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THE ROLE OF THE IMMUNE SYSTEM IN THE FORMATION OF ENDOTHELIAL DYSFUNCTION IN CASE OF VIOLATION OF THE UTEROPLACENTAL BLOOD CIRCULATION

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ABSTRACT

Background: This article considers the value of uterine-placental circulation in the process of growth and development of the fetus during pregnancy. The mechanisms of the formation of epithelial dysfunction in case of violation of the uterine-placental and surgery are considered and the significance of immunological and endothelial biomarkers is reflected. Violations of the uterine-placental blood flow leads to such complications of pregnancy as preeclampsia, fetal growth, hypoxia up to death. The regulation of the uteroplacental circulation is vital for the well -being of the mother and fetus.

KEYWORDS: Endothelial Dysfunction, Endothelium, Fetal Growth Retardation, Uteroplacental Blood Flow, Immunity.

INTRODACTION

Violation of the uteroplacental blood flow is a problem of modern obstetrics and neonatology. The disease is a clinical syndrome that develops in early pregnancy for a variety of reasons, such as chronic maternal diseases in 25% of cases (chronic hypertension, pregnancy-induced hypertension, and other vascular disorders), placental disorders (preeclampsia, abruption, heart attacks) and etc. Such an anomaly is diagnosed most often in the 2nd-3rd trimester of gestation, in about 4% of pregnant women. Failure in the uteroplacental vascular system in 85% of newborns, leads to hypoxia or congenital anomalies of varying severity. Pathologies of hemodynamics that have been developed before 16 weeks often end in spontaneous miscarriages.[3,6,17,22]

The uteroplacental circulation, which links the circulation of the mother and fetus, is established at the beginning of the second trimester. The growth and development of the placenta are critical to a successful pregnancy. Upon completion of embryonic development, around the end of the 10th week of pregnancy, the fetus begins to actively grow and develop in utero. The need for nutrients and oxygen increases as pregnancy progresses, which is met by increasing the blood supply to the placenta. At the same time, uteroplacental blood flow increases by 10–100 times, respectively, according to the term. To accommodate the abrupt change, the maternal cardiovascular system undergoes physiological adaptations, as evidenced by an increase in plasma volume and cardiac output, and a decrease in mean arterial pressure. As uterine vascular resistance decreases, uterine blood flow increases from ~50 ml/min in non-pregnant women to ~800 ml/min in late pregnancy. Studies conducted on experimental animals such as sheep, guinea pigs and rats show that more than 80% of uterine blood flow perfuses the placenta.[1,6,19,25]

Pathology of blood flow in the uterus can occur due to improper formation of the villous layer of the fetal membrane even before the laying of the placenta, or due to the influence of unfavorable endogenous and exogenous factors on the mother's body. The risk increases if a woman has diabetes mellitus - 35.5%, diseases of the kidneys, heart and blood vessels, hypertension 9.4–17.9%, carbohydrate metabolism disorders - 22.4%, against the background of anemia 40.6%, and dysfunction thyroid gland - in 10.5% of cases. At the heart of uterine blood flow disorders is a burdened obstetric history - late preeclampsia, threats of interruption, multiple abortions and miscarriages. Benign tumors of the uterus in 70-75% of cases. A high risk is also observed against the background of pregnancy with a Rhesus conflict.

The reason for the violation of the uteroplacental blood flow is often a genetic disease of the mother (with a bicornuate or saddle uterus, partitions in the organ cavity). As a rule, the likelihood of gynecological pathology also exists with genital infections. If a woman

has influenza, the frequency of their development is 24-45%. Exogenous factors contributing to impaired uteroplacental blood flow include work in hazardous industries, alcohol consumption and smoking. Negative factors include malnutrition, which leads to weight gain. Another factor to consider during pregnancy is the age of the mother, as women over 35 are more susceptible to developing fetal growth retardation and stillbirth. The risk of abnormal hemodynamics is present with constant stress and intense physical activity.[9,17,26]

The placenta is an organ formed during pregnancy that has a maternal and a fetal part. Its function is primarily to provide a specialized tissue for the exchange of substances between mother and unborn child. It is also an endocrine organ whose secretions are necessary for maintaining pregnancy.

