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# STUDY OF PATHOMORPHOLOGICAL CHANGES IN THE PLACENTA AT 11-12 WEEKS OF PREGNANCY

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**Summary:** The article discusses research in the field of classical morphological descriptions of the early development of the placenta. When morphologically studying the placenta, according to an analysis of a large amount of literature, before the ninth week of pregnancy, a restriction of arterial communication with the villous space is detected, which leads to low oxygen tension in the placenta. However, in the ninth week, there is a weakening of the arterial plugs, increasing the flow of oxygen to the placenta. Studies have also shown that replacing plasma protein-A with placental growth factor in screening for fetal trisomy and preeclampsia may improve screening accuracy. Taken together, these studies contribute to the understanding of early placental development and the factors influencing its normal functioning.
**Key words:** trophoblast, intervillous space, placental development, placental growth factor, terminated pregnancy, preeclampsia.

Relevance. Classic morphological descriptions of early development state that during implantation the trophoblast invades the capillaries and veins within the superficial endometrium, and that maternal erythrocytes are present in the progenitors of the intervillous space. However, this represents only the capillary circulation, and direct connections between the spiral arteries and the intervillous space cannot be observed until the ninth week of pregnancy. Before this stage, the distal segments of the arteries are occluded by aggregates of cytotrophoblast cells derived from the developing cytotrophoblastic membrane and columns of villous cells. Thus, arterial communication with the expanding intervillous space is limited to a network of narrow intercellular spaces, ensuring that any flow is slow or limited by plasma filtrate. Both of these phenomena may explain the low oxygen tension measured in the placenta due to the small amount of oxygen they deliver. The loosening of some arterial plugs around the 10th week allows maternal blood to flow more freely into the intervillous space, which explains the change in blood flow patterns detected on Doppler ultrasound at the end of the first trimester. As a result, the total amount of oxygen entering the placenta will increase, which will lead to an increase in PO2 in the intervillous space [Jauniaux E, Watson AL2020].

According to Yuldashev A.Yu., Komilov M.S. (2015) conducted a study on the concentration of placental growth factor (PPF) in blood serum and placenta homogenate during physiological and terminated pregnancies in the first trimester. A correlation analysis of their interrelated changes was carried out, and the role of the FRP value in aborted pregnancy was established. It has been shown that in blood serum and chorionic tissue several times less than in physiological pregnancy, there is a delay in the morphogenesis of the placental bed, decidualization of the endometrium, delayed development of the placenta, the formation of villi and blood vessels in them. This often

leads to termination of pregnancy in the early stages. Based on a comprehensive study, the following conclusions were drawn:

1. Placenta growth factor (PLGF) in women with interrupted pregnancy at 11–12 weeks is on average 6.5 and 3.5 times less in the blood serum and chorionic tissue, respectively, than during the physiological course of pregnancy.
2. A high concentration of PLGF in the blood serum during physiological pregnancy and a relatively low concentration during interrupted pregnancy characterizes morphogenetic processes in the area of the maternal bed, vasculoangiogenesis in the placenta, and the outcome of pregnancy at the end of the 1st trimester of pregnancy.
3. Correlation analysis of the concentration of PLGF in the blood serum and morphological processes in the endometrium and terminal villi of the placenta in the compared groups of pregnant women at the end of the 1st trimester establishes a direct relationship between them and makes it possible to predict the course of pregnancy.

According to Grinevich T.N. (2022) have now proven that the molecules matrix metalloproteinases MMP and their inhibitors TIMP play a critical role in ensuring the normal functioning of the placenta. Their main function is the remodeling of the extracellular substance of placenta structures during pregnancy and childbirth, primarily during cervical ripening, rupture of membranes and placental abruption. There are at least 3 cell lines at the uteroplacental interface that express all MMPs except MMP-20: trophoblast cells, endometrial stromal cells, and natural killer cells. MMP-2 and MMP-9 belong to the subfamily of gelatinases and are the most studied enzymes of this family, since they are of leading importance in the breakdown of collagen types IV, V, elastin, which is part of the basement membranes, denatured collagen (gelatin) and some proteins of the connective tissue matrix. Regulation of the expression of gelatinases occurs primarily at the transcriptional level, in the promoter region of the gene, and depends on the influence of endothelial growth factors and cytokines. In the early stages of pregnancy, MMPs prepare the environment for subsequent invasion of the placental bed.

