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Pathomorphological changes of the placenta in coronavirus disease (COVID-19) in pregnant women at 19-32 weeks of gestation

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Introduction. The morphology of the placenta (chorion) changes during pregnancy. Imm intermediate villi formed during the first two trimesters are developmental steps towards the villi. A cotyledon is the branching of a single stem villus into mature intermediate villi terminal villi. Villous maturation disorders led to placental dysfunction, fetal growth retard and intrauterine asphyxia. The formation of placental insufficiency in the case of corona disease (COVID-19) in the mother in the second trimester of pregnancy prompted us to cor this study. The choice of gestation periods in our study was related to the structural changes c villous chorion that occur at the end of the second and the beginning of the third trimest pregnancy. Purpose: to determine pathomorphological changes in the placenta of women contracted COVID-19 at 19-32 weeks of gestation.

Research methods. The research material is 52 placentas of live-born full-term infants w mothers contracted the coronavirus disease, confirmed by a positive PCR test (determinati SARS-CoV-2 RNA). Group I - placentas with COVID-19 in a pregnant woman at 19-25 wee gestation, group II - at 26-32 weeks. The obtained results were compared with the control g (n=30; placentas of women during physiological childbirth in 2017-2018). Macroscopic, microsc morphometric and statistical research methods were used.

Results. Chorioamnionitis was detected during microscopic examination of placentas of gro and II: n=20 (76.9% (95% CI: 58.2%-91.3%)) and n=16 (61.5% (95% CI: 41.5%-79.7%)), p_{1-2}=0.23; deciduitis: n=24 (92.3% (95% CI: 78.4%-99.4%)) and n=26 100% (95% CI: 92.9%-100%), p_{1-2} = respectively. The placenta with COVID-19 in the mother at 19-32 weeks of pregnancy characterized by exudative inflammation of the basal plate: basal deciduitis (+); p_{1-2}=0.01. percentage of stem and mature intermediate villi in groups I and II was 42.3 [37; 47] and 24.2 26], respectively; p_{1-2}=0.0001, with a reduced number of terminal villi in both groups – 100% CI: 92.9%-100%). A deficiency of mature intermediate villi and distal villous immaturity del the chorion were revealed: in the group I, the percentage of fibrotic stem villi increased, deficiency of mature intermediate villi and terminal villi 16.5 [12; 21]. In the group II ther mature intermediate villi with deficiency of terminal villi 16.8 [10; 25] against 25.6 [21; 29] i comparison group, p<0.001.

Conclusions. COVID-19 in a pregnant woman in the second and early third semesters is a factor for the occurrence of structural changes in the villous chorion – deficiency of m intermediate villi and distal villous immaturity delay. Villous maturation disorders is cause the SARS-CoV-2 coronavirus damage to the villi (endothelial necrosis, proliferative changes i smooth muscle, obliteration of the lumen of the arterioles, fibrosis of the villus stroma) existi the time of infection. Remodeling of blood vessels, which is prolonged in time and due t duration and change of phases of the inflammatory process, explains the formation of ch placental insufficiency, which can manifest itself clinically and become the cause of intraut hypoxia of the fetus precisely with the increase in the duration of the post-COVID interval.

Keywords: COVID-19, SARS-CoV-2, Pregnancy, Placenta, Chorionic villi.

Introduction

Spike Protein of the envelope of the SARS-CoV-2 coronavirus, the causative agent of the coronavirus disease (COVID-19), binds to the receptor (angiotensin-converting enzyme 2, ACE2) of cells of many organs with a high level of ACE II enzyme expression [1, 2]. Despite the fact that the placenta is an organ with a reduced level of activity (co-expression) and protein concentration of angiotensin-converting enzyme type II (ACE II) and transmembrane serine protease type 2 (TMPRSS2) [3], the coronavirus (SARS-CoV-2) enters the cell and damages endothelium (phase of alteration), which was manifested by necrotic changes in the endothelium of vessels [4]. In response to cell damage [1], macrophages and neutrophils are activated (exudation phase), platelets are activated, with further disruption of microcirculation [5, 6] and, as a result, activation of fibroblasts – the development of fibrosis. According to scientists, COVID-19 in the second trimester of pregnancy is a risk factor for the formation of chronic placental insufficiency, associated with the proliferation phase with subsequent fibrosis: arteriolosclerosis of the arterioles of the stem villi, fibrosis of the stroma of the villi and obliteration of the intervillous space [4, 7], which increases the likelihood of malperfusion maternal vessels in the placenta [8]. Also, despite the barrier mechanisms of the placenta [9, 10], there are cases of intrauterine infection of the fetus [11, 12, 13, 14].

