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V.S. Fomina, D.K. Garmaeva

MACRO- AND MICROMORPHOLOGICAL CHARACTERISTICS OF PLACENTA IN PHYSIOLOGICAL PREGNANCY AND COVID-19 AT DIFFERENT STAGES OF PREGNANCY

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Our article presents the macro- and micromorphological characteristics of placenta during physiological pregnancy and COVID-19 according to domestic and foreign literature. A search was made for foreign and domestic scientific publications on the morphological assessment of the placentas of healthy pregnant women and women with a confirmed diagnosis of COVID-19 (positive PCR test for SARS-CoV-2 virus).

In connection to the pandemic caused by a novel coronavirus infection, the study of the pregnancy and search for specific changes in women with a confirmed diagnosis of COVID-19 is of great interest among scientists around the world. Recent scientific publications focused mostly on nonspecific changes and signs of maternal and fetal vascular malperfusion. We reviewed publications, scientific articles, dissertations, literary reviews on E-library, Pubmed, Cyberleninka with access to the full text, whereas publications with paid access or abstract only were omitted.

Keywords: COVID-19, SARS-Cov-2, macroscopic changes, microscopic changes, placenta, umbilical cord, macrometry, morphological changes.

Despite the fact that pregnancy is a physiological process, its result is

FOMINA Valeria Simonovna – anesthesiologist and ICU specialist of the Regional emergency department of the State Budgetary Institution RS(Y) Yakutsk Republican Clinical Hospital, postgraduate student of the Department of Normal and Pathological Anatomy, Operative Surgery and Topographic Anatomy from the Courses of Forensic Medicine of the MI M.K. Ammosov NEFU, fomina.valeria.89@mail.ru, ORCID: orcid.org/ 0000-0001-9620-9754; **GARMAEVA Darima Kyshektovna** – Doctor of Medical Sciences, Professor, Head of Department of Normal and Pathological Anatomy, Operative Surgery and Topographic Anatomy from Forensic Medicine Courses of the MI M.K. Ammosov NEFU; dari66@mail.ru, ORCID: orcid.org/ 0000-0002-6341-0109

an adaptive mechanism [1]. Herewith changes in a woman's body should be maintained within the framework of average homeostasis and functional indicators, so-called "pregnancy norm" [6]. At the same time, during adaptive mechanisms, the body undergoes functional changes, taking into account hereditary, climatic-geographical, constitutional, age-related and other factors, which undoubtedly affect the course of pregnancy [8]. In the study of adaptive mechanisms, functional and morphological indicators, the placenta is a frequent object of research by anatomists, histologists, physiologists, and pathologists [3, 9]. The "mother-placenta-fetus" system during physiological pregnancy is in complex functional harmony. The

placenta is an intermediate barrier organ (hemato-placental barrier) that develops during pregnancy, promotes the growth and development of fetus, structurally and functionally connecting the mother and fetus. Therefore, the placenta is an accurate record of the child's prenatal experience [5]. And without a doubt, the actualization of modern morphometric data on the placenta, on individual variability, age, ethnic characteristics and variability, taking into account the influence of external factors, is necessary in modern medicine. These data can be valuable scientifically and practically for establishing the norm of indicators and provide a personalized approach.

