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MODERN VIEW ON THE FEATURES OF PATHOMORPHOLOGICAL CHANGES IN THE PLACENTA IN THE 3rd-8TH WEEKS OF PREGNANCY

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Summary: The article draws attention to the significant advances in genetics and biology, which have made it possible to expand our understanding of the molecular basis and mechanisms of histo- and organogenesis. She emphasizes that the structural basis of interactions between mother and fetus is formed as a result of complex processes of cellular differentiation that determine the development of the fetus and its organs. The article points to the significant role of chronic placental insufficiency in the structure of perinatal morbidity and mortality. This article summarizes current research in the field of placental insufficiency and fetal growth restriction syndrome, highlighting its importance and implications in perinatal medicine.
Key words: critical periods, perinatal complications, placental insufficiency, fetal growth restriction syndrome, chronic placental insufficiency, extragenital pathology.

Relevance. Thanks to significant advances in genetics and biology in general, in recent years the understanding of the molecular basis and mechanisms of histo- and organogenesis has seriously expanded. It is known that the structural basis of interactions between mother and fetus, starting from the zygote, is established as a result of complex processes of cellular differentiation, which leads to the formation of the fetus and additional provisional organs. Moreover, disruptions to this process can occur at different stages of development under the influence of various reasons, that is, during critical periods.

One of the most common perinatal complications during high-risk pregnancy is placental insufficiency and fetal growth restriction syndrome (FGR). Chronic placental insufficiency (PI) is one of the most important problems of modern obstetrics and perinatology. The average frequency of this pathology (despite some differences in classifications and diagnostic criteria in different regions of the world) ranges from 22–45% of all pregnancies [Ignatko I.V. 2015].

In the structure of perinatal morbidity and mortality, a significant role is played by complications caused by chronic PN. The most common, clinically significant and contraversive complication of PN is FGR. Around the world, about 30 million newborns are born with growth retardation every year. Moreover, in developed countries the frequency of FGR is 6–8%, and in developing countries it reaches 30%. Even in developed countries, however, there is an increase in the frequency of FGR, which is due to both the increasing role of extragenital pathology in the genesis of PN and the improvement of antenatal diagnosis of this condition. Fetal growth restriction is the cause of a 3–10-fold increase in perinatal mortality, perinatal morbidity and long-

term developmental disorders in newborns and young children, as well as increased morbidity in adults. Moreover, the greatest perinatal mortality and high perinatal morbidity resulting in disability are caused by the critical condition of the fetus. It is no coincidence that the leading place of this pathology is given, since, according to various authors, the associated frequency of perinatal losses ranges from 19 to 28.7‰ and more, the level of perinatal morbidity ranges from 58.7 to 88.0‰ [Strizhakov A. N. et al. 2012].

The placenta exhibits greater morphological and histological diversity between species than any other organ. These differences may be due to factors such as the degree of maturity of the offspring required for survival at birth, exposure to pathogens and the risk of vertical transmission to the fetus, acquisition of ancient transmissible elements, and environmental and habitat stability that influences maternal food intake and therefore, on the flow of nutrients across the mother-fetus interface.

An article by English scientists at the University of Cambridge [Burton GJ, Jauniaux E., 2023] provides new views on the role of the placenta at the beginning of gestation. The placenta has evolved to support the development of the embryo and fetus during various periods of intrauterine life. By necessity, its development must precede the development of the embryo. There is currently evidence that during embryogenesis and organogenesis, the development of the human placenta is supported by histotrophic nutrition secreted from the endometrial glands, and not from the maternal blood. These secretions provide an abundant supply of glucose, lipids, glycoproteins, and growth factors that stimulate rapid proliferation and differentiation of the villous trophoblast.

In addition, data from endometrial organoids indicate that the expression and secretion of these products are increased following sequential exposure to estrogen, progesterone, trophoblastic and decidual hormones, particularly prolactin. Thus, a direct signaling dialogue is proposed between the trophoblast, deciduoses and glands, which allows the placenta to stimulate its own development, independent of the development of the embryo. Many common complications of pregnancy represent a spectrum of disorders associated with insufficient trophoblast proliferation. Increasing evidence suggests that this spectrum is reflected in the form of impaired decidualization, potentially compromising histotroph secretion through decreased prolactin secretion and decreased glandular function. Thus, optimizing endometrial well-being before conception may help prevent common pregnancy complications such as miscarriage, growth restriction, and preeclampsia.