The placenta (chorion) is a temporary organ whose morphology changes during pregnancy. The cotyledon is the structural and functional unit of the full-term placenta, it accommodates the branching of one stem villus [15]. The growth of the chorion occurs with the progression of pregnancy, and the presence of corresponding villi is inherent in its various terms. In the first two trimesters of pregnancy, immature intermediate (embryonic) villi are formed, which are the source of the formation of stem villi. In the second trimester, mature intermediate (semi-stem villi) are formed from stem villi, and in the third, terminal villi appear [16, 17]. A sufficient amount of the latter is observed in full-term pregnancy and ensures a satisfactory condition of the fetus. Violation of chorion formation leads to placental dysfunction, fetal growth retardation and intrauterine asphyxia [4, 7, 18]. The main structural changes of the villous chorion with the formation of stem, mature intermediate and terminal villi occur at the end of the second and beginning of the third trimester of pregnancy, which was the reason for the choice of gestational dates in our study.

Purpose: to determine pathomorphological changes in the placenta of women who contracted COVID-19 at 19-32 weeks of gestation to study the morphogenesis of placental dysfunction.

Materials and methods

The material of the study is 52 placentas of live-born full-term infants whose mothers contracted the coronavirus disease during this pregnancy, confirmed by a positive PCR test (determination of SARS-CoV-2 RNA). The placentas were obtained in the Department of Pathological Anatomy of the NSCH "OHMATDYT" Ministry of Health of Ukraine in the period from December 2020 to December 2022. Placentas of women with gestosis of pregnant women were not included in the study group. The material was divided into groups depending on the duration of the disease: Group I – COVID-19 in the mother at 19-25 weeks of gestation, group II – COVID-19 at 26-32 weeks. The obtained results were compared with the control group (n=30; placentas of women during physiological childbirth in 2017-2018). The course of the coronavirus disease in pregnant women was mild in 29 cases, 21 women had a moderately severe course, and two pregnant women had a severe course of the disease with pneumonia. Caesarean section was performed in 9 cases of group I and 7 cases of group II. Children were born with high Apgar scores (8-9) and a negative PCR test. Research methods were used: macroscopic, microscopic with staining with histological dyes – hematoxylin and eosin (H&E), MSB for the detection of fibrin and collagen fibers. To determine the number of terminal villi, their number was calculated through a microscope in one field of view at a magnification of 400. The immunohistochemical method: stained immunohistochemically for CD34 and smooth muscle actin to determine the condition of the endothelium of arterioles and the muscle layer. To determine the percentage of stem and mature intermediate villi of the chorion, archival photographs (×40) were uploaded in JPEG format to ONLINE JPG TOOLS (onlinejpgtools.com/find-dominant-jpg-colors). In Microsoft Paint, the examined histological structures were painted in a color that differs from the color of the histological staining of the structures in the photo (green). The number of colors was indicated – 5, the percentage of which needs to be calculated. The percentage of color in the photo is the percentage of the studied structures. The statistical method of the study was carried out using the STATISTICA 8.0 program package (StatSoft, USA), serial number STA862D175437Q and MedStat serial number 85684586. To assess the difference between the compared average values of two independent populations for small samples, the non-parametric Mann-Whitney U-test was used U Test). Rank data are presented in median format with lower and upper quartiles (Me [Q1; Q3]). Differences were considered statistically significant if the probability value was greater than or equal to 95% ($p \leq 0,05$).

The results

Placentas with COVID-19 in mothers at 19-32 weeks of gestation were studied. During the organometric study, no significant difference in placenta mass was found (p=0.90), in the 1st group this indicator was 580 [350; 990] and in II – 551 [320; 750].Microscopic examination of placentas of groups I and II (Table 1; Fig. 1) revealed chorioamnionitis: n=20 (76.9% (95% CI: 58.2%-91.3%)) and n=16 (61 .5% (95% CI: 41.5%-79.7%)), p_{1-2}=0.23; basal deciduitis: n=24 (92.3% (95% CI: 78.4%-99.4%)) and n=26 100% (95% CI: 92.9%-100%), p_{1-2} =0.15, respectively. But there was no significant difference between the groups.

Table 1

Pathomorphological changes of the placenta in case of COVID-19 in the mother at 19-32 weeks of pregnancy