The formation of the placenta begins with the implantation of the blastocyst in the mother's decidua.

Up to the end of the 2nd week of pregnancy, the embryo is supplied with nutrients and oxygen exclusively by diffusion. At the beginning of the 3rd week, the trophoblast, the outer boundary of the blastocyst, has numerous primary villi. These consist of a nucleus of cytotrophoblast cells surrounded by a layer of syncytiotrophoblast cells. During further development, cells of the extraembryonic parietal mesoderm invade the nucleus of the primary villi. The cells of the syncytiotrophoblast are pushed back and replaced by mesodermal cells. One now speaks of a secondary villus, with a primarily connective tissue core. These processes take place within a few days. Towards the end of the 3rd week and from the middle of the 4th week the mesodermal cells begin to differentiate. Blood cells and capillaries form. Angiogenesis, the formation of new blood vessels, marks the transition from the secondary to the tertiary villi. These vessels initially have no connection to the vascular system. They connect to the vessels of the chorionic plate and the adhesive stalk via various mechanisms. The vessels of the chorionic plate and the adhesive stalk are not initially connected to the vascular system of the embryo either, but only establish this connection.

At the end of the 4th week, the embryonic heart has started to function. Around this time, the vessels of the chorionic plate and adhesive stalk have found their connection to the embryonic vascular system. The supply of the embryo is now guaranteed by vessels - and no longer only by diffusion.[2,4,16,29]

In the course of further development, the cells of the cytotrophoblast penetrate from the villi into the syncytium. In doing so, they break through the syncytium and form between it and the maternal endometrium of the uterus. This surrounds the entire germ as the outer cytotrophoblast envelope. The chorion is thereby firmly anchored in the endometrium. Around the 5th week, the anatomical structures of the placenta are formed and the vasculature is active. The spiral arteries carry blood to the placental structures. A special feature is that the cells of the cytotrophoblast are able to erode the maternal vessels, so that the blood flows into the intervillous spaces.

The mature placenta has two main functions: the exchange of metabolic products and gases between maternal and fetal blood and the formation of hormones.

Trophoblast cells, lacking HLA class II molecules, are characterized by a unique distribution of HLA class I molecules. not the highly polymorphic molecules HLA-A and HLA-B. Conversely, they express the relatively unpolymorphic molecules HLA-C, as well as the non-classical, non-polymorphic HLA class I molecules, HLA-G (also in soluble form), HLA-E and HLA-F. As for the syncytiotrophoblast, it lacks any membrane expression of class I HLA molecules. Several groups have however identified the soluble HLA-G1 isoform (also called HLA-G5), secreted in the culture supernatant of the syncytiotrophoblast in primary culture.

The syncytiotrophoblast is in contact with the maternal blood of the intervillous space which contains, like peripheral blood, the various effector cells of the maternal immune system: CD8+ T lymphocytes, CD4+ T lymphocytes, B cells, NK cells, monocytes, dendritic cells, etc. of the extravillous cytotrophoblast which form the chorionic membrane are also in contact with the maternal blood of the intervillous space, whereas those which have migrated and invaded the spiral maternal arteries, to replace the endothelial cells lining their wall, are in direct contact with the maternal peripheral blood. The extravillous trophoblast cells that invade the decidua basalis are in contact with the same types of cells of the maternal immune system. However, the distribution of these maternal cells in decidua basalis differs from that observed in peripheral blood: NK cells (~70%), CD14+ macrophage-like cells (~20%), dendritic cells (~1%), T cells CD4+ cells, including regulatory T cells (~10%), Tγδ cells, killer NK cells, rare CD8+ T cells and B cells.

