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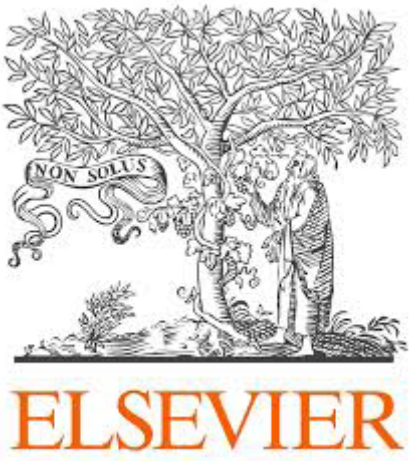

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The place and role of violations of angiogenesis in placental insufficiency

Abstract: The article examines the characteristics of angiogenesis in placental insufficiency and fetal growth retardation.

Keywords: fetoplacental insufficiency, vascular factors, fetal growth retardation syndrome, angiogenesis.

Currently, placental insufficiency (PI), complicating pregnancy, is the most common syndrome in obstetric practice and is a major problem not only for Obstetrics, Perinatology, Pediatrics, but also the health of the nation as a whole. This pathological condition leads to the development of severe complications such as ante- and intrapartum fetal death, infant mortality and morbidity, adverse long-term consequences for the child. [1] Functional failure of the placenta is a major cause of fetal hypoxia, fetal growth retardation (IUGR), its injuries during childbirth. PI occurs in pregnancy, combined with extragenital pathology - in 24 to 45%, in gestosis - at 32%, with miscarriage - 50 - 77%, and in pregnant women who have had viral and bacterial infections - more than 60% of cases. [2].

Mostly in the development of placental insufficiency involves several etiological factors, one of which is the leading. It is almost impossible to single out any one factor in the development of this complication. Until now, the pathogenesis, classification, methods of diagnosis, prevention, treatment, choice of the optimal timing of delivery with the PI remain the subject of debate. Conventional functional tests used to diagnose PI and FGR are highly informative only in severe forms of this complication (ultrasound bio- and placentometry, dopplerometry of the vessels "mother-placenta-fetus" system, cardiotocography). The biochemical and hormonal tests have low specificity and wide border of individual oscillations.

The growth rate of PI and its consequences necessitates the search for new diagnostic criteria of the presence and severity of this universal syndrome which would allow most early identification of patients at high risk for this disease. The placenta has a unique rapid growth in the regulation of which involve numerous growth factors and their receptors. In recent years, actively discussed the role of vascular growth factors in the pathogenesis of various obstetric complications, including PI and FGR. First of all, disturbed relationship correlation between the expression of placental VEGF (vascular endothelial growth factor) and PLGF (placental growth factor) in FGR. Of particular importance in the event of a breach of PI given to the formation of villous tree, which is a consequence of a breach of angiogenesis in the placenta, since it is largely determined by the development of different types of villi. This leads to a decrease in the area of structures to ensure the exchange of oxygen between the mother's blood and the fetus or increase the distance between intervillous space, containing the mother's blood and fetal capillaries, which ultimately leads to the development of fetal hypoxia and IUGR. This processes of angiogenesis and vasculogenesis directly depends on the normal development of the placenta. Vasculogenesis - the formation and development of new blood vessels from mesodermal cells – precursors, and angiogenesis is a creation of the new vessels from existing vascular structures. Both processes are of decisive importance, as they depend on the transport of nutrients, oxygen metabolism and excretion of metabolic products [3]. These two processes regulated by plurality signaling molecules: cytokines, growth factors, endothelial cell interaction characteristics and microenvironmental cells: macrophages, smooth muscle cells, fibroblasts and mast cells. Angiogenesis processes in the placenta depend on the balance between pro-angiogenic and anti-angiogenic factors in endothelial cells microenvironment. Factors that stimulate the proliferation of endothelial cells and increase their vitality are essential for the development of the vascular network of the placenta. While apoptosis of endothelial cells - a process necessary for normal physiological development of the vascular network by placental angiogenesis and vascular changes in the structure [4].

According to the literature, there is a change at the ratios of vascular growth factors with PI, which cause disturbances of the normal processes of angiogenesis and the repair of the edothelium during pregnancy [5]. Therefore to study the role of

vascular growth factors in violation of the formation of the placenta and the fetus allows a detailed study of the foundations of feto-placental angiogenesis, which is extremely important and allows you to develop a complex method to identify groups at risk surveys and forecasting the development of PI and FGR, determine the severity of the pathological process, early diagnosis and prevention of PI, as well as choose tactics of pregnancy and childbirth.

The aims and objectives of the study: The study of the diagnostic value of vascular growth factors to predict the development of PI and FGR and optimization of obstetric tactics.

Materials and Methods: I group were 89 women with FGR and PI, II group consisted of 42 apparently healthy pregnant women. Depending on the severity of the FGR, I group was divided into three subgroups. I A subgroup consisted of 35 patients with FGR I degree of severity, I B subgroup consisted of 29 pregnant women with FGR II degree of severity, I C subgroup consist of 25 patients with FGR III degree of severity.

FGR diagnosis was made in identifying fetal biometric parameters below the tenth percentile. The degree of severity was determined by FGR fetometry lagging indicators of adequate gestational age: I degree - lag for 2 weeks, II stepen- lag of 3-4 weeks, III degree - the backlog of more than 4 weeks. Age of pregnant women in the target groups did not differ significantly and averaged 29,2 ± 1,3 years.