Groups	I (n=26)	II (n=26)	P (Mann-Whitney U-test)
Chorioamnionitis	n=20 76.9% (95% CI: 58.2%-91.3%)	n=16 61.5% (95% CI: 41.5%-79.7%)	p_{1-2}=0.23
Intervillositis	n=6 23.1% (95% CI: 8.7%-41,8%)	n=6 23.1% (95% CI: 8.7%-41,8%)	-
Villitis	n=3 11.5% (95% CI: 2.1%-27.2%)	n=2 7.7% (95% CI: 0.6%-21.6%)	p_{1-2}=0.68
Basal deciduitis	n=24 92.3% (95% CI: 78.4%-99.4%)	n=26 100% (95% CI: 92.9%-100%)	p_{1-2}=0.15
Obliteration of the lumen of arterioles	n=4 15,4% (95% CI: 4.0%-32.4%)	n=4 15.4% (95% CI: 4.0%-32.4%)	p_{1-2}=0.68
Proliferative changes in the wall of arterioles	n=16 61.5% (95% CI: 41.5%-79.7%)	n=16 61.5% (95% CI: 41.5%-79.7%)	p_{1-2}=0.76
Thrombosis of capillaries of terminal villi	n=2 7.7% (95% CI: 0.6%-21.6%)	n=6 23.1% (95% CI: 8.7%-41.8%)	p_{1-2}=0.12
An increase in the number of syncytial nodules	n=26 100% (95% CI: 92.9%-100%)	n=26 100% (95% CI: 92.9%-100%)	-
Chorangiosis of terminal villi	n=8 30.8% (95% CI: 14.2%-50,5%)	n=12 46.2% (95% CI: 26.9%-66,1%)	p_{1-2}=0.16
Infarction, obliteration of the intervillous space	n=26 100% (95% CI: 92,9%-100%)	n=26 100% (95% CI: 92,9%-100%)	-
Distal villous immaturity delay	n=26 100% (95% CI: 92.9%-100%)	n=26 100% (95% CI: 92.9%-100%)	-

Note: (Mann-Whitney U Test) – statistical significance of differences between groups; p<0.05

The severity of chorioamnionitis in group I was estimated (+) in 19.2% (95% CI: 6.2%-37.5%); (++) – 23.1% (95% CI: 8.7%-41.8%); (+++) in 26.9% (95% CI: 11.3%-46.2%); (++++) in 7.7% (95% CI: 0.6%-21.6%) versus (+) 30.8% (95% CI: 14.2%-50.5%); (++) and (+++) – 11.5% (95% CI: 2.1%-27.2%) and (++++) 7.7% (95% CI: 0.6% -21.6%) in the group II (Table 2).

Table 2

Manifestations of chorioamnionitis (ChA) and basal deciduitis (BD) in the placenta with COVID-19 in mothers at 19-32 weeks of pregnancy

	Signs	Expressiveness of manifestations				
		+	++	+++	++++	+++++
Group I	ChA	n=5 19.2% (95% CI: 6.2%-37.5%)	n=6 23.1% (95% CI: 8.7%-41.8%)	n=7 26,9% (95% CI: 11.3%-46.2%)	n=2 7.7% (95% CI: 0.6%-21.6%)	n=0% (95% CI: 0.0%-7.1%)
	BD	n=4 15.4% (95% CI: 4.0%-32.4%)	n=13 50% (95% CI: 30.3%-69.7%)	n=6 23,1% (95% CI: 8.7%-41.8%)	n=1 3.8% (95% CI: 0.0%-15.1%)	n=0% (95% CI: 0.0%-7.1%)
Group II	ChA	n=8 30.8% (95% CI: 14.2%-50.5%)	n=3 11.5% (95% CI: 2.1%-27.2%)	n=3 11.5% (95% CI: 2.1%-27.2%)	n=2 7.7% (95% CI: 0.6%-21.6%)	n=0% (95% CI: 0.0%-7.1%)
	BD	n=12 25% (95% CI: 46.2%-66.1%)	n=6 23.1% (95% CI: 8.7%-41.8%)	n=4 15.4% (95% CI: 4.0%-32.4%)	n=4 15.4% (95% CI: 4.0%-32.4%)	n=0% (95% CI: 0.0%-7.1%)
		(ChA) p_{1-2}=0.34 (BD) p_{1-2}=0.01	(ChA) p_{1-2}=0.27 (BD) p_{1-2}=0.04	(ChA) p_{1-2}=0.16 (BD) p_{1-2}=0.48	(ChA) p_{1-2}=1 (BD) p_{1-2}=0.16	-

Note: (Mann-Whitney U Test) – statistical significance of differences between groups; $p < 0.05$

