

## METHODOLOGICAL APPROACHES TO ASSESSING MORPHOLOGICAL CHANGES IN THE UMBILICAL CORD IN FETOPLACENTAL INSUFFICIENCY: RESEARCH RESULTS

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**Abstract:** Analysis of the modern morphological classification and features of the main lesions of the placenta.

**Materials and methods.** A literature review of the modern international morphological classification of placental lesions developed by the Amsterdam Working Group on Placental Studies (2014) is presented. According to this classification, all changes in the placenta are grouped into three groups: so-called vascular diseases, inflammation, and others. Vascular diseases are divided into two subgroups: maternal and fetal diseases, which in turn are divided into disorders of development, perfusion and integrity of blood vessels. Inflammatory lesions are also divided into two groups: inflammatory-infectious and immune (idiopathic). Other placental lesions include placental abruption, placental shape abnormalities, and umbilical cord attachment.

**Results.** It is noted that the main task of the morphological classification is to adopt a consensus on the definition and characteristics of the main placental lesions in order to determine their clinical significance and use them in research practice in order to develop targeted interventions. The modern terminology of the placenta and its structures, presented in the Russian version of the International Embryological Terminology, is also given. Later, the features of taking samples of placenta tissue for histological examination are shown.

**Keywords:** placenta classification, terminology, complications of pregnancy.

An indispensable key to successful diagnosis and treatment of diseases is the use of unified classifications and terms by doctors of different specialties and researchers from different countries. Only uniform, internationally agreed classifications allow medical professionals to speak the same language, greatly facilitate mutual understanding and cooperation, and allow comparison of the results of their research with the data of the world literature.

Similar problems arise in obstetrics. Thus, it is well known that the placenta plays a very important role in regulating the interaction between the mother and the fetus during pregnancy. Disruption of its structure and function is the basis for the development of various complications of pregnancy and childbirth, including stillbirth and maternal death [1-3]. Accordingly, the changes in the placenta detected during the morphological examination help to determine the reasons for the development of complications, as well as determine the prognosis of the development of the newborn and the course of the future pregnancy. That is, the main task of the pathomorphological examination of the placenta is to identify signs of pathological

changes and compensatory processes that determine the relationship between the pathogenesis of dysfunction of the maternal-placental-fetal system and a number of diseases of newborns.

The topic of this lecture is information about the modern international morphological classification and characteristics of the main placental lesions.

When talking about damage to the placenta, first of all, it is necessary to dwell on its normal components, in particular, their symptoms in the local literature. The main source for the correct spelling of terms is the "Encyclopedic Dictionary of Medical Terms".

It seems more correct to use special morphological terms. Thus, the modern terminology of the placenta and its structures is presented in the International Embryological Terminology, published in Latin and English in 2013. The Russian version of the official international publication Terminologia Embryologica, which includes Latin and English terms, as well as their Russian equivalents, was published at the end of 2014 [4].

This publication lists embryology terms used to describe reproduction (reproduction), ontogeny, embryogenesis, and organogenesis. The following basic terms are recommended to describe the placenta: chorionic plate, cotyledon (or lobule), villi, intervillous space, basal plate. In the umbilical intestine there is amnion, mucous connective tissue, umbilical arteries and unpaired umbilical vein, in fetal membranes - amnion, chorion, amniochorion. However, there is no such term as the last.

To date, the recommendations and classifications of the American College of Pathologists [5] and the International Federation of Placental Associations [6] have been used to describe and systematize the morphological damage of the placenta. The most authoritative local guide to the study of the placenta is AP Milovanova [7].

Today, the most up-to-date recommendations are those developed by the Amsterdam Placenta Workshop Group, which is represented by 26 pathologists specializing in the study of the placenta. These recommendations, unfortunately, have not yet been published, but were reported in the 2014 "2014 International Conference on Stillbirth, SIDS and Infant Survival" and the 2015 "IPPA Updated Pediatric Pathology Course". Partial materials were published by one of the members of the RW Redline working group [8].

According to the developers of these recommendations, the main task is to adopt a consensus on the definition and characteristics of the main placental lesions to be used in research practice to determine their clinical significance and develop targeted interventions.

The basis for an objective and complete morphological study of the placenta is the development of research methods and the combination of taking tissue samples for further histological examination. The first stage is a macroscopic examination, which describes the condition of the placenta itself, umbilical cord and fetal membranes, taking into account dimensional characteristics. Thus, weighing the placenta should be done after cutting the membranes and the umbilical cord before taking tissue samples and fixing the drug. The dimensions of the placenta are expressed in three dimensions: the maximum diameter, the longest line perpendicular to the maximum diameter, and thickness (minimum and maximum values). If lesions are present, their nature, location, and size are noted.

When describing the umbilical intestine, its attachment type, length, diameter, turning indicators and macroscopic changes are shown. In the membrane, their color, integrity and the shortest distance from the place of rupture to the edge of the placenta are recorded.

