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HISTOLOGIC CHANGES OF THE PLACENTA IN CHRONIC SUBCOMPENSATED PLACENTAL INSUFFICIENCY IN WOMEN WITH COVID-19 OF MODERATE SEVERITY IN THE SECOND AND THIRD TRIMESTERS OF PREGNANCY

Introduction. COVID-19 in pregnant women is associated with inflammatory damage to the placenta, leading to impaired uteroplacental and fetal-placental circulation and the development of chronic placental insufficiency. Objective. To perform histologic study of placental tissues in women with chronic subcompensated placental insufficiency associated with COVID-19 of moderate severity. **Materials and methods.** Placentas from women who developed chronic subcompensated placental insufficiency against the background of moderate COVID-19 in the second and third trimesters of pregnancy (main group, n = 40). The control group consisted of placentas from women not infected with SARS-CoV-2 (n = 20). Histological study and morphometric analysis of placenta slice preparations were performed. **Results.** Histologic study of placenta from women of the main group revealed the following uncharacteristic specific signs of viral tissue damage: decidual vasculopathy, lymphoplasmacytic infiltration, thrombi in the venous vessels of the stem villi, villitis and intervillusitis, deposition of intervillous fibrinoid, hyperplasia of syncytiotrophoblast and chorangiosis. Morphometric analysis showed an increase in the proportion of perivorsinchal fibrin and capillaries in terminal villi, and a decrease in the density of syncytiotrophoblast membranes. In addition, an increase in the number of syncytial nodules and intermediate immature villi, as well as capillary bleeding in intermediate and terminal villi were found. **Conclusion.** The moderately severe course of COVID-19 in the second and third trimesters of pregnancy is associated with structural changes in the placenta, which, with insufficient efficiency of compensatory and adaptive mechanisms, is one of the causes of the development of chronic subcompensated placental insufficiency.

Keywords: pregnancy, COVID- 19, chronic subcompensated placental insufficiency, placental histology, morphometry.

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Introduction. Pregnancy is accompanied by physiologic restructuring of immune, endocrine and hemostatic regulation, which makes the placenta vulnerable to systemic inflammation and microcirculatory disturbances in COVID-19 [2, 3, 15]. Against this background, infection in the second and third trimesters of pregnancy is associated with remodeling of the intervillous space and villous tree of the placenta due to systemic inflammatory response, endothelial dysfunction and hypercoagulability, which is manifested by a complex of signs of maternal and/or fetal vascular malperfusion [5]. Morphological signs of maternal vascular insufficiency in COVID-19 include decidual vasculopathy with hypertrophy of the vascular wall, increased fibrin deposition and thrombosis in the intervillous space, accelerated maturation of villi with increased formation of syncytial nodules, signs of distal hypoplasia of villi, formation of retroplacental hematomas and infarcts of villi. Changes in fetal blood flow are manifested as chorangiosis, thrombosis of the choroidal plate, avascular villi, and perivorhinal fibrin deposition. In addition, some cases show signs of marked chorioamnionitis and umbilical cord vasculitis, as well as chronic inflammation in the form of lymphohistiocytic intervillusitis and villitis [6, 7, 8, 11]. At the same time, specific pathomorphologic changes characteristic of the moderate course of COVID-19 have not been established. Even with confirmed virosemia, the detectable spectrum of morphologic changes often coincides with abnormalities observed in other obstetric pathologies [4, 9]. However, there is evidence in the literature that in some cases of moderate and severe course, there is a characteristic phenotype of placentitis associated with SARS-CoV-2, represented by the triad: chronic or subacute intervillusitis, diffuse fibrin deposition in the intervillous space and necrosis of syncytiotrophoblast [12]. These changes, according to the authors, are associated with placental insufficiency, intrauterine fetal death, and unfavorable perinatal outcomes [14]. To correctly interpret structural changes in the placenta, many researchers rely on the Amsterdam Placental Workshop Group recommendations of 2014, which standardize protocols for material collection, terminology and diagnostic criteria for maternal and/or fetal malperfusion, as well as take into account the nature of inflammatory damage and the presence of thrombi in the vascular lumen [10, 13]. We believe that the above emphasizes the relevance of our study.

Purpose of the study: to perform histological study of placental tissues in women with chronic subcompensated placental insufficiency associated with COVID-19 of moderate severity in the second and third trimesters of pregnancy.

Materials and methods of research

We studied 40 placentas from women with chronic subcompensated placental insufficiency who underwent COVID-19 of moderate severity in the second and third trimesters of pregnancy (main group) and 20 placentas from women not infected with SARS-CoV-2 (control group). All women were delivered at 38-40 weeks of gestation. Retrospectively, to confirm subcompensated placental insufficiency, screening ultrasound examinations in the third trimester of pregnancy were analyzed (medical records of pregnant women, women in labor and delivery receiving inpatient medical care (Form N 096/1u-20), individual medical records of pregnant women and women in labor and delivery (Form N 111/u-20)).