The expression of manifestations of basal deciduitis in the 1st group was estimated (+) in 15.4% (95% CI: 4.0%-32.4%); (++) – 50% (95% CI: 30.3%-69.7%); (+++) in 23.1% (95% CI: 8.7%-41.8%); (++++) in 3.8% (95% CI: 0.0%-15.1%) versus (+) 25% (95% CI: 46.2%-66.1%); (++) 23.1% (95% CI: 8.7%-41.8%) and (+++) and (++++) 15.4% each (95% CI: 4.0% -32.4%) in the group II. Moreover, a significant difference between the groups was noted only for the manifestation of (+) basal deciduitis: p_{1-2}=0.01; for (++) – p_{1-2}=0.04. Intervillositis was detected in 6 observations of each group (23.1% (95% CI: 8.7%-41.8%), and in two cases of group I and three of group II it was localized subchorially. In the placentas of both groups, a decrease in the number of terminal chorionic villi was observed – 100% (95% CI: 92.9%-100%) (Fig. 1.A). The number of terminal villi between the I and groups II was not significantly different and was 16.5 [12; 21] in the group I in one field of view at a magnification of 400 and in the group II – 16.8 [10; 25]; compared to the control group 25.6 [21; 29], p_{1-2}<0.001. In 16 cases of group I (61.5% (95% CI: 41.5%-79.7%)) and in 12 cases of group II (46.2% (95% CI: 26.9%-66.1%)) the shape of the terminal villi was elongated (Fig. 1.A). In 7 cases of group I (26.9% (95% CI: 11.3%-46.2%)) and in 8 cases of group II (30.8% (95% CI: 14.2%-50.5%)) dissociated maturation of chorionic villi (a sufficient number of terminal villi of mostly oval shape (Fig. 1.B) alternated with a reduced number of terminal villi of elongated shape in different fields of view).

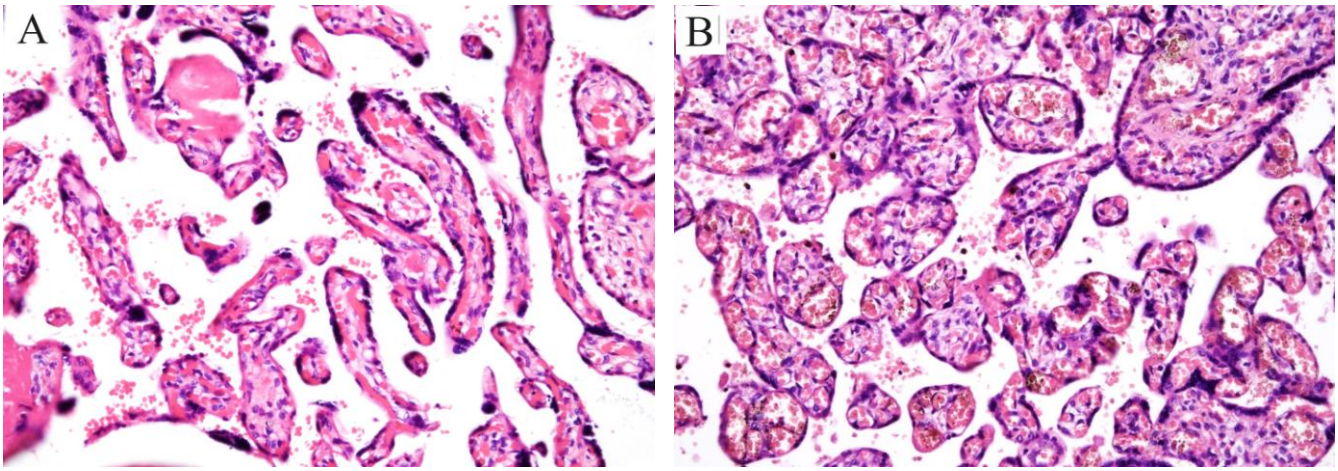

Figure 1. Structural changes in the placenta during COVID-19 in a pregnant woman. A, B – terminal villi of placentas at 39-40 weeks of gestation, H&E staining, ×200; A – history of COVID-19 at 27-28 weeks; villous paucity, thin and elongated villi; B –COVID-19 at 30-31 weeks of pregnancy; rounded villi, chorangiosis

The placentas of both groups were characterized by focal infarctions with focal obliteration of the intervillous space by fibrinoid, fibrosis of the stroma of the stem and mature intermediate villi (Fig. 2), an increase in the number of syncytial nodules by 100% (95% CI: 92.9%-100%); as well as proliferative changes of smooth muscle fibers in the walls of arterioles of stem and semi-stem villi in 16 cases of each group – 61.5% (95% CI: 41.5%-79.7%) with narrowing of the lumen in 5 cases of group I – 19.2 % (95% CI: 6.2%-37.2%) and in 11 cases of II group – 42.3% (95% CI: 23.5%-62.3%) (Fig. 3). In 3 cases of each group – 11.5% (95% CI: 2.1%-27.2%) showed fibrotic stem villi with obliterated vessel lumen. In the placentas of both groups, a decrease in the expression of CD34 in the endothelium of vessels was detected (Fig. 4) in comparison with the expression of CD34 in the endothelium in the placentas of the control group (Fig. 5). Thrombosis of the capillaries of terminal villi was detected in two observations of group I – 7.7% (95% CI: 0.6%-21.6%) and in 6 cases of II – 23.1% (95% CI: 8.7%- 41.8%); but no significant difference between the groups was observed: p_{1-2}=0.12.