Embryogenesis occurs in a protective, low-oxygen environment. One of the most significant advances has to be the realization that hemochorial organization is not established in humans until 13 weeks of gestation [Moffett A, Shreeve N. 2023].

It was previously assumed that, based on the presence of maternal red blood cells in the lacunae, the precursors of the intervillous space in which maternal blood later circulates, the arterial supply is established soon after implantation, from approximately the fourth week of pregnancy. This situation is still described in many embryology textbooks, often with allusion to oxygen exchange, despite the fact that the number of red blood cells observed was surprisingly low and they were pale. The change in thinking was stimulated by a combination of results from various techniques, including Doppler ultrasound imaging and in vivo hysteroscopy and in vitro perfusion of pregnancy hysterectomy specimens. All of these approaches showed no evidence of significant blood flow in the intervillous space during the first trimester. The findings were highly controversial at the time due to controversy over the sensitivity of imaging equipment and ex vivo uterine vasoconstriction. Surprisingly, earlier claims that connections between the maternal spiral

arteries and the intervillous space could not be detected in histological material from in situ placentas during the first trimester were ignored in the debate.

The first trimester of pregnancy corresponds to the periods of embryogenesis and organogenesis, and in order to appreciate the significance of a low-oxygen environment, it is necessary to take into account the needs of the embryo. There is no doubt that the order of mammals evolved from an oviparous ancestor, and in this context the chicken is an insightful model. All the nutrients needed to maintain a chick are contained in the albumin and yolk, with the only additional requirement being a supply of oxygen. Respiratory gas exchange in the egg is carried out by a highly vascularized chorioallantoic membrane, equivalent to the chorioallantoic placenta of mammals, which fits tightly to the inside of the shell. However, the chorioallantois is formed only on the 10th day of incubation, and then rapidly expands, lining almost the entire shell by the 12th day [Freeman BM, Vince MA.].

Complete establishment of the maternal arterial blood supply to the placenta. Moving echoes, observed on Doppler ultrasound and indicating significant flow, are detected in the intervillous space of the placenta at the beginning of the second trimester of pregnancy, at approximately 12–13 weeks. At the same stage of pregnancy, the oxygen concentration in the placenta increases to approximately 60 mmHg. This rise precisely corresponds to the end of the period of organogenesis, when the risk of free radical-mediated teratogenesis drops sharply. However, the increase still poses an oxidative challenge to placental tissues, and transient swelling of the mitochondrial intracrystalline space is observed in the syncytiotrophoblast.

According to M. L. Chekhonatskaya (2018), some morphological, metric, hormonal, biochemical parameters of the antenatal ontogenesis of the testicles of the fetus and newborns were considered, depending on the pathology of pregnancy and childbirth. A comparative analysis was carried out and risk factors for the development of morphofunctional changes in the testicles in fetuses and newborns from mothers with normal and pathological pregnancy were presented. Intrauterine development of the testes involves not only growth and differentiation, but also migration into the scrotum. Without this, the further process of maturation of full-fledged sperm is impossible. Cryptorchidism is a pathology of the antenatal period, which leads to infertility in the fertile age, delayed sexual development, the formation of a certain body type, hypogonadism, androgen deficiency, a decrease in testosterone levels and an increase in gonadotropins, as well as malignancy of an undescended testicle. The absence of effective treatment for up to two years leads to the irreversibility of the process.

Hormones of the fetoplacental system are involved in the formation, differentiation and migration of the fetal testicles and can significantly increase or decrease in a number of pathological conditions (preeclampsia, threatened miscarriage, post-term pregnancy, somatic pathology, smoking, etc.). In case of severe somatic pathology and complications of pregnancy, suppression of the hormonal function of the placenta and fetal adrenal glands is possible. But there is clearly not enough work on the connection between impaired development of the genital organs in boys and the pathology of pregnancy and childbirth, the organometric parameters of the testicles of fetuses and newborns from mothers during physiological and complicated pregnancy.

