патології, що свідчить про необхідність подальших досліджень, а розроблення та впровадження підходів до профілактики ЗРП дозволить покращити перинатальні наслідки розродження.
Ключові слова: *вагітність, затримка росту плода, фактори ризику, патогенез, акушерські та перинатальні ускладнення.*

Fetal growth retardation (FGR) takes a significant place among the causes of child morbidity and mortality, and is also an important medical and social problem due to a wide range of pregnancy complications and negative consequences in the postnatal period [1–4, 8, 14]. FGR is manifested by a violation of the development of fetus in the mother's womb. In more than half of cases of neonatal mortality that occur in the world every year, there are cases of FGR, premature

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birth and congenital malformations and are both a leading problem of perinatal medicine and an important medical and social problem [6, 10, 14, 15, 36, 42, 43].

FGR occurs in approximately 5–15% of pregnancies and is often seen in combination with other pregnancy complications such as preeclampsia (PE) [3, 5, 6, 9, 47]. Arbeille P. and co-authors noted a ten-fold increase in perinatal mortality in the group of newborns with FGR, and the frequency of fetal distress in this group was 50% [29]. Hypoglycemia, hypocalcemia, polycythemia, and hypothermia occur often in this contingent of newborns. After prematurity FGR ranks 2nd among the causes of death of infants [11, 13]. The frequency of FGR in antenatal fetal death reaches 20%, and in premature pregnancy – from 15% to 22% [1, 7, 11, 16].

The causes of FGR can be conditionally divided into several groups. First, these are conditions associated with pathology on the part of the mother (hypertension, preeclampsia, heart pathology, excessive weight gain, diabetes, obesity, diseases of the kidneys and lungs, connective tissue, hemoglobinopathy, a long period of infertility, miscarriages in the anamnesis, the birth of children with FGR in previous pregnancies, the mother's young age, the mother's intake of beta-blockers, antimetabolites of folic acid, anticonvulsants, indirect anticoagulants, tetracyclines and other drugs, insufficient nutrition during pregnancy, smoking and alcoholism of the mother, drug addiction, a short interval between pregnancies, the presence of negative production factors, such as overheating, hypothermia, mental stress, antiphospholipid syndrome in the mother due to the formation of placental thrombosis and platelet aggregation, in particular in women with arterial hypertension, multiple pregnancy, prenatal infections).

As it is known, cardiovascular pathology (CVP) takes the first place among extragenital diseases [1, 23], and arterial hypertension (AH) takes the leading place in the structure of causes of perinatal morbidity and mortality. Hypertension contributes to the development of long-term vascular and metabolic disorders and complications of pregnancy and childbirth in future [23, 40, 43, 44]. Hypertensive disorders of pregnancy, in turn, are associated with accelerated cardiovascular aging and more diverse cardiovascular conditions than previously appreciated [1, 44].

It is worth noting that an increase in blood pressure during pregnancy in most cases is accompanied by a normal course of pregnancy, and a moderate increase in pressure can be considered as a physiological mechanism for maintaining the necessary level of feto-placental blood circulation and preparation for childbirth, as well as an element of the general process of adaptation of a woman's body to pregnancy [1, 23, 41, 44]. The frequency of hypertension in pregnant women ranges from 5 to 30% [1, 20].

Recent studies have established that it is chronic arterial hypertension (CAH) that causes a number of pathological changes in a pregnant woman's body, in particular, it increases the risk of developing FGR. Maternal prognosis in pregnant women with CAH in the absence of obstetric complications is quite favorable in most cases [1, 3, 21, 22, 24, 34]. However, the extremely large number of complications during pregnancy and childbirth against the background of the disease, the presence of which is noted by almost all researchers, determines the significant risk of pregnancy and childbirth for both the mother and the fetus.

Research results have established that even moderate CAH, which develops in the 1st trimester, represents an increased risk of developing cerebrovascular disorders and complications of the normal course of pregnancy [1, 43, 44]. To date, models for predicting placental dysfunction (PD) in pregnant women with a mild degree of chronic obstructive pulmonary disease have been proposed. Thus, to predict such complications in the first trimester of pregnancy, the degree of nocturnal decrease in blood pressure (BP), the mass of the myocardium of the left ventricle, the time index of daytime blood pressure and the level of malondialdehyde should be determined. To predict them in the II trimester, it is necessary to determine the degree of nocturnal decrease in BP and the level of malondialdehyde [11, 29].

The placental blood circulation decreases due to changes in the functioning of the cardiovascular system in pregnant women with chronic obstructive pulmonary disease. At the same time, a number of compensatory mechanisms aimed at restoring placental perfusion are included. The placenta begins to produce a number of pressor factors, which include vasoactive substances of the endothelium: nitric oxide and prostacyclins (vasodilators), and endothelin, thromboxane, fibronectin (vasoconstrictors). Violation of the normal ratio between these factors in CAH is accompanied by dysregulation of vascular tone and leads to PD [19–24, 31, 33, 37, 45].