Inclusion criteria for the main group: spontaneous singleton pregnancy; age 20-35 years; moderately severe course of COVID-19 in the second and third trimesters of pregnancy, confirmed clinically and laboratory by polymerase chain reaction; chronic subcompensated placental insufficiency; informed consent for the study.

Inclusion criteria for the control group: spontaneous singleton pregnancy uncomplicated by COVID-19 and other infectious and inflammatory diseases; age 20-35 years; informed consent for the study.

Exclusion criteria: multiple pregnancy; pregnancy after IVF; anemic syndrome; cardiovascular diseases; exacerbation of chronic non-infectious diseases; presence of chronic nonspecific lung diseases; presence of specific diseases of the bronchopulmonary system; genital anomalies; gestational diabetes mellitus; presence of sexually transmitted infections; presence of hormonal support with gestagens; smoking; alcohol consumption during pregnancy; patients' refusal to be tested

Material was collected in the period 2022-2023 on the basis of the maternity department of the State Autonomous Health Care Institution of the Amur Region "Blagoveshchensk City Clinical Hospital" (Blagoveshchensk). Histological studies were performed in the scientific laboratory of the mechanisms of etiopathogenesis and restorative processes of the respiratory system in nonspecific lung diseases of the Federal State Budgetary Scientific Institution "Far Eastern Scientific Center of Physiology and Pathology of Respiration" (Blagoveshchensk). The study was performed taking into account the ethical principles of the Declaration of Helsinki of the World Medical Association and was approved by the local ethical committee at the DNC FPD (Protocol No. 148, 15.11.2023).

For histologic analysis, sections from the central, paracentral and marginal parts of the placenta (up to 6 samples) were taken immediately after delivery. Samples were fixed in 10% neutral formalin solution, pH 7.2-7.4 (HistoSafe, BioVitrum, Russia) at room temperature for 48 hours. After that, they were washed in water and dehydrated in a series of alcohols according to the generally accepted method. Slices up to 3 μm thick were made from the obtained blocks on a Thermo Fisher Scientific HM 325 rotary microtome (USA). Sections were stained with hematoxylin and eosin [1]. Microscopic studies were performed using a digital microscope MEIJI MT 4300L (Japan) at magnification ×100, ×200, ×400.

Morphometric measurements were performed on digital images of slices using Aperio ImageScope software (Leica Biosystems, USA), with preliminary scale calibration using Micron micrometer scale (Russia). Each measurement was performed in five fields of view. Quantitative values were indicated in terms of 1 mm2, fractional values in %. We evaluated: the proportion of fibrin in the intervillous space (%), the number of terminal villi with 5 or more capillaries (%), the number of full blood capillaries in terminal villi (%) and vessels of intermediate villi (%), the proportion of intermediate immature villi (%), the number of syncytiocapillary membranes in terminal villi (per 1 mm2), syncytial nodules (per 1 mm2), as well as desquamation of syncytiotrophoblast on the scale: 0 – absent, 1 –partial, 2 – total.

Statistical analysis was performed using GraphPad Prism, version 9.0 (GraphPad Software, San Diego, CA, USA). The normality of data distribution was assessed using the Shapiro-Wilk criterion. In pairwise comparisons of quantitative data in independent groups, Student's t-test was used in case of normal distribution of the trait or Mann-Whitney U-test when the distribution did not follow the law of normal distribution. Quantitative data are presented as median (Me) and interquartile range (Q25%-Q75%). Differences were considered statistically significant at a significance level of $p<0.05$.

Results and discussion. The results of histologic examination of placenta preparations of the main group are presented in figure 1.

Histologic signs of basal deciduitis infiltration of basal decidual tissue with lymphocytes and plasma cells – were detected quite often in the decidual laminae (fig. 1A). At the same time in the vessels of the stem villi there were signs of moderate or pronounced vasculitis, and in some cases thrombi in the lumen of the veins were detected (fig. 1B, C). The presence of combined inflammatory vascular lesions and thrombus formation indicates the involvement of the maternal part of the placenta in the general pathomorphologic process of placental hemodynamic disorders. This combination is an objective morphologic criterion of blood flow disturbance in the maternal placental vessels (maternal vascular malperfusion).