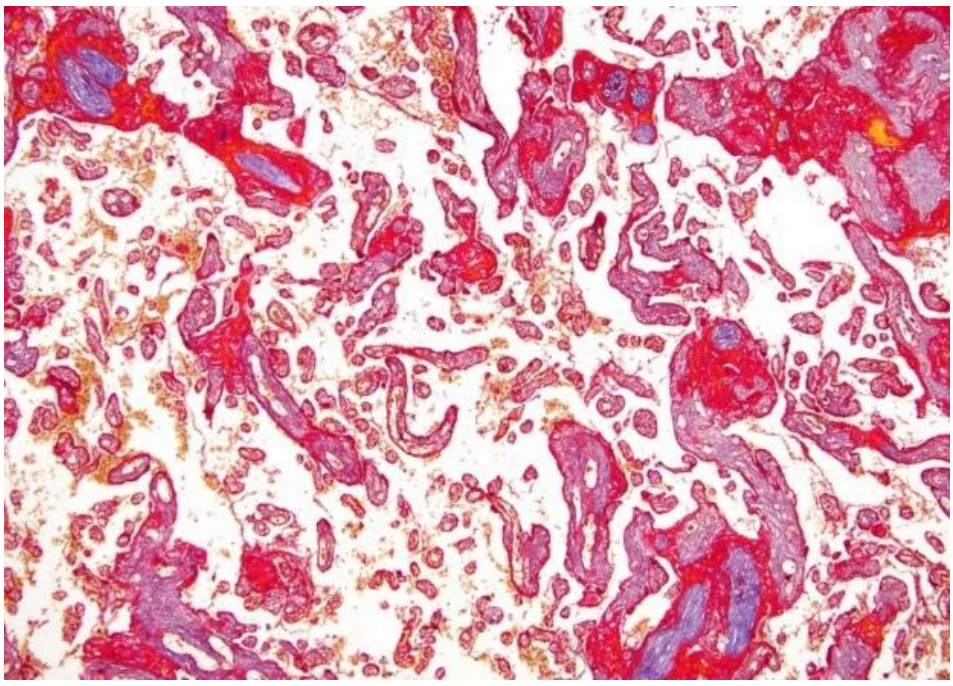

Figure 2. Structural changes of the placenta during full term pregnancy with COVID-19 in the mother at 30-31 weeks of gestation: fibrosis of the stroma of the villi (blue color), the presence of "young" fibrin (red color); MSB staining, ×40

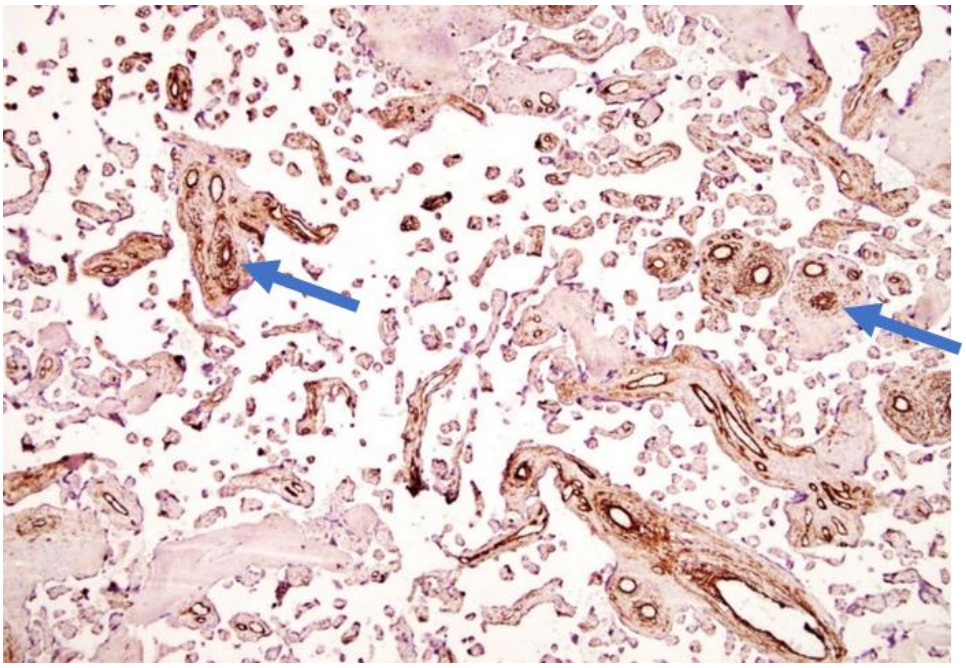

Figure 3. Structural changes of the placenta during full-term pregnancy with COVID-19 at 27-28 weeks of gestation; expression of smooth muscle actin in the wall of arterioles of stem and semi-stem villi of the chorion with fibrotic stroma, narrowing of the lumen of arterioles (arrow). An increase in the number of stem and mature intermediate villi with terminal hypoplasia; ×40