In connection with the changes in the functioning of uteroplacental and fetoplacental vessels, adaptive mechanisms are shifted at all levels, which leads to the occurrence of PD. These shifts contribute to disruption of transport, trophic, endocrine, metabolic and antitoxic function of the placenta, and subsequently to the pathology of a fetus and newborn. In case of changes in the mother-placenta-fetus system and the occurrence of disorders of the uteroplacental blood circulation, a violation of the arterial blood flow and venous outflow from the intervillous space develops, the rheological and coagulation properties of the blood of the mother and fetus change (hypercoagulation, hyperaggregation and increased viscosity), occurs due to a decrease in capillary blood flow in the chorionic villi [32, 34, 37].

A decrease in blood pressure in the intervillous space in combination with an imbalance of prostanoids leads to thrombus formation, hypercoagulation, increased blood viscosity, fibrin deposition, decreased microcirculation and the development of ischemia [18, 20, 34, 35, 37]. Hypertension in pregnant women is also accompanied by pronounced changes in the immunological properties of blood, which underlie the pathogenesis of the development of hemolytic disease of a fetus and newborn [35, 38]. To date, a correlation has been established between blood pressure indicators and dopplerometry data. Thus, BP changes detected during daily monitoring are accompanied by corresponding blood flow velocity violations in the vessels of the uterus and umbilical cord [44, 45].

The variability of blood pressure also affects the formation of pregnancy complications. In pregnant women with PD, it was higher and showed the higher amplitude of oscillations. Long-term BP variability was also higher in patients with complicated pregnancy. Thus, high long-term variability of systolic blood pressure (SBP) at the end of the second trimester of pregnancy can be a predictor of the development of preeclampsia and disorders in the mother-placenta-fetus system in pregnant women with normal BP values [21, 24].

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At the beginning of research, the concept of FGR was considered only as an extreme degree of disturbances in the mother-placenta-fetus system and the main clinical manifestation of which was considered to be a decrease in body weight of newborns below the 10th percentile relative to gestational age. Thus, the expansion of knowledge about the pathogenesis of PD and FGR made it possible to establish that the basis of its formation is primarily caused by changes in the uteroplacental blood circulation, which lead to metabolic disorders [2, 7, 8, 11, 16, 25–28, 37, 45].

The asymmetric form occurs mainly in the II and III trimesters of pregnancy against the background of secondary PD and is associated with insufficient nutritional substrate for the fetus. The etiology, pathogenesis, diagnosis, and approaches to the treatment of FGR continue to be studied actively, and many fundamental studies performed from different positions are dedicated to the study of this problem [7, 11, 12, 18]. It is known that physiological transformation with remodeling of the utero-placental spiral arteries is the key to successful placentation and normal function of the placenta. This is a complex process that includes, but is not limited to, a complex interaction between maternal decidual immune cells and invasive trophoblasts in the uterine wall. During normal pregnancy, the smooth muscle cells of the arterial sheath of the uteroplacental spiral arteries are replaced by the invasion of trophoblasts and fibrinoid and the diameter of the artery increases 5–10 times [2, 8, 21].

During the II and III trimesters of pregnancy the placenta is an organ that develops rapidly and has numerous changes in this structure, as well as in the fetus. Despite the relatively short stay of the placenta in a woman's body, it should be considered the most important organ of pregnancy. The main functions of the placenta include: exchange between mother and fetus, endocrine activity, barrier and protective activity as well as fetal programming [17, 21]. Placenta-related fetal growth retardation occurs mainly due to insufficient remodeling of the uterine spiral arteries that supply the placenta in early pregnancy. The result of improper perfusion is cellular stress in placental tissues, which leads to selective suppression of protein synthesis and decreased cell proliferation [18, 31].

Also, factors related to the placenta itself: insufficient mass of the placenta and its structural abnormalities (infarcts, fibrosis, calcinosis, vascular thrombosis, inflammatory changes), placental detachment, placental malformations, certain variants of placenta localization are no less important in the formation of FGR. An absolute or relative decrease in the mass of the placenta causes FGR. Therefore, vascular pathology of the placenta, partial premature detachment of the placenta, placenta previa, placenta accreta, placental infarctions and placental hemangiomas contribute to the development of fetal hypotrophy [2, 3, 8, 16, 18, 25–28].

A decrease in the area of placenta, determined by ultrasound examination, is a symptom of early diagnosis of FGR [12, 26, 30]. In late pregnancy, a relative decrease in the mass and function of placenta can inhibit the growth of a fetus [28, 33, 37]. Congenital anomalies of the placenta, such as a single umbilical artery, have been identified as the cause of some cases of FGR [11]. Several studies demonstrate less trophoblastic invasion of spiral arteries of the placental bed, which was accompanied by thinning and fibrinoid degeneration of the inner lining of these arteries, as well as acute atherosclerosis [3, 11]. These processes lead to violation of contractile function of blood vessels, narrowing of their lumen, and, as a result, a decrease in the placental blood flow.