In addition, the villitis (mixed infiltration of the stroma of intermediate and terminal villi with lymphocytes, macrophages and single plasma cells) and intervillusitis (lymphohistiocytic infiltration of the intervillous space), expansion of the intervillous space, as well as fibrin deposition with the formation of fibrin "bridges" between the villi were noted in the villous tree (fig. 1D, E). The presence of villitis and intervillusitis may indicate an inflammatory lesion of the villous tree and intervillous space with the involvement of cells of innate and adaptive immunity, which is consistent with our previous work [2]. Fibrin deposition in the intervarsinal space is interpreted as a sign of chronic maternal hypoperfusion and syncytiotrophoblast damage [14].

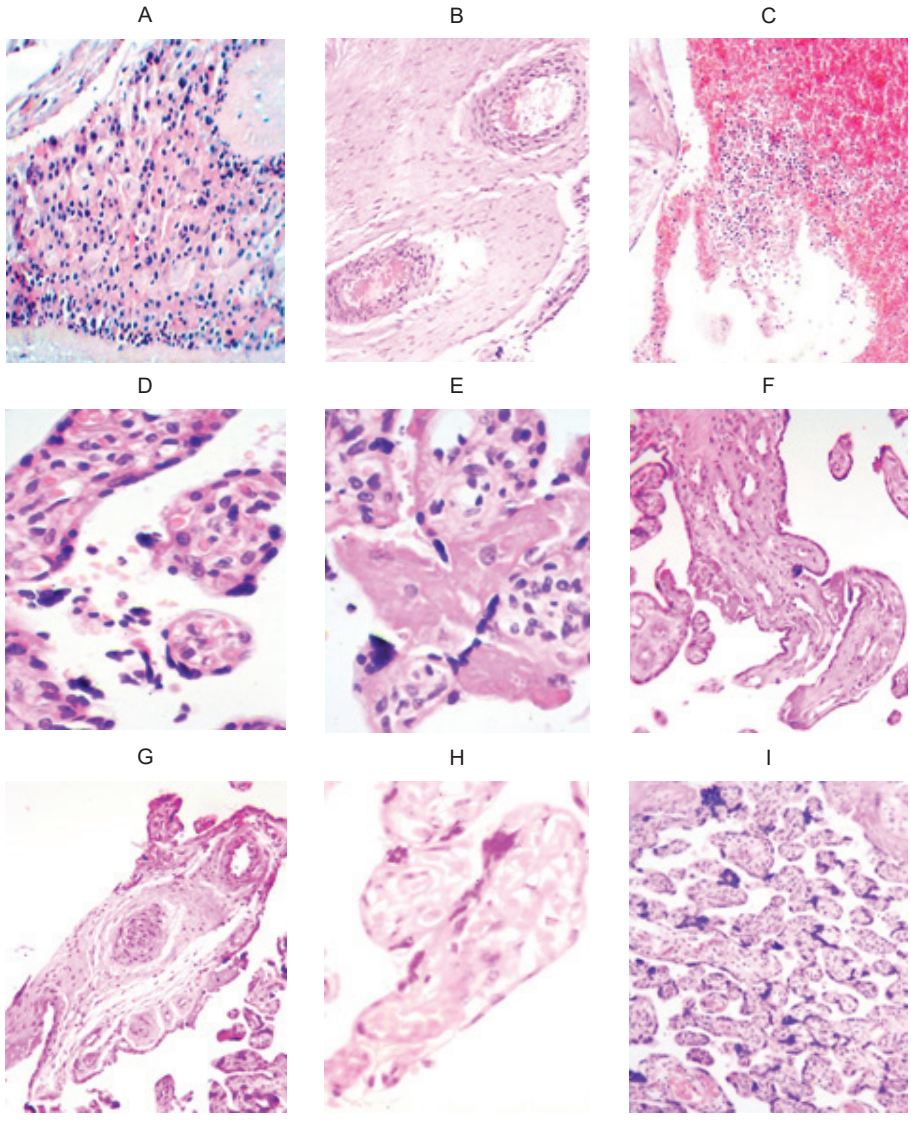
It can be concluded that the totality of the detected disorders is the result of a decrease in the effective surface area of syncytiotrophoblast, which limits the metabolic processes between mother and fetus [16]. This was confirmed by the presence of foci of necrosis of stem and intermediate villi (fig. 1F), and arterial wall fibrosis with partial obliteration of the arterial lumen (fig. 1G). In addition, chorangiosis of intermediate and terminal villi was also encountered (fig. 1H), hyperplasia of syncytiotrophoblast and increase in the number of syncytial nodules (fig. 1I), which also indicated circulatory and involutional-dystrophic changes in the placenta.

Comparative analysis of morphometric parameters of placenta of the main and control groups is presented in the table.