MMP-2 expression dominates over MMP-9 expression in the first 6–8 weeks with a subsequent decrease in concentration, whereas MMP-9 expression increases from 8 to 11 weeks and remains the predominant gelatinase until the end of pregnancy. Thus, MMP-2 plays a major role during trophoblast implantation, and MMP-9 during invasion. In turn, successful trophoblast invasion ensures normal development of placental and embryonic tissues. With mutations of the MMP-2 gene in the terminal villi, there is a decrease in the content of type IV collagen in the basement membranes, which can probably lead to disruption of the formation of the fetoplacental barrier. The expression of metalloproteinases as a diagnostic marker can be assessed in biopsies, serum and other biological fluids. Many of the MMP family members are inducible enzymes, and therefore their levels change during organ injury, which could potentially correlate with various inflammatory and destructive processes. Therefore, studying the immunohistochemical features of the expression of matrix metalloproteinases directly in the placental tissue may be valuable for assessing the implantation process during pregnancy, the disruption of which is often the main cause of miscarriage in early gestation.

In a study by Mazer Zumaeta A., Wright A. (2020), it was found that serum pregnancy-associated plasma protein-A (PAPP-A) and placental growth factor (PlGF) at 11-13 weeks of gestation decrease in pregnancies with fetal trisomy and in those who subsequently develop preeclampsia (PE). In trisomy screening, the established biochemical marker is PAPP-A, whereas in screening for PE, PlGF is the preferred marker. The authors of this study examined the effect of replacing PAPP-A with PlGF in first-trimester screening for trisomies 21, 18, and 13 as a function

of maternal age, fetal nuchal translucency thickness (NT), and free β-human chorionic gonadotropin (β-hCG).

In contrast to trophoblasts obtained from abortion material, trophoblasts grown from explanted chorionic villus samples (CVS) at 11–14 weeks of gestation have the potential to allow the study of preeclampsia and other pregnancy disorders because pregnancy outcome will be known later. Excess CVS for diagnostic purposes were cultured as explants on Matrigel or gelatin, and the outgrowing cells were characterized. The morphology of the cells was studied and stained for cytokeratin-7 and HLA-G. Outgrowing trophoblasts stained strongly for HLA-G and cytokeratin-7. While the growths on Matrigel grew faster and were 100% positive for cytokeratin-7, they turned out to be embedded in the matrix and difficult to pass. The growths on gelatin could be released by trypsinization, subcultured, and further characterized before and after freezing. These cells should prove to be a valuable resource for the study of pregnancy disorders [Campbell S, Park JH., 2007].

Chorionic villus sampling (CVS) and amniocentesis are two methods of prenatal diagnosis. The medical records of 1,624 women who underwent medical treatment between 2008 and 2016 were analyzed. for medical reasons, amniocentesis or CVS was performed. Data on age, severity, parity, gestational age, procedure type, neonatal weight (and percentile), trisomy, abortion, intrauterine growth restriction (IUGR), severe IUGR, preeclampsia, and gestational hypertension were recorded. Ultimately, 1215 cases were assessed. Mean maternal age, severity, and gestational age were significantly different between the two groups. Preeclampsia, gestational hypertension, IUGR, severe IUGR, and intrauterine fetal death were not significantly different between the two groups. Trisomies 18 and 21 were common in patients who underwent amniocentesis [Shirazi M, Rabiei M., 2019].

Maternal and/or placental factors play a fundamental role in the pathogenesis of PE, which determines the time of onset of clinical manifestations and their severity. Impaired proliferation and differentiation of trophoblast cells at the preimplantation stage in the case of disorders in the embryonic period, as well as at subsequent stages of implantation due to inflammatory changes in the decidua, can affect the interaction of trophoblast and endometrial cells and further placentogenesis.

Impaired differentiation of extravillous trophoblast cells leads to insufficient remodeling of the spiral uterine arteries: first, this occurs in the decidual segment before the 10th week of pregnancy in the form of a decrease in arterial obstruction through endovascular trophoblast cells and, as a consequence, damage to the placental villi by active forms of oxygen and nitrogen, and then - in the myometrial segments from the 16th to 18th week of pregnancy, and then - in the myometrial segments from the 16th to 18th week of pregnancy. The result of abnormal restructuring of the uterine arteries is an increase in their resistance and mechanical damage to the placental villi due to increased blood pressure entering the intervillous space. There is a disturbance in the uteroplacental blood flow, which leads to hypoxic/ischemic changes in the placental tissue. Various biological factors are released from the ischemic placenta, causing systemic damage to the vascular endothelium and the occurrence of acute multiple organ failure in the mother. Decreased concentrations of circulating placental factors such as pregnancy-associated plasma protein A (PAPP-A) and placental growth factor (PlGF), as well as increased production of soluble fms-like tyrosine kinase-1, vascular endothelial growth factor A (VEGF-A) levels , inhibin A, actin A, procoagulant P-selectin, proinflammatory interleukin 2 and tumor necrosis factor alpha are associated with PE. Maternal pathogenetic factors include genetic predisposition, immunological factors, metabolic syndrome and diabetes mellitus; Chronic