During pregnancy, the fetus, or more exactly the different types of trophoblast cells, are therefore theoretically the potential targets of humoral and cellular effectors of the mother's immune response. The fetus must therefore face three types of potential threats from the mother, and specifically directed against paternal antigens: complement-fixing cytotoxic antibodies, cytotoxic CD8+ T cells and killer NK cells. In fact, the fetus, in the absence of any pathology or infection, manages to thwart these various threats by setting up protective, specific and transient molecular mechanisms.

The presence of cytotoxic maternal alloantibodies directed against HLA class I molecules was demonstrated in approximately 15% of primiparous and

75% of multiparous. Three main mechanisms have been described that prevent this threat.

First, trophoblast cells do not express HLA class II molecules. This absence of expression prevents the stimulation of B lymphocytes (producers of antibodies), as well as that of CD4+ T lymphocytes (stimulators of B cells via the secretion of interleukins 4, 5 and 10). Furthermore, the human placenta resists lysis by cytotoxic maternal antipaternal antibodies, by inhibiting the activation of complement by regulatory molecules. This is how the proteins MCP, which oppose the fixation of complement on immunoglobulins, and DAF, which promote its inactivation, have been described.[9] Some early abortions in humans could thus be due to defects in the expression of such complement regulatory proteins. In mice, inactivation of the Cry protein, which regulates the C3 and C4 components of the complement cascade, leads to 100% abortions, due to the deposition of C3 on invasive trophoblast cells and the resulting placental inflammation. Complement activation therefore seems critical at this level.[3,5,10]

Finally, maternal antipaternal B cells are partially deleted during gestation. Experiments, carried out in mice by the group of Colette Kanellopoulos in Paris, have demonstrated that maternal cells specific for fetal paternal H2-Kk antigens are partially deleted from the spleen, peripheral blood and bone marrow during the second half of gestation. The main target of this deletion is the population of immature B lymphocytes, also called transient B cells.

Second threat: cytotoxic CD8+ T cells specific for paternal class I histocompatibility antigens. A combination of several mechanisms allows the fetus to prevent this second threat. Firstly, trophoblast cells do not express the most polymorphic molecules HLA-A and HLA-B which are, like class II HLA molecules, known to initiate the recognition of allografts by the host, and therefore their rejection. Although HLA-C molecules are also polymorphic (but to a lesser degree), their expression on the surface of extravillous trophoblast cells is low and HLA-C-specific CD8+ T cells are rarely observed after transplantation.

In addition, there is a local secretion of immunosuppressive molecules, found locally at the level of the fetomaternal interfaces and making it possible to control the activity of T cells, but also NK: soluble HLA-G molecules, TGFβ, PIBF, IDO enzyme and Fas ligand (CD95L).

Soluble HLA-G molecules, secreted by both the extravillous cytotrophoblast and the syncytiotrophoblast, induce apoptosis of activated CD8+ T cells by binding specifically to the CD8 molecule, which could explain the low number of CD8+ T cells in the decidua basalis. Concerning TGFβ, the administration of anti-TGFβ antibodies to mice inhibits embryonic implantation. GDPF, which induces the secretion of Th2-type cytokines, is an anti-abortion protein, the absence of which seems to be a predictor of early spontaneous abortions. Expression by some macrophages of the enzyme IDO, which catabolizes tryptophan in response to interferon γ, results in rapid depletion of tryptophan and subsequent inhibition of T cell proliferation. This enzyme is also expressed and secreted by the syncytiotrophoblast in contact with the maternal blood of the intervillous space. Andrew Mellor's group showed that IDO inhibition results in complement deposition at the fetomaternal interface in mice, and T cell-mediated rejection of conceptus semi - allogenic, but not syngenic; such a type of inflammatory rejection could also be partly caused by CD4+ T cells. In mice deficient in Fas ligand, normally expressed by the trophoblast, pregnancy is associated with necrosis at the fetomaternal interfaces, which leads to fetal resorption. A link with soluble HLA-G molecules has also been established, since it induces the production of soluble Fas ligand by activated CD8+ T cells, inducing their apoptosis by binding to membrane Fas molecules.[4,8,16,19,22]