According to modern morphometric general data, placenta has a disk-like

shape with a diameter of 15–20 cm and a thickness of 2.5–3.5 cm, and the mass reaches 500–600 g [2]. During physiological pregnancy, the umbilical cord is 50–55 cm long and 1–1.5 cm in diameter (up to 2–2.5 cm in the fetal region) [13]. During embryogenesis up to 12–16 weeks, the surface of the chorion is covered with villi, part of the villi adjacent to the basal plate forms the fetal part of placenta (villous chorion), and the villous and smooth chorion form placenta [9]. In turn, the maternal part of placenta, which faces the uterus wall, is rough, formed by the structures of the basal part of the decidua. The fetal part of placenta, which faces the fetus, is covered by the amniotic membrane [4]. During the normal course of pregnancy, starting from the 2nd trimester placenta is characterized by the predominance of intermediate undifferentiated and differentiated villi, and syncytiotrophoblastic membranes appear subsequently. The proportion of intervillous space ranges from 25.5 to 33% depending on age, and the magnitude is quite stable throughout the reproductive period [7]. The proportion of elements of the chorionic plate varies from 5.0 to 8.0%; the proportion of elements of the maternal part of placenta is 1.8–5.2%; intervillous maternal fibrinoid - 1.8–5.4%; vascular bed of villi - 5.5–11.4%; their epithelium - 10.5–14.6%; peripheral trophoblastic elements - 5.3–6.0%; local pathological changes (calcifications, inflammatory infiltrates, areas of necrosis) - 3.8–7.5%. In the mature placenta, the terminal (30.2–43.5%), mature intermediate (28.0–32.0%) and stem (16–18% of the total) villi are predominant in relative quantity; mesenchymal villi are minimally represented (0.5–1.5%) [7].

The morphology of placenta depends on various factors, maternal diseases and environmental influence. Currently, one of the main trends in medical science is the study of the COVID-19 pandemic. A year after the recognition of the first outbreak, it spread throughout the world, grew into a global pandemic with more than 3.1 million deaths worldwide [24]. Even first publications related to COVID-19 confirmed the vertical transmission of the infection in a retrospective analysis of 10 newborns born from mothers with COVID-19 [27]. Over time, there are different information about the route of transmission of the infection and the detection of the virus in the tissues of the placenta. So, despite the available molecular and ultrastructural data on the SARS-CoV-2 virus in placental tissues of COVID-19 positive mothers, newborns were not infected [25]. And the

teratogenic effect of COVID-19 infection in neonates has not been reported. Gajbhiye, Modi et al. (2020) noted that only 24 (8%) of 313 newborns born to mothers with COVID-19 had a positive PCR test for SARS-CoV-2 [15], which raises an important question about the problem possible transplacental viral transmission. Notably, maternal infection does not equate to placental infection. Similarly, evidence of viral infection of the placenta does not guarantee intrauterine vertical transmission to the fetus [19].

For these reasons, the study of the morphological features of placenta and umbilical cord in COVID-19 becomes necessary to determine and study the prenatal history of the fetus, the risks to the child and mother due to the disease.

In December 2021, authors from Slovakia Pavel Babal, Lucia Krivosikova et al. described a clinical case of fetal death in a pregnant woman with confirmed COVID-19 but no other noteworthy clinical or obstetric disorder, indicating that fetal death is a possible consequence of SARS-CoV-2 infection during pregnancy. On macroscopic examination, placenta corresponded to gestational age, the umbilical cord was varicose. Cross section of placenta showed numerous confluent grayish-white areas of infarction and dark red hemorrhagic lesions. The authors suggest that SARS-CoV-2 viral infection of the fetus was not the direct cause of death. Persistence of viral protein expression by trophoblasts results in extensive intercoupling fibrinoid deposition with successive placental infarction and ischemia which in turn leads to fetal death. This rare complication of pregnancy can occur regardless of the severity of the clinical course of COVID-19 in a pregnant woman [10].

A Swiss study (Thomas Menter, Kirsten Diana Mertz et al) describes cases of transplacental transmission of SARS-CoV-2 viral infection and the presence of viral RNA in both placenta and the umbilical cord. In an immunohistological study of a case of acute COVID-19, lymphohistiocytic villitis was found, which may be potentially associated with infection. The cellular composition of the inflammatory infiltrate was similar to cytomegalovirus placentitis or chronic villitis. The study also confirms pathological findings about maternal and fetal malperfusion, which may be associated with an altered coagulation state caused by SARS-CoV-2 infection, but this cannot be consistently proven due to confounding factors [18]. Another study by Lausanna University Hospital (David

Baud, Gilbert Greub, et al.), 2020, in placental histology describes macrophage infiltrates and fibrin deposits, which the authors most likely attribute to direct viral infection. However, such intervillitis may be of a different etiology and therefore may not be associated with the presence of the SARS-CoV-2 virus [12]. Similar reports of the most frequently recurring features such as infarcts, fibrin deposits were in Zhang P., Salafia C. et al. (2020) and Hecht J.L., Quade B. et al. (2020) [26,16].