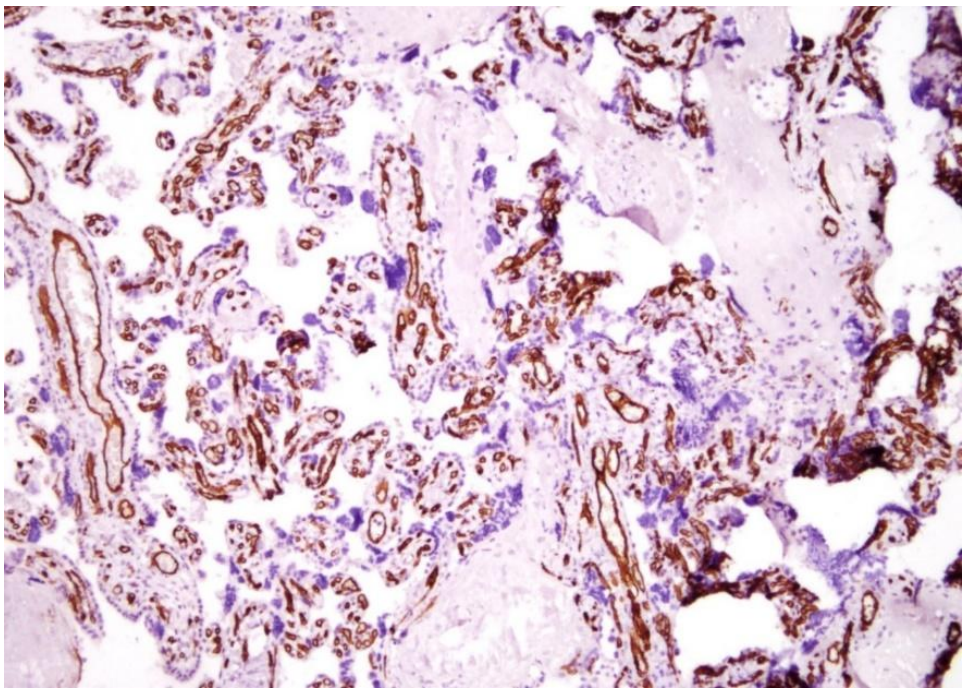

Figure 4. Structural changes of the placenta during full-term pregnancy with COVID-19 at 27-28 weeks of gestation. Reduction of CD34-positive staining in vascular endothelium of elongated terminal villi and in arterioles of fibrotic mature intermediate villi; ×100

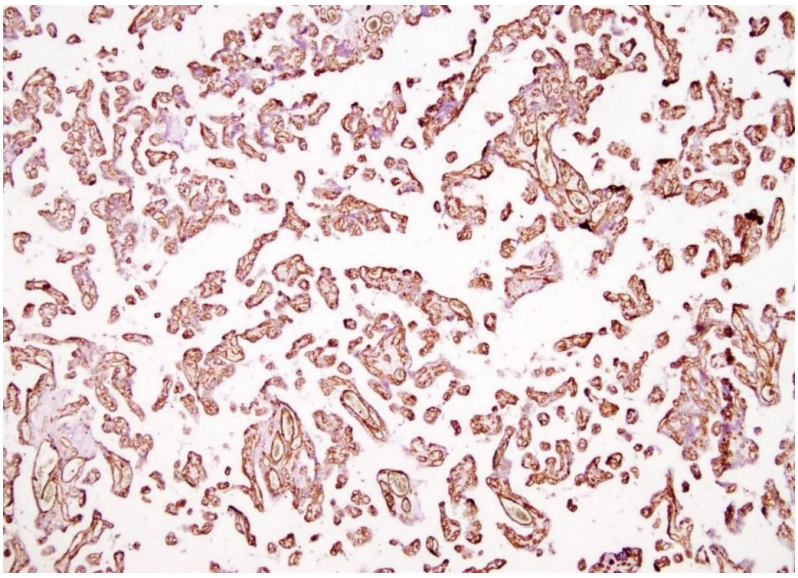

Figure 5. Structural changes of the placenta during full-term pregnancy (comparison group); stained immunohistochemically for CD34 in vascular endothelium, × 40