Finally, during gestation, a state of transient tolerance of the T cells specific for the paternal alloantigens, present in the intervillous space and the decidua basalis, develops. In order to follow the fate of T cells reactive towards paternal antigens in pregnant mice, experiments were carried out in a model of transgenic mice for a T cell receptor (TCR) recognizing the H-2Kb molecule. Unlike syngenic or allogeneic pregnancies not expressing H-2Kb, mice carrying Kb+ conceptus have a reduced number of T cells reactive towards the H2-Kb molecule and accept transplants expressing the same Kb molecule. The response of these T cells (rejection of grafts bearing Kb) is restored after delivery. The conclusion of these results is that, during gestation, maternal T cells acquire a transient and reversible state of tolerance towards paternal alloantigens. Another study carried out in mice demonstrates that fetal antigen-specific T cells decrease in number during gestation, suggesting that a specific clonal deletion could be a mechanism of tolerance.

One of the possible functions of dNK cells could be to control uterine vascular remodeling in early gestation. This hypothesis is based on various observations. dNK cells produce cytokines involved in the control of angiogenesis: angiopoietin 2, VEGF-C or PIGF. Immunohistochemical studies carried out on sections of decidua basalis from the first trimester of pregnancy have shown that dNK cells could be closely associated with the spiral maternal arteries. Moreover, the engagement of the KIR2DL4 receptor of dNK cells by its specific soluble HLA-G ligand, produced by the extravillous trophoblast, leads to the production by dNK cells of pro-angiogenic type mediators, such as TNFα, IL -1β, IL-8 and interferon γ.[1,3,17,28,29]

Regulatory T cells represent a subpopulation of CD4+ T cells characterized by high constitutive expression of the α chain of the IL-2 receptor (CD25). These cells, which represent about 5% to 10% of peripheral CD4+ T cells, exert a suppressive effect on antigen-specific immune responses, and are therefore important for inducing tolerance to allografts and for the prevention of autoimmune diseases. An expansion of these CD4+ CD25+ regulatory T cells in the maternal circulation, spleen and draining lymph nodes was recently observed in pregnant mice. This cell population would exert a suppressive effect against an allogeneic-type response directed against the fetus; in fact, their absence prevents any gestation from coming to an end. Regulatory T cells inhibit T cell proliferation by anti-CD3 stimulation. Similarly, an increase in the number of regulatory T cells in the peripheral circulation of pregnant women has been observed. They have also been detected in decidua. Their proportion is significantly reduced in decidua from repeated spontaneous abortions. It is also interesting to note that regulatory T cells induce the production of IDO by dendritic cells.[6,9,15,27]

The defective remodeling of the spiral arteries then leads to recurrent alterations in the uteroplacental circulation due to the production of superoxide ion during oxidative stress. is normally converted by cytosolic-type superoxide dismutase into hydrogen peroxide, which is also active. Invalidation of the gene for the cytosolic form of this enzyme in mice is lethal, in particular due to the absence of placental development; its overexpression in the trophoblast in vitro or in trisomy 21 is associated with reduced syncytiotrophoblast formation. In animal models of hypertension, an increase in the production of but also of nitric oxide (NO) is observed. However, the bioavailability of NO is reduced, as it quickly goes into the complex state. In the preeclamptic placenta, although the activity of constitutive and inducible NO synthases is reduced, the increase in nitrotyrosines of peroxidized proteins and lipids indicates the existence of oxidative stress. Associated with NO forms toxic peroxynitrite (ONOO-). The latter inhibits the electron transport chain, reduces intracellular NAD+ and ATP pools, triggers lipid peroxidation and produces DNA breaks. These effects result in premature senescence of endothelial and trophoblast cells.

