RELATIONSHIP OF PLACENTAL GROWTH FACTOR WITH DEVELOPMENT OF FETAL GROWTH RESTRICTION (FGR) IN WOMEN (LITERATURE REVIEW)

Abstract. Fetal growth restriction syndrome (FGR) is a complex problem and, despite the currently used highly informative methods, which do not exclude both false positive and false negative results of assessing the state of the fetus and the uteroplacental complex, it is necessary to use several differently directed methods. In this area, placental growth factor may be a promising biomarker for detecting abnormalities in fetal growth. Determination of changes in the production and functioning of growth factors at the preclinical stage, possibly, will make it possible to predict the risk and influence its implementation.

Keywords: Fetal growth restriction syndrome, placental growth factor.

Among the leading obstetric causes leading to childhood morbidity and mortality, an important place is occupied by the fetal growth restriction syndrome (FGR), pathogenetically caused by placental insufficiency [3].

In recent years, increasing importance in the formation of pathological conditions and diseases is given to the fetal growth restriction syndrome, which
occupies one of the leading places in the structure of perinatal morbidity throughout the world, and also has a negative impact on the subsequent development of the child. According to domestic authors, fetal growth restriction syndrome occurs in 5.0-17.6% of pregnant women, and the frequency of fetal growth restriction in premature babies is higher, and amounts to 15.7-22% [1,2].

FGR is a clinical definition and applies to neonates for clinical signs of malnutrition. Globally, 24% of newborns are affected by FGR, and about 30 million children suffer from FGR each year. Fetal growth restriction syndrome occurs mainly in Asia, which accounts for almost 75% of all newborns. In Africa and Latin America, there are also 20% and 5% of cases, respectively. In our own observations, the incidence of very low birth weight FGR is 43% [9].

Fetal growth restriction syndrome is a major public health problem and modern obstetrics, despite the advances in modern science. The urgency of this problem is due to its relationship with fetal death, neonatal mortality, childhood and neonatal diseases, and the risk of cardiovascular diseases in adulthood. Timely detection of this disease is important for a favorable pregnancy outcome [12].

Early detection of intrauterine growth restriction is essential for maternal and child health. Restrictions of intrauterine growth of the fetus due to a pathological process are unable to achieve normal growth for gestational age, which leads to an increased risk to the fetus, such as distress syndrome or fetal death during pregnancy or childbirth. Insufficient fetal growth is also associated with perinatal morbidity and an increased risk of chronic disease later in life. These include cerebral palsy, systolic arterial hypertension and cardiovascular diseases, diabetes mellitus, obesity [7].

By the time of formation, it is customary to distinguish early and late restrictions on the growth of the fetus. Early restriction of fetal growth is due to defective invasion of the trophoblast into the myometrial segment of the spiral arteries. At the same time, changes in the uteroplacental circulation (UPC) consist in the absence of physiological gestational changes in the spiral arteries, their spasm and damage to the vascular wall, as in autoimmune processes. This leads to impaired blood circulation in the intervillous space, slowing blood flow in the spiral arteries,
impaired blood microcirculation between the mother and the fetus. As a result, ischemic heart attacks may develop in the placenta. The leading pathogenetic mechanism of late fetal growth restriction is a violation of UPC, which manifests itself in chronic hypoxia, redistribution of fetal blood flow, with predominant perfusion of the fetal brain. [8]

One of the primary links in the chain of functional mechanisms for the formation of this complication of pregnancy are disorders of the uteroplacental blood flow and, as a result, hemodynamic changes in the mother-placenta-fetus system. The relevance of studying the problem of fetal growth restriction syndrome (FGR) is due to difficulties in assessing the degree of its severity, low treatment effect and the need for early delivery in severe forms of FGR. Currently, the question of the timing of delivery in severe forms of FGR remains open and requires further research [4; 5].

It has been proven that the tactics of maximal prolongation of pregnancy are not justified due to the high risk of perinatal morbidity and mortality. But, having completed the pregnancy prematurely, there are complications associated with prematurity [10]. Due to the lack of effective treatment of FGR at the moment, clinicians are faced with the task of only monitoring the intrauterine state of the fetus, and in case of its deterioration, decide the issue of delivery in order to preserve the life of the intrauterine fetus.

Thus, FGR and delivery of women with this pathology is a complex problem and, despite the currently used methods for assessing the state of the fetus and the uteroplacental complex, it is necessary to use several differently directed methods to optimize the management of women with severe form of FGR [11].