In the analysis of somatic disease were detected significant differences in the examined groups. Since chronic cystitis was significantly more common in patients of the main group compared to the control group - in 34.1% (30) and 6.5% (3), respectively ($p < 0.05$). Pregnant of the main group often suffered from kidney disease. Chronic pyelonephritis in pregnant women with FGR and PI met in 18.6% (16) compared with healthy - 8.3% (3), respectively, ($p < 0.05$). Significantly more frequent in the examined group met the primary diseases such as mitral valve prolapse, thyroid disease, varicose veins.

In the study of infectious status it has been revealed that in the history of pregnancy main group significantly more often mentioned carrier microorganisms such as chlamydia, ureaplasma, mycoplasma, cytomegalovirus, herpes simplex virus type I and II, human papilloma virus. Therefore patients with PI and FGR are more

burdened somatic history compared with the control group and a higher infection index.

At 41.3% (37) of the main group of women held prematurity, timely deliveries - at 58.7% (52), and in 46% (41) - cesarean section was performed. The course of postpartum period in pregnant women with FGR and PI significantly more complicated endometritis 5.6% (5) and hematometra 6.3% (6).

Analysis of postnatal outcomes showed that the respiratory distress syndrome of varying severity has been ranked in the structure of morbidity of the newborns in women of the main group and more common in the IC subgroup in comparison with I B subgroup: 54.8% (14) and 37.6% (11), respectively ($p < 0.05$). Also, neonatal pneumonia, urinary tract infection and enterocolitis significantly more met in women of IC subgroup.

It was conducted determining the levels of vascular factors: PLGF, sFlt - 1, sEng (endoglin) in serum by ELISA at 27-37 weeks of gestation in pregnant women with FGR and PI, as well as in healthy women. PLGF - refers to the factors that have expressed angiogenic properties and controlling the growth of the placenta. Provides proliferation of extravillous trophoblast, with no effect on the processes of its migration and invasion. Affects angiogenesis only interacting with VEGF -R 1 (receptors) although affects on the mobilizing of mesenchymal progenitor endothelial cells which involved in vasculogenesis [6]. Anti-angiogenic factors are a deterrent to excessive invasion of trophoblast cells, and their products are part of the normal angiogenesis. These include VEGF -R1 (Flt-1) -fms like tyrosine kinase, VEGF -R2 (Flk-1, KDR), VEGF-R3 (Flt-4) and endoglin. Soluble forms of these receptors are capable of binding growth factors in the circulation by slowing down or inhibiting angiogenesis. sFlt -1 a representing a soluble isoform of Flt-1, is able to bind VEGF and PLGF, preventing the binding of growth factor to the transmembrane receptor, that is, has anti-angiogenic activity. Soluble endoglin (sEng) can bind TGF-β (transforming growth factor beta), which is a pro-angiogenic molecule. At a high level of sEng, having antiangiogenic properties it is inactivated. Consequently sEng plays an important role in the development of endothelial dysfunction and in the pathogenesis of the PI [7].

The research results analysis of the proangiogenic growth factor level in serum showed significant differences. PLGF concentration in patients of the main

group was 135.6 ± 34 pg/ml and was significantly lower compared with the control group - 227,2 ± 57,8 pg/ml (p <0,05). Depending on the severity of IUGR, in pregnant women with FGR III and II severity the level of PLGF was significantly lower than in women with FGR I severity and with the healthy pregnant women: 19,8 ± 11,2 pg/ml, 38,7 ± 23,3 pg/ml, 211,6 ± 78,3 pg/ml, respectively (p <0.05). PLGF level in healthy patients was 241,2 ± 63,7 pg/ml. Low values of PLGF in patients with PI and FGR compared with the control group show significant lesion of the uteroplacental complex, severe hypoxia and reduction of compensatory mechanisms.

The content of sFlt-1 in patients of the main group made up 17685,5 ± 2884,7 pg/ml and was significantly higher than the average level of the control group - 3210,3 ± 576,1 pg/ml, respectively (p <0.05). Comparison of different subgroups of the main group has shown that in pregnant women with FGR III the level of sFlt-1 is higher than the FGR II and I degree: 25453,6 ± 5985,6 pg/ml, 22344, ± 5443,3 pg/ml and 13432 ± 4356,2 pg/ml, respectively (p <0.05). Therefore in severe PI and FGR is a significant shift in the balance of growth factors upward to the level of antiangiogenic factors, in particular sFlt-1. endoglin level in patients of the main group was significantly increased compared with sEng levels in healthy women and averaged: 23602 ± 1736 pg/ml and 5835 ± 630 pg/ml, respectively (p <0.05). In patients with FGR I, II and III degree there was a significant increase in sEng compared with control: 10540 ± 1112,3 pg/ml, 18432 ± 1523,7 pg/ml, 23602 ± 6547 pg/ml and 5835 ± 630 pg/ml, respectively (p <0.05). The gradual increase in endoglin indicate violations expressed in fetoplacental complex.

Conclusions. For a differentiated approach to the management of pregnancy in patients with PN and FGR along with conventional methods can be used method of determining the level of vascular factors in the selection of optimal obstetric tactics and forecasting of pregnancy outcomes.

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