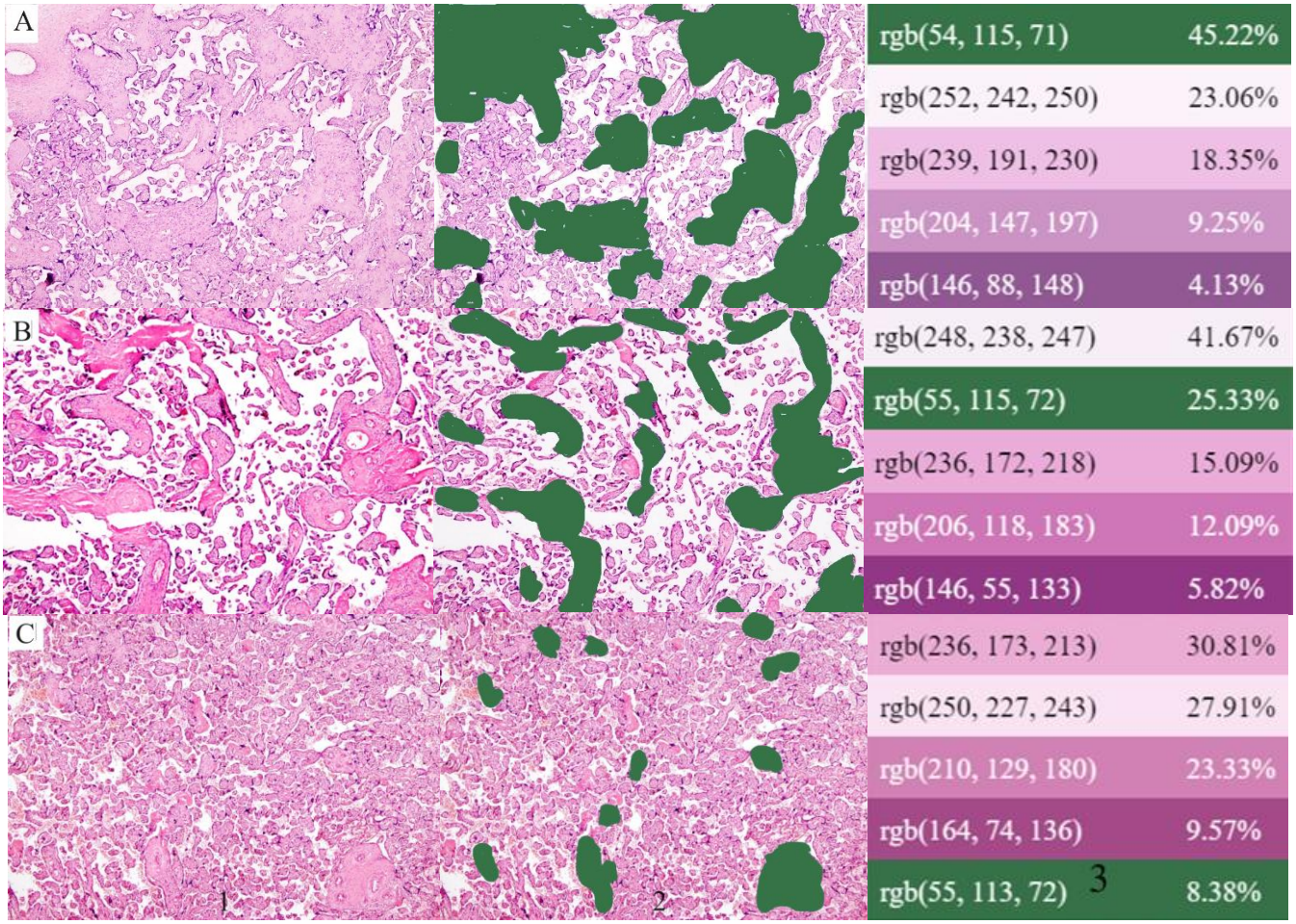

Figure 6. Quantitative determination of the structural changes of the placenta in case of COVID-19 in a pregnant woman at different stages of gestation: 1 (A, B, C) – microscopic sections of the placenta of full-term live-born children in case of COVID-19 in the mother at 19-20; 28-29 and 38-39 weeks of gestation, respectively, ×40. Staining with hematoxylin and eosin. 2 (A, B, C) – stem and mature intermediate villi painted in Microsoft Paint in a color that differs from the color of the histological staining of the structures in the photo (green). 3 (A, B, C) – determination of the percentage of chorion villi in the ONLINE JPG TOOLS program

For the quantitative assessment of structural changes in the placenta, the percentage of the studied structures was determined (Fig. 6. A, B, C). In the placentas of groups, I and II, the percentage of stem and semi-stem villi in one field of view was 42.3 [37; 47] and 24.2 [23; 26], respectively; p_{1-2}=0.0001 (Fig. 6. A, B,). Moreover, stem villi predominated in the group I with the practical absence of mature intermediate villi, while mature intermediate villi and a reduced number of terminal villi were present in the group II. In the placentas of full-term children with COVID-19 in mothers at 38-39 weeks of pregnancy, the percentage of stem and semi-stem villi was 7.7 [7; 9] and was not significantly different from the comparison group (Fig. 6. C). A large number of terminal villi with single mature intermediate villi were found in the control group.