According to the literature, at a normal rate of increase in fetal growth and its compensated state, delivery can be carried out not earlier than the 37th week of gestation. With a decrease in uteroplacental and fetoplacental blood flow without their critical disturbances, it is necessary to monitor the condition of the fetus using daily cardiotography and Doppler ultrasound and a wire to prepare for delivery [6].

Assessment of the state of the fetus with the determination of the level of
growth factors will help to develop rational obstetric tactics in severe form of FGR. It is known that growth factors, participating in the processes of formation of the placenta, contribute to the normal functioning of the uteroplacental complex [13]. Recently, the attention of scientists has been attracted by the study of vascular growth factors and their role in the regulation of angiogenesis [14]. FGR is associated with an imbalance in the production and circulation of angiogenic [placental growth factor (PIGF) and vascular endothelial growth factor (VEGF)] and anti-angiogenic (soluble VEGFR-1 receptor and soluble endoglin s-Eng) growth factors [15].

VEGFR-1 was found in the placenta, villous trophoblast and blood vessel endothelium. VEGF is mainly involved in the formation of the vasculature - embryonic vasculogenesis and angiogenesis. The intermediate trophoblast of the placental site plays a major role in the formation of the uteroplacental complex due to its invasive properties (infiltration of the decidua of the spiral arteries and myometrium) [11].

Fetal growth restriction syndrome (FGRS) is associated with a decrease in fetal weight and size compared with normal values for a given gestational age. ARPA can be classified as early or late depending on the time of diagnosis. Early SORP (<32 + 0 weeks of gestation) is associated with significant changes in the mother-placenta-fetus system with increased risks of hypoxia and preeclampsia, high perinatal morbidity and mortality. With an early onset of SORP, abnormalities in the uterine arteries, venous duct progress, biophysical parameters change, which often requires premature delivery. In the late form of SORP (≥ 32 weeks 0 days of gestation), outcomes are more favorable [2, 3]. SORP with a late onset is considered a more favorable form, but it is more difficult to diagnose with a constitutionally small fetus. Thus, the differences between early and late onset of SORP have great pathophysiological implications, and their research is important. The concept of "low birth weight" unites a heterogeneous population with the following main phenotypes:

1) caused by placental insufficiency and are true cases of FAD, the so-called fetal growth restriction syndrome;
2) without any signs of placental insufficiency, the so-called "constitutionally small" or "small for gestational age" - small gestation age and

3) with congenital malformations (including chromosomal abnormalities, infection). The last group is small in number \([4,5]\). RF is an early prognostic marker of SROP, presenting a quantitative indicator. The dynamics of VEGF A-165 concentrations and its role in angiogenesis during physiological pregnancy have been written by a number of researchers \([6]\). The most pronounced changes on the part of VEGF production took place in patients with sub- and decompensated forms of placental insufficiency and SROP \([8]\). Lascowska M. et al. have shown higher levels of VEGF-A in pregnant women with isolated SROP compared with physiologically ongoing pregnancy, as well as in combination of SROP with preeclampsia or isolated preeclampsia \([2]\). Strizhakov et al. found that a VEGF concentration of \(\geq 67.12 \pm 6.51 \text{ pg / ml at 16-22 weeks}, \geq 121 \text{ pg / ml at 23-29 weeks}\) indicates a high risk of decompensated placental insufficiency with a sensitivity of 83% and a specificity of 95% \([12]\).

Changes in the content of growth factors and vasoactive compounds in the blood serum of women with FGR indicate that the development of the placenta occurs in conditions of violation of the formation of its vascular system and a decrease in hemodynamics. In connection with the above, it was of interest to study the nature of the production of these components directly in the placental tissue in order to assess its metabolic "potential" by the time of delivery \([7]\).

Assessment of the indices of angiogenic growth factors, carried out in combination with ultrasound and Doppler studies, makes it possible to monitor the state of the fetoplacental system in pregnant women at risk for fetal growth restriction syndrome, starting from 16 weeks of pregnancy. The presented criteria for predicting the syndrome of limiting the development of the fetus on the basis of determining the indicators of angiogenic growth factors allow timely prevention of this complication, and with the development of the clinical picture - assessment of the severity, monitoring the effectiveness of therapy and the choice of rational obstetric tactics. The complex of the listed measures allows to achieve a decrease in perinatal morbidity and mortality \([1]\).
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