A team of American researchers [Jauniaux E, Watson A.L., 2020] measured changes in oxygen tension in the human placenta associated with the onset of maternal arterial circulation at the end of the first trimester of pregnancy and the effect on placental tissue. Using a multiparameter probe, it was found that oxygen tension increases sharply from <20 mmHg. at 8 weeks of gestation to >50 mm Hg. at 12 weeks. This increase coincides with morphological changes in the uterine arteries, which allow free flow of maternal blood into the placenta, and is associated with increases

in the mRNA concentrations and activities of the antioxidant enzymes catalase, glutathione peroxidase, manganese and copper/zinc superoxide dismutase in placental tissues. Between 8 and 9 weeks, there is a sharp peak in the expression of the inducible form of heat shock protein, the formation of nitrotyrosine residues, and disruption of mitochondrial cristae in the syncytiotrophoblast. The authors further concluded that a surge in oxidative stress occurs in the normal placenta when maternal circulation improves. They suggested that this may play a physiological role in stimulating normal placental differentiation, but may also be a factor in the pathogenesis of preeclampsia and early pregnancy loss if antioxidant defenses are depleted.

Thompson BB, Holzer PH. (2023) consider signs of placental pathology in unexplained pregnancy losses. There are approximately 5 million pregnancies each year in the United States, of which 1 million end in miscarriage (a loss that occurs before 20 weeks of gestation) and more than 20,000 end in stillbirth at 20 weeks of gestation or later. Up to 50% of these losses remain unexplained. The authors assessed the effect of expanding the diagnostic categories of placental pathology to include the explicit categories of (1) dysmorphic chorionic villi and (2) small placenta when studying previously unexplained losses. The most common pathological finding observed in unexplained miscarriages was dysmorphic chorionic villi (757 cases; 86.2%), a marker associated with genetic abnormalities. The most common pathological finding observed in unexplained stillbirths was a small placenta (128 cases; 33.9%). The proposed classification system confirmed the usefulness of placental studies to elucidate potential mechanisms of miscarriage. Improved diagnostic rates appear to be a result of filling a gap in previous pregnancy loss classification systems by including the categories of dysmorphic chorionic villi and small placenta.

Histotrophic nutrition during embryogenesis. In all species, the initial nutritional support of the fertilized egg and then the blastocyst is provided by the oviductal fluid secreted by the cells lining the fallopian tube. Once the continuum enters the uterus, the uterine or endometrioid glands take over this role. Histotroph is a general term used to describe the mixture of cellular secretions, cellular debris and extravasation that is released into the space between the maternal and fetal surfaces and is phagocytosed by the trophoblast [Wildman DE, Chen C. 2006]. The combination of the trophoblast's ability to enhance glandular function and changes in glycosylation in early pregnancy provides a unique and powerful mechanism for safely autostimulating placental development. The clinical implications are that the endometrium plays a much more important role in promoting placental formation and pregnancy.

PN in general is a multifactorial and polyetiological pathology, caused by both maternal and fetal-placental causes, and in a number of cases, genetically determined and difficult to control. However, knowledge of the basics of the pathogenesis of PN allows us to understand the mechanism of development of its decompensated form and the critical condition of the fetus, as well as to develop adequate approaches to obstetric tactics. Because of the critical role of the placenta in determining pregnancy outcome and the role of placental insufficiency in the etiology of stillbirth, postpartum placental histology is a commonly used test that can provide important information for clinicians.

Significant advances in genetics and biology in general have significantly expanded our understanding of the molecular basis and mechanisms of tissue and organ development. Research has shown that the interaction between mother and fetus begins at birth and is determined by complex processes of cellular differentiation that lead to the formation of the fetus and organs.

One of the most common complications during pregnancy is placental insufficiency and fetal growth restriction syndrome (FGR). The frequency of this pathology ranges from 22-45% of all pregnancies. Chronic placental insufficiency is a serious problem in obstetrics and perinatology.

Fetal growth restriction is responsible for significant increases in perinatal mortality, morbidity in newborns and young children, and increased morbidity in adults. Even in developed countries, the incidence of FGR is 6-8%, and in developing countries it can reach 30%. The rate of perinatal morbidity and mortality associated with FGR accounts for a significant proportion of all cases.

There is currently evidence that during embryogenesis and organogenesis, the development of the human placenta is supported by histotrophic nutrition secreted from the endometrial glands, and not from the maternal blood.

In addition, data from endometrial organoids indicate that the expression and secretion of these products are increased following sequential exposure to estrogen, progesterone, trophoblastic and decidual hormones, particularly prolactin. Thus, a direct signaling dialogue is proposed between the trophoblast, deciduoses and glands, which allows the placenta to stimulate its own development, independent of the development of the embryo.

Thus, understanding the molecular mechanisms of histo- and organogenesis, as well as the factors influencing the development of placental insufficiency and fetal growth restriction, is important for the development of new strategies for the prevention and treatment of these pregnancy complications.

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