Some oxygenated derivatives have a vasomotor action: has a vasoconstrictor effect and ONOO- attenuates the vascular response to constricting or dilating agents. Endothelial dysfunction also triggers increased production of vasoconstrictor agents (thromboxane and endothelin), greater vascular sensitivity to angiotensin II, while the production of relaxant agents (prostacyclin and NO) is decreased. These changes in vascular tone cause an increase in uterine impedance on Doppler ultrasound

The expression of certain inflammatory and immunoregulatory cytokines produced during oxidative stress, such as TNFα (tumor necrosis factor α) and the interleukins IL-1α and IL-10, is increased in preeclamptic placentas, and TNFα concentrations and IL-6 rise in maternal blood. We also observe in the maternal blood a disorder of the blood coagulation system favoring platelet aggregation. Increased release of endothelial-like adhesion molecules has been reported. The endothelium of the maternal peripheral circulation is involved, but the placenta remains an essential player in triggering pre-eclampsia, since, in the majority of cases, hypertension and other clinical manifestations disappear after delivery. The mechanism of diffusion of placental alterations to the mother remains obscure. The excess of necrotic or apoptotic microfragments of syncytiotrophoblast in the maternal circulation could lead to a dysfunction of the endothelium of the maternal vessels and thus participate in the amplification of the maternal inflammatory reaction predisposing to hypertension. Through the prematurely senescent villous trophoblast, maternal-fetal exchanges are impoverished, leading to intrauterine growth retardation which may be accompanied by an increase in umbilico-placental impedance.

Although VEGF is an undisputed component in EC activation for both physiological and pathological angiogenesis, other factors have been found to contribute to a well-functioning vasculature. Among these, semaphorin- and plexin -mediated signaling, previously identified as key mechanisms for axon guidance, are known to play important roles in vessel formation. This is not surprising, since the vascular and neuronal systems have a similar pattern of development. In addition, it should be noted that filopodia emanating from the endothelial cells of the tip and the tip that leads to axon elongation are morphologically similar and share the expression of some receptors; this is notable for the control signals of two such systems, which have different roles in the body. Membrane-bound and secreted semaphorins signal through plexin and neuropilin receptors with either pro- or anti-angiogenic effects, making these pathways potential therapeutic targets for pathological angiogenesis. In addition, other molecules and signaling pathways such as gap and ring (Robo) receptors, netrin / deletion pathways in colorectal cancer (DCC), and netrin /homologous UNC5 pathways have been reported to play a role during both vascular and neural processes in tissue development.[5,6,9,24]

Oxygen can also affect the ontogeny of fetal villi, the phenotypes of which differ according to the diseases and their degree of severity. A hypoxic appearance (hyper-branching and hyper-capillarization of terminal villi) has been noted in preeclampsia. The situation of early hypoxia maintained in pre-eclampsia can therefore be followed by compensatory villous ontogeny allowing normal blood circulation in the villous vessels. A hyperoxic appearance (deficient villous branching associated with angiogenesis) predominates in pre-eclampsia with intrauterine growth retardation associated with absent or reversed diastolic velocity (VDAI) or in

intrauterine growth retardation without pre -eclampsia with VDAI. A morphometric evaluation of pre-eclamptic placentas with intrauterine growth retardation also concludes a reduction in villous development (length and area) with capillary vasodilation. Ischemia and hypoxia can therefore cause a profound alteration of ontogenesis manifested by a reduction in the number of terminal villi and capillary dilatation. Capillaries sometimes present with erythrocyte circulatory embolization in intrauterine growth retardation with AIDV. These changes may be responsible for the high umbilicoplacental vessel impedance seen in intrauterine growth restriction and preeclampsia with AIIV.[1,2 ,17,29]

Endothelial dysfunction is currently considered one of the first manifestations of vascular disease and arteriosclerosis. Various factors can modify the functions of the endothelium and cause what is known as endothelial dysfunction. Endothelial dysfunction can be defined as an imbalance in the bioavailability of active substances of endothelial origin that predisposes to inflammation, vasoconstriction, and increased vascular permeability, and that can facilitate the development of arteriosclerosis, platelet aggregation, and thrombosis.[8,14,25,28]