Another case study by French authors Alexandre J. Vivanti, Christelle Vaulop-Fellous et al. showed that, on microscopic examination, the placenta also showed signs of perivillitis, fibrin deposits with infarction and intervillitis. In this case, the neonate tested positive for PCR and required intensive care unit assistance for respiratory support [22]. Another publication (USA, June 2020, Rebecca N Baergen, Debra S Heller) reports placental histological changes. In a study of placentas from 20 women, there was a positive SARS-CoV-2 PCR test when routinely tested during pregnancy (32 to 40 weeks), 10 placentas showed evidence of possible fetal vascular malperfusion or fetal vascular thrombosis as a result of intramural fibrin deposition and stromal vascular karyorrhexis. However, there was no control group for comparison, which made it difficult to interpret the findings. The results were mostly of poor quality and may be related to other etiologies [11]. In a study by Elisheva D. Shanes, Leena B. Mitchal et al., May 2020, USA, placental results from 16 PCR-positive women were published. The placentas were from mothers between the ages of 16 and 40, with 11 maternal SARS-CoV-2 infections diagnosed around the time of birth and five diagnosed earlier in pregnancy. It has been reported that 12 out of 15 third trimester placentas show signs of maternal vascular malperfusion: abnormal and damaged maternal vessels, chorangioma, or decidua arteriopathy [20]. These are quite statistically significant changes, for the reliability of the results, but the pathologists who conducted the examination were not blind to the mother's PCR-positive status. Since pathological changes have been shown in mothers with SARS-CoV-2 infection in most cases, and histological evidence of placental vascular malperfusion is somewhat subjective, these results must be interpreted with caution [23].

Studies by Brazilian scientists in 2021 show transplacental transmission of the SARS-CoV-2 virus only in some cases

(depending on the premorbid state of the pregnant woman), the virus was found in the amniotic fluid, umbilical cord, peripheral blood, but exclude reliable direct evidence of transplacental transmission of infection and specific morphological changes in placenta [17]. Also, pathologic histological patterns in the placentas of mothers infected with SARS-CoV-2 have not been established, as shown in the review by Sharps M.C., Hayes D.J.L., et al. (2020) of 20 studies [21].

A 2020 study of Chinese scientists published at the beginning of 2021 (S. Chen, B. Huang et al.), in a retrospective analysis of 3 clinical cases of pregnant women with COVID-19 infection in the 3rd trimester of pregnancy, revealed that in the study group, placental changes are similar to manifestations as in women with normal pregnancy who are not infected (control group), and no serious adverse pregnancy outcomes were found. Pathological analysis shows that there are no morphological changes associated with viral infection in the placental tissue, and no vertical transmission of intrauterine infection from mother to fetus was found [14].

Conclusions. Our review shows a diverse range of outcomes in women infected with SARS-CoV-2. Care is being taken to treat pregnant women as a homogeneous group as outcomes may depend on the current status of the pregnant woman in light of the COVID-19 phenomenon. In acute COVID-19, marked lymphohistiocytic villitis may occur, which may be associated with infection of placenta with SARS-CoV-2. In addition, there are pathological findings of maternal and fetal malperfusion that may be related to the altered coagulative state caused by SARS-CoV-2 infection; however this cannot be consistently proven given the many confounding factors. In the literature, we did not find works related to the description of morphometric changes in the architectonics of the vessels of placenta and umbilical cord, and other histological changes in the tissue structures of the placenta, which could provide important information about the state of the fetus and perinatal outcomes in women with COVID-19.

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