The localization of the placenta also affects the FGR. Placenta previa, even without bleeding, is already a risk factor, since low placentation is not optimal for ensuring uteroplacental blood circulation [25–27, 33]. In a twin pregnancy, the relative weight of the placenta to the weight of fetuses is lower than in a singleton pregnancy. That is why FGR occurs more often in multiple pregnancies [7, 11].

Socio-biological factors (low socio-economic and educational level of the mother, adolescence, living in a mountainous area, out-of-wedlock pregnancies) are also important etiological reasons for the occurrence of FGR. The consumption of narcotic substances can be accompanied by the occurrence of FGR due to insufficient nutrition. In mothers who smoke, symmetric hypotrophy of fetuses occurs due to a decrease in uteroplacental blood flow and impaired oxygenation of the fetus [18, 29, 47]. As is known, alcohol abuse, as well as the use of coumarin or hydantoin derivatives leads to specific dysmorphic changes in combination with fetal growth disorders. Some authors found a serious increase in the risk of FGR, which is associated with the consumption of one or two doses of alcohol per day [7, 11, 48].

The mother's advanced age is a risk factor for the occurrence of FGR [11]. According to the results of the study, it was established that the age of the mother has no correlation with the FGR, provided that the mothers' hypertension and other accompanying pathology were controlled and corrected [7]. It has also been proven that under the condition of correction of possible complications of pregnancy, the age of the mother is not related to the frequency of FGR [1, 7]. For a long time, low maternal weight was considered a risk factor for FGR. There is some controversy here; however, maternal malnutrition may play a role in the development of FGR. The study of the mass of newborns whose pregnancy lasted during starvation indicates a low impact of such food restriction on fetal development [7].

However, limiting protein consumption after 26 weeks of pregnancy does not affect fetal development. Decreased nutrition in pregnant women may be due to limited gastrointestinal absorption caused by such pathology as Crohn's disease or ulcerative colitis. In general, these cases do not affect the frequency of occurrence of FGR.

Over the past decades, both clinical and experimental studies have shown that fetal growth retardation caused by adverse effects of the uterine environment is a risk factor for hypertension as well as various diseases in adults. This observation shaped and informed the now widely accepted theory of the origins of health and disease (DOHaD). There is a large body of evidence supporting the association of FGR with an increased risk of hypertension in adults, but the mechanisms underlying this correlation remain unclear. Both clinical and fundamental scientific studies confirm the theory of intrauterine programming of arterial hypertension in adults [49]. Therefore, in many countries, programs for the prevention of FGR have been developed. Scientific studies confirm the close relationship between social adaptation and the birth of children with low birth weight [11, 27, 39, 47].

Based on modern literature data, it is possible to distinguish three main groups of factors that lead to the development of FGR. Maternal risk factors include the age of the pregnant woman, socio-economic status, obstetrical and gynecologi-

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cal factors, racial and ethnic characteristics, as well as constitutional characteristics. Special attention is paid to somatic diseases of the mother, namely hypertension, autoimmune diseases, anemia, chronic cardiopulmonary diseases, chronic kidney diseases, diabetes with vascular changes, chronic and acute infections, etc., as well as complications of pregnancy.

Uteroplacental risk factors: placental infarcts, placental development abnormalities, placental abruption, placenta accreta, hemangiomas, low placentation, placenta previa, and placental mosaicism. Among fetal risk factors, the following are distinguished: constitutional (genetic features, gender), chromosomal anomalies, defects and anomalies of fetal development, intrauterine infections, multiple pregnancy. Thus, the range of reasons for the occurrence of FGR in pregnant women is quite wide, among which the presence of somatic diseases deserves special attention.

Scientific data on the influence of certain factors on fetal growth disorders do not provide a comprehensive answer to the aspects of this problem, however, there is a certain dependence between the influence of these factors and the occurrence of FGR. During the analysis of international clinical guidelines and modern articles that consider the problem of FGR, it was noted that the diagnostic approaches coincide in most of them. That is why it is necessary to emphasize the need for careful anamnesis collection in the pre-gravid stage or in the 1st trimester of pregnancy in order to assess the risk factors of FGR and take timely preventive measures.

However, despite the progress achieved in recent years in the prevention of gestational pathology, the problem of optimal prevention of the occurrence of FGR is still far from being solved. The absence of a reduction in perinatal morbidity and mortality with FGR indicates difficulties caused by polyetiological factors and certain pathogenetic mechanisms of this complication. Today, the search for an effective pathogenetically justified therapy for this pathology continues, which indicates the need for further research. The development and implementation of approaches to the prevention of FGR will improve the perinatal consequences of childbirth.

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