The endothelium of the arteries is a cell monolayer connected by intercellular junctions that restrict the traffic of macromolecules between the blood and the vascular wall. The gradual loss of the endothelium's ability to control the traffic of macromolecules into the wall allows a greater deposition of circulating molecules, such as fibrinogen and low-density lipoproteins (LDL), initiating the process of endothelial dysfunction. The most common junctions between ECs are adherens junctions, which are formed by transmembrane adhesion proteins belonging to the cadherin family. The increase in endothelial permeability seems to be linked to a calcium-mediated cell contraction process and to a disorganization of the cell cytoskeleton. Various prothrombotic, inflammatory, or lipid stimuli (such as thrombin, lipopolysaccharide, or lipoproteins) produce significant changes in endothelial permeability.[2,25,29]

Activation of the endothelium leads to the expression/secretion of cytokines, such as interleukin-1 (IL-1), platelet-derived growth factors (PDGF), basic fibroblast (bFGF), and chemotactic factors monocyte chemotactic protein 1(MCP-1), and the exposure of surface proteins that act as adhesion molecules (CAM) to specific receptors of circulating leukocytes.

The adhesion process begins with the sliding of leukocytes over the endothelial surface, the subsequent adhesion and finally their transmigration. The rolling and adhesion phase results from the specific interaction between leukocytes and adhesion molecules expressed by the endothelium. Rolling represents the interaction between leukocytes and selectins, with the consequent adhesion in which other CAMs of the immunoglobulin family participate, such as ICAM and VCAM. CAM expression levels in atherosclerotic lesions are higher than those in areas without atherosclerosis; this CAM overexpression, together with the induction of chemoattractants such as MCP-1, facilitates the attachment and migration of monocytes in areas of injury. The endothelium activated by proinflammatory and atherogenic agents (cytokines, oxLDL, etc.) expresses CAM that does not they are present in the normal endothelium, such as VCAM-1, and overexpress others, such as ICAM-1.[1,4,10,13,21]

The defective remodeling of the spiral arteries then leads to recurrent alterations in the uteroplacental circulation due to the production of superoxideion during oxidative stress. It is normally converted by cytosolic-type superoxide dismutase into hydrogen peroxide, which is also active. Invalidation of the gene for the cytosolic form of this enzyme in mice is lethal, in particular due to the absence of placental development; its overexpression in the trophoblast in vitro or in trisomy 21 is associated with reduced syncytiotrophoblast formation. In animal models of hypertension, an increase in the production of but also of nitric oxide (NO) is observed. However, the bioavailability of NO is reduced, as it quickly goes into the complex state. In the preeclamptic placenta, although the activity of constitutive and inducible NO synthases is reduced, the increase in nitrotyrosines of peroxidized proteins and lipids indicates the existence of oxidative stress. Associated with NO forms toxic peroxynitrite (ONOO-). The latter inhibits the electron transport chain, reduces intracellular NAD+ and ATP pools, triggers lipid peroxidation and produces DNA breaks. These effects result in premature senescence of endothelial and trophoblast cells.

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alterations to the mother remains obscure. The excess of necrotic or apoptotic microfragments of syncytiotrophoblast in the maternal circulation could lead to a dysfunction of the endothelium of the maternal vessels and thus participate in the amplification of the maternal inflammatory reaction predisposing to hypertension. Through the prematurely senescent villous trophoblast, maternal-fetal exchanges are impoverished, leading to intrauterine growth retardation, which may be accompanied by an increase in placental impedance.

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Over the past two decades, endothelial pathways have proven to be an effective diagnostic and therapeutic target in several inflammatory diseases in adults, which has increased interest in the role of endothelial cells in many fields of medicine. To date, examples of studies such as anti-angiogenetic therapy with anti-vascular endothelial growth factor (VEGF) drugs for retinopathy of prematurity are already available. In addition, several studies have documented endothelial dysfunction in preterm adults with an increased incidence of high blood pressure, type 2 diabetes, and stroke, suggesting that prematurity may be responsible for an unfavorable endothelial phenotype. Interestingly, placental and pregnancy studies have shown that this endothelial dysfunction may have started very early and be associated with an unfavorable intrauterine environment caused by pregnancy complications that lead to preterm birth.