The location of tissue sampling is determined by the research objectives. During the routine morphological examination of the placenta, the number of sections and the subsequent histological methods of their

staining are determined only by the pathologist performing the section based on the needs of maximum diagnostic reliability [9].

It is recommended to take at least four samples when conducting a scientific study for microscopic examination of a visually unchanged placenta and comparison of structural changes with data from other research methods: one from each of the 4 parts (quadrants) of the placenta, including fetal and maternal surfaces [10]. In this case, each of the four pieces obtained should be divided into two parts, one of which is sent to morphological research, and the other to other methods, including molecular genetic research.

According to the aforementioned Amsterdam group, the minimum requirement is four tissue samples. One of them should represent a cross-cut section of the umbilical cord, and the other should be a cross-cut shift of the extraplacental membranes that hold the edge of the placenta. It is also necessary to take samples representing cross-sections along the entire thickness of the visually intact placenta (representing the inner 2/3 of its thickness), including the area adjacent to the umbilical cord.

According to the recommended classification (table), all changes in the placenta are grouped into three groups: so-called vascular diseases, inflammation, and others.

Since the main function of the placenta is the exchange of nutrients and gases between the blood of the mother and the fetus, vascular diseases are in the first place among all its injuries. In order to better understand and perceive these processes, vascular diseases are divided into two subgroups: maternal and fetal diseases. Although, in fairness, it should be said that not all classified signs have a clearly defined cause.

A fairly reliable sign of maternal diseases is the detection of decidual arteriopathy characterized by fibrinoid necrosis of the walls of spiral arteries, including the presence of atherosclerosis, the expansion of the lumen and the development of thrombosis. Similar changes are mainly observed in preeclampsia [11] as well as fetal growth restriction (FGR) [12].

Another sign of the chronic hypoxic state of the placenta is an increase in the size of the immature extravillous trophoblast. In addition, the sensitivity of this indicator to the presence of preeclampsia is associated with decidual arteriopathy and an increase in the number of giant cells in the placenta [13]. The most obvious manifestation of extravillous trophoblast is the detection of so-called cellular islands [14].

Circulatory disorders in the maternal compartment are primarily caused by improper development of spiral arteries, as a result of which they are divided into two subgroups [13]. The first is a total or partial violation of the mother's blood circulation, which leads to rapid ripening of the villi. Accelerated villous maturation is understood as all histological changes in the villous tree under conditions of reduced blood flow rate, but with a larger volume compared to normal values.

Such changes are characterized by an increase in the number of syncytial nodes against the background of a decrease in branched villi and the presence of areas of villi agglutinated with villous fibrin deposits. If the lesions involve more than 30% of the total number of distal villi, then the term distal villus hypoplasia is used.

The second subgroup includes segmental or complete circulatory disorders, characterized by the presence of villous infarcts located around blocked spiral arteries. It should be noted that only small infarcts, which are considered as a physiological phenomenon, are almost always detected in the peripheral zones of the mature placenta. Therefore, pathological infarcts are considered to be all those detected in an immature placenta.

Violation of the integrity of maternal vessels is also represented by two processes. First, premature separation of the placenta, as a rule, is secondary to the defective remodeling of the spiral arteries in preeclampsia, representing their rupture in conditions of restored blood flow after atherosclerosis or ischemia. At

the same time, various injuries, as well as the use of a number of vasoactive substances, can be complicated by bleeding.

Separation of the placenta occurs in its central part under conditions of high pressure blood flow. In most cases, placental abruption leads to termination of pregnancy, but in some cases, villous infarcts may occur with minor bleeding.

The second type of placental abruption is called marginal placental abruption, in which the maternal veins rupture mainly along the periphery of the placenta [15]. Such separation is mainly caused by premature rupture of membranes and acute development of cervical insufficiency. Risk factors for its development include implantation in the lower segment of the uterus, inflammation in the decidua, and increased venous pressure in a pregnant woman.

Acute marginal placental abruption almost always results in preterm delivery, but rarely causes fetal hypoxia. Chronic marginal separation of the placenta, acute marginal separation is said in cases where the development of labor has not reached. Chronic detachment of the placenta is supported by blood clots, as well as deposition of hemosiderin granules, identified by organizational signs at the edge of the placenta during morphological research [16].

Vascular diseases of the fetus, like maternal diseases, are divided into three groups. The first group consists of the violation of maturity. Slow (delayed) villous maturation or distal villus maturation is characterized by a decrease in the fetoplacental mass index, a central location of capillaries in the stroma, and a clear location of the trophoblast with syncytio-capillary membranes in the villi [17]. Similar changes occur in pregnant women with diabetes mellitus, obesity, FGR, as well as chronic obstruction of umbilical vessels, including its excessive tortuosity [18]. Because distal villi maturation leads to fetal hypoxia, the risk of intrauterine death is 70 times higher in these observations [19].