hypertension may increase maternal susceptibility to factors released by ischemic placental tissue and precipitate the onset of maternal clinical symptoms. Considering the role of epigenetic mechanisms regulating the differentiation, migration and invasion of trophoblast cells, one of the main components of which are small non-coding RNAs (sncRNAs), numerous studies have been conducted to assess the qualitative and quantitative composition of microRNAs in women with PE compared with physiological pregnancy. microRNAs are small (about 20-24 nucleotides in length) single-stranded molecules that reduce gene expression at the post-transcriptional level by destabilizing mRNA and/or inhibiting protein translation. During pregnancy, miRNAs can control trophoblast cell invasion and migration and angiogenesis, in particular by regulating the expression levels of VEGF, sFlt-1 and HIF-1α. Specific microRNA expression patterns were identified in the placenta and peripheral blood of pregnant women with PE. Winger E. et al. analyzed the prognostic potential of the expression levels of 30 microRNAs in peripheral blood leukocytes of women to predict the development of PE in the 1st trimester of pregnancy using quantitative PCR. In addition, the composition of microRNAs in the blood plasma of pregnant women was analyzed and it was revealed that a third of the 368 identified microRNAs were not packaged into exosomes; only 8 exosomal microRNAs (miR-134, miR-196b, miR-302c, miR-346, miR-376c, miR-486-3p, miR-590-5p and miR-618) were significantly different in PE from physiological pregnancy at the time childbirth, and of these, only 4 microRNAs (miR-134, miR-376c, miR-486-3p and miR-590-5p) predicted the development of PE in the 1st trimester of pregnancy. Gromadnikova I. and colleagues assessed the potential of miR-516b-5p, miR-517-5p, miR-518b, miR-520a-5p, miR-520h and miR-525-5p in exosomes of blood plasma of pregnant women to predict PE and gestational hypertension during timing of screening in the first trimester of pregnancy. Caterina Licini discovered the early circulating biomarker PE-miR-125b, which targets trophoblast cell surface antigen ((Trop)-2) and is involved in the regulation of cell-cell adhesion and cell proliferation. Despite the identified prognostic significance of certain microRNAs in the diagnosis of the development of PE at the preclinical stage, recent studies have focused only on pPE, but not rPE, which is characterized by a more severe course with adverse maternal and perinatal consequences. In connection with the above, the purpose of this study was to identify tissue-specific placental microRNA molecules that have prognostic significance in assessing the likelihood of developing rPE and pPE by analyzing the blood serum of women at 11-14 weeks of gestation using deep sequencing followed by validation using quantitative PCR in real time.

Studies conducted in the field of classical morphological descriptions of early development indicate the penetration of trophoblast into the capillaries and veins of the superficial endometrium during implantation. However, direct connections between the spiral arteries and the intervillous space are not observed until the ninth week of pregnancy. At this early stage of development, arterial communication with the intervillous space is limited to narrow intercellular spaces, resulting in slow or restricted plasma filtrate flow. Measurements show low oxygen tension in the placenta due to the limited amount of oxygen supplied by the mother's blood. However, in the ninth week of pregnancy, a weakening of the arterial plugs is observed, which allows maternal blood to penetrate more freely into the intervillous space. This change in blood flow patterns at the end of the first trimester results in an increase in the total amount of oxygen reaching the placenta and an increase in oxygen levels in the intervillous space.

The studies conducted by Yuldashev and Komilova focused on placental growth factor (PGF) concentrations in serum and chorionic tissue during normal and miscarried pregnancies in the first trimester. They found that PRP concentrations were significantly lower in aborted pregnancies compared to normal pregnancies. This indicates a delay in the morphogenesis of the placental bed,

decidualization of the endometrium and a delay in the development of the placenta in the case of an interrupted pregnancy. Thus, all of these studies contribute to the understanding of the early development of the placenta, the factors influencing its normal functioning, and the possible problems that may arise in the event of a miscarriage.

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