Thus, identifying, understanding, and quantifying the contribution of pre- and postnatal processes to endothelial dysfunction is challenging and requires early evaluation of the endothelium to limit confounding factors. Although many fetal processes are not fully understood, the endothelial biomarkers available for this assessment in the NICU (neonatal intensive care unit) are numerous. They await further research to confirm their diagnostic and therapeutic potential.

REFERENCES

1. Agafonova, A.V. V.V. Vasiliev, V. Rogozina Morphological characteristics of the placenta in infectious lesions // Practical Medicine, 2021; 19(1): 8–14.
2. Byvaltsev V.A., I.A. Stepanov, N.A. Tetyushkin The role of inflammatory cytokines in the formation and rupture of arteriovenous malformations of the brain // Pathological Physiology and Experimental Therapy, 2018; 62(4): S. 185-194.
3. Doronina, P.Yu. Modern view on the problem of fetoplacental insufficiency // Alley of Science, 2018; T. 7: 11(27): 143–155.
4. Karapetyan A.O., Baeva M.O., Baev O.R. The role of fetal extracellular DNA in the prediction of major obstetric syndromes. Obstetrics and gynecology, 2018; (4): 10–5. https://doi.org/10.18565/aig.2018.4.10-15.
5. Kruglyakova, M.V. Characteristics of the cytokine profile in physiological and complicated pregnancy //Culture, science, education: problems and prospects: Proceedings of the IX International Scientific and Practical Conference, Nizhnevartovsk, November 10, 2021 Nizhnevartovsk: Nizhnevartovsk State University, 2021; - C 548–555.
6. Kuznetsova I.V., Gavrilova E.A. Clinical experience in the correction of endothelial dysfunction at the stage of preparation for pregnancy in patients with polycystic ovary syndrome. // Effective pharmacotherapy, 2020; 16(28): 36–40.
7. Mironov, A.V. The role of endothelial dysfunction in the development of maternal, perinatal and child morbidity // Obstetrics, gynecology and reproduction, 2020; 14(5): 600-610.
8. Pestrikova, T.Yu. Placental insufficiency as a basic pathology of complications and outcomes of the gestational period // Russian Bulletin of the Obstetrician-Gynecologist, 2020; 20(1): 5–15.
9. Tastanova G., Yunusov S., Shanievaa S. MODERN VIEW ON THE PROBLEM OF FETOPLACENTAL INSUFFICIENCY // Journal "Medicine and Innovations", 2022; 3: 304-312.
10. Troshina, E.A. The role of cytokines in the processes of adaptive integration of immune and neuroendocrine reactions of the body // Problems of Endocrinology, 2021; 67(2): P. 4–9.
11. Shulzhenko, A.E. Antiviral immunity of the reproductive tract: from studying the system to correcting work // Russian Medical Journal. Medical review, 2019; 3(12): 14–19.
12. Brewster LM, Garcia VP, Levy MV, et al. Endothelin-1-induced endothelial microvesicles