Changes in the capillaries of the villi reflect their angiogenesis disorder and include cholangiosis, chorangioma, and multifocal chorangiomatosis. Cholangiosis refers to an increase in the number of capillaries of the terminal villi of the placenta. This process is considered as an indicator of chronic prenatal hypoxia rather than a tumor process. Its formation takes place over several weeks. The diagnosis of cholangiosis is made if at least 10 villi are detected in each of three or more sections taken from different parts of the placenta outside the infarct and ischemia zones during microscopic examination (lens magnification  $\times 10$ ). contains at least 10 capillaries. In this case, depending on the number of vessels, three levels of cholangiosis are distinguished. A high correlation between cholangiosis and perinatal mortality has been shown [20].

Chorangioma is a benign tumor of placental vessels, multifocal chorangiomatosis, immature intermediate villi means an increase in the number of small vessels in the peripheral areas [20, 21].

Despite the existing differences in the above processes, they all reflect maternal hypoxemia and/or increased expression of fetal growth factors. In some cases, such changes are combined with congenital pathology, in particular, Bickwit-Wiedemann syndrome [22].

Villus dysmorphism refers to a relatively common villi damage in the form of architectural disturbances similar to those observed in aneuploid pregnancy: distortion of the outline, inclusion of trophoblasts, degeneration of cysts, stroma proliferation, disproportion of villi, proximal dysmorphism. villous vascularization [23, 24]. The most obvious changes are represented by mesenchymal dysplasia [25, 26]. Individual observations of villous dysmorphism may be a manifestation of focal placental mosaicism.

The second group of vascular diseases of the fetus is divided into two subgroups: segmental and complete disorders. Most of the general/partial changes develop as a result of blood flow disorders in the vessels of the umbilical cord, as a result of the pathology of the umbilical cord itself, in particular, due to strictures,

hypertortosis and attachment anomalies. In our opinion, the weakest point in the umbilical cord is the border between the hypertortous and hypotortous sections [27]. The presence of a long umbilical cord and its wrapping around parts of the fetus is also accompanied by a violation of blood flow in its vessels. At the same time, there are signs of congestive venous high pressure in the form of dilatation of large fetoplacental veins with parietal fibrin deposition in the placental tissue, as well as signs of decreased blood supply in the distal parts of the villous tree. avascular villi in the form of diffuse small areas. Notably, the presence of chronic partial umbilical vein obstruction is associated with damage to the fetal central nervous system (CNS) [28].

On the other hand, segmental occlusion of a large fetoplacental vessel by a thrombus leads to damage and necrosis of only blood-supplied villi [29]. In the initial stages, karyorrhexis of the vascular wall and stroma cells is observed in such villi, and eventually the vessel "disappears" and avascular villi are formed. If there are clear changes, such disorders are defined as embryonic thrombotic vasculopathy, which is often accompanied by damage to the central nervous system and other organs.

Violation of the integrity of fetal vessels is expressed by bleeding and swelling. The source of bleeding can be a rupture of a relatively large vessel, for example, vasa previa (vasa previa) or small vessels with distal villi. The latter may be in the form of a villous thrombus [30].

The development of villous edema, as a rule, occurs in cases of fetal hydrops. At the same time, the morphological examination of the placenta allows to make a differential diagnosis between fetal anemia (with an increase in the number of nucleated red blood cells) and parvovirus damage.

It should also be added that swelling of the immature intermediate villi in the placenta as a result of preterm birth is often accompanied by perinatal death, damage to the fetal central nervous system, and the development of neurodevelopmental disorders in the newborn [31, 32]. And the presence of distal villi tumors in the mature placenta was associated with severe cord blood acidemia at birth [33].

The second large group of placental lesions is represented by inflammatory-immune processes. It is known that the placenta serves as a special barrier in contact with the external environment (uterine cavity) and two organisms with different antigenic properties (mother and fetus). Accordingly, its tasks include ensuring the need for immunological tolerance and protection from exogenous microorganisms for the fetus. The main manifestation of inflammation in the placenta is the development of a cellular reaction without vascular changes.

According to the proposed classification, depending on the nature of inflammation, the developing changes are divided into acute and chronic. Acute inflammatory cellular responses develop during acute bacterial infection and reflect two distinct immune system responses [34]. The first is the entry of the mother in the form of neutrophils into the chorioamnion from the venules of the decidua to the membranes and from the interspinal space to the chorionic plate - acute chorioamnionitis. And secondly, fetal reaction, chorionic plate and Wharton's jelly in the form of neutrophils through the walls of large chorionic and umbilical vessels - fetal and / or umbilical vasculitis.

The development of these reactions is stereotypical, and the degree of severity is evaluated [35]. The mother's inflammatory response has three stages of development:

Stage 1: initial reaction localized in the area of subchorionic fibrin and internal choriodecidual membranes (subchorionitis, chorionitis);

Stage 2: damage to the connective tissue between the chorion and the amnion (chorioamnionitis);

Stage 3: necrosis of the amniotic epithelium (necrotizing chorioamnionitis).

According to the Amsterdam criteria, only stages 2 and 3, which represent histologically advanced chorioamnionitis, should be used to evaluate the inflammatory response.

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