The placentas of the main group showed an increase in the proportion of fibrin in the intervillous space by 2.85 times ($p<0.001$) compared to the control group. The number of capillaries in terminal villi was also increased by 1.99 times ($p<0.001$). At the same time, the density of syncytiocapillary membranes decreased by 1.34 times ($p<0.001$) compared to the control group. Reduced contact zones of syncytiotrophoblast with the capillary network in the presence of hypervascularization of villi may indicate fetal blood flow disturbance.

The indicators characterizing the maturation of the villous tree in the placentas of the main group also underwent changes. An increase in the number of intermediate immature villi by 1.63 times ($p<0.001$) was detected, indicating morphological immaturity of the villous tree and decreased blood flow velocity. There was also an increase in the number of syncytial nodules by 2.09 times ($p<0.001$) compared to the control group, which may be a sign of preplacental hypoxia and changes in placental villi.

The increase in the indices of full blood



Histologic changes in the placenta from women of the main group: A – basal deciduitis with lymphoplasmacytic infiltration. Hematoxylin and eosin, magnification ×200. B – lymphocyte infiltration of stem villous vessels (vasculitis). Hematoxylin and eosin, magnification ×200. C – thrombus with admixture of endotheliocytes, lymphocytes in the lumen of the stem villous vein. Hematoxylin and eosin, magnification ×200. D – infiltration of the stroma of intermediate and terminal villi by lymphocytes, macrophages and single plasma cells (villitis), lymphohistiocytic infiltration of the intervillous space with a single accumulation of erythrocytes (intervillusitis). Hematoxylin and eosin, magnification ×400. E – perivorsinc fibrin with formation of fibrin "bridges" between intermediate and terminal villi. Hematoxylin and eosin, magnification ×400. F – focal necrosis of the stroma of stem and intermediate villi. Hematoxylin and eosin, magnification ×100. G – arterial wall fibrosis with partial obliteration of the lumen. Hematoxylin and eosin, magnification ×200. H – increased number of vessels (capillaries) in the stroma of intermediate and terminal villi (chorangiosis). Hematoxylin and eosin, magnification ×400. I – hyperplasia of syncytiotrophoblast and increased number of syncytial nodules. Hematoxylin and eosin, magnification ×100.

flow of terminal and intermediate villi, respectively, 1.36 times (p<0.001) and 1.54 times (p<0.001) compared to the control group was also noteworthy. It is likely that placental vascular hypertension is also a sign of changes in the microcirculatory system of mother–placenta–fetus.

An additional criterion of villous damage was desquamation of syncytiotrophoblast, the severity of which was higher in the main group (p<0.001) compared to the control group.

Conclusion. Summarizing our results, we can conclude that COVID-19 of moderate severity in the second and third trimesters of pregnancy causes structural placental abnormalities, which, when compensation mechanisms fail, often lead to the development of chronic subcompensated placental insufficiency. The main morphologic criteria of placental abnormalities in COVID-19 include decidual vasculopathy, perivascular inflammation with thrombus formation in the lumen of stem villous veins, villitis, intervillusitis, syncytiotrophoblast hyperplasia, and chorangiosis. Morphometric analysis showed an increase in the number of fibrinoid masses in the intervillous space, the number of capillaries in terminal villi, the number of full-blooded capillaries in terminal villi and vessels of intermediate villi, a decrease in the density of syncytiotrophoblast membranes, and an increase in the number of syncytial nodules.

The results obtained are not definitive and require further studies to investigate the morphologic features of the placenta at different severity and timing of SARS-CoV-2 infection during pregnancy.

Conflict of interest. The authors declare no conflict of interest in the submitted article.

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Morphometric indices of the placenta

Indicators	Main group (n=40)	Control group (n=20)	p
Fibrin in the intervillous space.	46.8 (40.8; 60.5)	16.4 (10.6; 26.5)	<0.001
Terminal villi with 5 or more capillaries	50.6 (37.7; 60.7)	25.4 (16.3; 37.1)	<0.001
Syncytial nodules	18.6 (15.8; 21.7)	8.9 (7.2; 11.7)	<0.001
Syncytiocapillary membranes	39.4 (34.8; 44.5)	52.8 (48.8; 57.7)	<0.001
Full blood capillaries in terminal villi	1.9 (1.6; 2.2)	1.4 (1.2; 1.7)	<0.001
Full blood vessels in intermediate villi	2.0 (1.8; 2.4)	1.3 (0.9; 1.7)	<0.001
Intermediate immature villi	42.9 (29.5; 53.0)	26.3 (18.7; 38.3)	<0.001
Desquamation of syncytiotrophoblast	1.0 (1.0; 2.0)	0.0 (0.0; 1.0)	<0.001

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