impair endothelial cell function. // J Appl Physiol, 2020 Jun 1; 128(6): 1497-1505.
13. Chang X, Yao J, He Q, et al. Exosomes from Women with Preeclampsia Induced Vascular Dysfunction by Delivering sFlt (Soluble FmsLike Tyrosine Kinase)-1 and sEng (Soluble Endoglin) to Endothelial Cells. // Hypertension, Dec 2018; 72(6): 1381-1390.
14. Coban U, Takmaz T, Unyeli OD, Ozdemir S. Adverse Outcomes of Preeclampsia in Previous and Subsequent Pregnancies and the Risk of Recurrence. // Sisley Etfal Hastan Tip Bul, 2021 Sep 24; 55(3): 426-431.
15. de Moreuil C, Alavi Z, Pasquier E. Hydroxychloroquine may be beneficial in preeclampsia and recurrent miscarriage. // Br J Clin Pharmacol, 2020 Jan; 86(1): 39-49.
16. Erez O, Romero R, Jung E, et al. Preeclampsia and eclampsia: the conceptual evolution of a syndrome. Am J Obstet Gynecol, Feb 2022; 226(2S): 786-803.
17. Filipek A, Jurewicz E. Preeklampsja – choroba kobiet w ciąży [Preeclampsia - a disease of pregnant women]. // Postepy Biochem, 2018 Dec 29; 64(4): 232-229.
18. Frishman M, Radin M, Schreiber K. Hydroxychloroquine and antiphospholipid antibody-related pregnancy morbidity: a systematic review and meta-analysis. // Curr Opin Obstet Gynecol, 2020 Oct; 32(5): 351-358.
19. Gabryel B, Bontor K, Jarząbek K, et al. Sulodexide up-regulates glutathione S-transferase P1 by enhancing Nrf2 expression and translocation in human umbilical vein endothelial cells injured by oxygen glucose deprivation. // Arch Med Sci, Feb 11, 2019; 16(4): 957-963.
20. Gamble DT, Brikinns B., Myint PK, et al. Hypertensive disorders of pregnancy and subsequent cardiovascular disease: Current national and international guidelines and the need for future research. // front. Cardiovasc. Med, 2019; 6: 55.
21. Garrido-Gimenez C, Mendoza M, Cruz- Lemini M et al. Angiogenic factors and long-term cardiovascular risk in women that developed preeclampsia during pregnancy. //Hypertension, 2020; 76: 1808–16.
22. Gottardi E, Lecarpentier E, Villette C, et al. Preeclampsia before 26 weeks of gestation: Obstetrical prognosis for the subsequent pregnancy. // J Gynecol Obstet Hum Reprod, March 2021; 50(3): 102000.
23. Marques BCAA, Klein MRST, da Cunha MR, et al. Effects of Oral Magnesium Supplementation on Vascular Function: A Systematic Review and Meta-analysis of Randomized Controlled Trials//. High Blood Press Cardiovasc Prev, Feb 2020; 27(1): 19-28.
24. Nakahara A, Nair S, Ormazabal V, et al. Circulating Placental Extracellular Vesicles and Their Potential Roles During Pregnancy. //Ochsner J, 2020 Winter; 20(4): 439-445.
25. Orabona R., Sciatti E., Vizzardi E., et al. Endothelial dysfunction and vascular stiffness in women with previous pregnancy complicated by early or late pre-eclampsia. Ultrasound Obstet. // Gynecol, 2017; 49: 116–123.
26. Perera C, Zheng S, Kokkinos MI, et al. Decidual mesenchymal stem/stromal cells from preeclamptic patients secrete endoglin, which at high levels inhibits endothelial cell attachment in vitro. // Placenta, 2022 Aug; 126: 175-183.
27. Rana S, Lemoine E, Granger JP, et al. Preeclampsia: Pathophysiology, Challenges, and Perspectives//. Circ Res, 2019 Mar 29; 124(7): 1094-1112.
28. Saleh L., van den Meiracker AH, Geensen R., et al. Soluble fms -like tyrosine kinase-1 and BULLETIN MEDICAL SCIENCES №3 (27) 2022 73 placental growth factor kinetics during and after pregnancy in women with suspected or confirmed pre-eclampsia. Ultrasound Obstet. // Gynecol, 2018; 51: 751–757.
29. Tomimatsu T, Mimura K, Matsuzaki S, et al. Preeclampsia: Maternal Systemic Vascular Disorder Caused by Generalized Endothelial Dysfunction Due to Placental Antiangiogenic Factors. // Int J Mol Sci, 2019 Aug 30; 20(17): 42-46.
30. Vahedian-Azimi A, Karimi L, Reiner Ž, et al. Effects of statins on preeclampsia: A systematic review. Pregnancy Hypertens. March 2021; 23: 123-130. Wu R, Wang T, Gu R, et al. Hypertensive Disorders of Pregnancy and Risk of Cardiovascular Disease-Related Morbidity and Mortality: A Systematic Review and Meta-Analysis. // Cardiology.