Discussion

The study of the structural changes of the placenta in the case of COVID-19 in the mother at 19-32 weeks of gestation is substantiated by the previous evidence of scientists who proved that the coronavirus disease in the mother in the second trimester of pregnancy is a risk factor for the formation of placental dysfunction and antenatal death of the fetus [4]. In our study, children were born with high Apgar scores and a negative PCR test, despite the fact that the severity of the course of the coronavirus disease in 21 women was moderately severe and two pregnant women had a severe course of the disease with pneumonia. The groups were divided to compare the structural changes of the placenta with COVID-19 in pregnant women. The group I of COVID-19 at 19-25 weeks of gestation, the group II – at 26-32 weeks. Moreover, in group I, the post-COVID interval (time from diagnosis of COVID-19 to delivery) was longer: 15-20 weeks, against 8-14 weeks in group II, which explains the presence of manifestations (exudative, proliferative changes or fibrosis) depending on the phase inflammatory process. Expressive exudative changes (placentitis) were described by researchers and are more common in premature babies at a post-COVID interval of 1-4 weeks [4, 5, 6]. In our case, the observed manifestations of exudative inflammation were found in the placentas of both groups. In group I: 23 cases had severity of manifestations from (+) to (+++) and 3 observations – (++++). In the II group, there are 20 cases from (+) to (+++) and 6 observations from (++++) on a five-point scale. Thus, pathomorphological changes in the placentas of live births with COVID-19 in a pregnant woman at 19-32 weeks of gestation were characterized by exudative inflammation of moderate severity: (+), (++) and (+++) with predominant infiltration of the basal lamina; database (+); p_{1-2}=0.01; the intensity of the changes decreased with an increase in the duration of the post-COVID interval. Infiltration of leukocytes mainly from the basal plate (maternal part of the placenta) and subchorial intervillositis indicates the preservation of the protective function of the placenta, which explained the satisfactory condition of the fetus with high scores on the Apgar scale at birth. Also, the condition of the fetus depended on the compensatory capabilities of the placenta, namely, on the ability to form the branching of villi from villi affected by the SARS-CoV-2 coronavirus [7]. There is evidence of vascular remodeling of stem and semi-stem villi caused by the SARS-CoV-2 coronavirus: manifested by consecutive changes: necrosis of the endothelium, thrombosis and proliferative changes of the muscle membrane, obliteration of the lumen of arterioles, fibrosis of the stroma of the villi, which are significantly expressed in antenatal asphyxia of the fetus [4, 7, 19]. In our study, proliferative changes in arterioles and obliteration of their lumen were found in 61.5% (95% CI: 41.5%-79.7%) and 15.4% (95% CI: 4.0%-32.4 %) respectively, of each group. Therefore, the period of chorion formation is critical when a pregnant woman is infected, as damage to the villi by the SARS-CoV-2 coronavirus can lead to a delay in the development of the placenta [7]. The division into groups is associated with the time of formation of chorionic villi. At 19-25 weeks of gestation, the period of formation of stem villi continues, which explains the increase in the percentage of fibrotic stem villi in the group I – 42.3 [37; 47], against the control group – 7.7 [7; 9]; a small amount of immature intermediate villi (due to the failure of their formation from the stem villi affected by COVID-19) and deficiency of terminal villi – 16.5 [12; 21]. In the last trimester of pregnancy, mature intermediate and terminal villi of the chorion are formed, therefore the placentas in the group II had mature intermediate villi, the percentage of which was 24.2 [23; 26]; p_{1-2}=0.0001 and a reduced number of terminal villi – 16.8 [10; 25], against 25.6 [21; 29] in the comparison group, $p<0.001$. The number of terminal villi was reduced compared to the control group – 25.6 [21; 29], $p_{1-2}<0.001$. But there was no significant difference between the I and groups II. In the group I, the indicator was 16.5 [12; 21] and in the group II – 16.8 [10; 25]. Terminal villi differed in shape: they were elongated in 61.5% of the group I and in 46.2% of the group II. Dissociated villous maturation disorder was also observed in 26.9% of the group I and 30.8% of the group II, which indicated a focal lesion of the mature intermediate villi. Both groups showed compensatory changes in the form of an increase in the number of syncytial nodules.

In conclusions:

COVID-19 in a pregnant woman in the second and early third semesters is a risk factor for the occurrence of structural changes in the villous chorion – deficiency of mature intermediate villi and distal villous immaturity delay. Villous maturation disorders is caused by the SARS-CoV-2 coronavirus damage to the villi (endothelial necrosis, proliferative changes in the smooth muscle, obliteration of the lumen of the arterioles, fibrosis of the villus stroma) existing at the time of infection. Remodeling of blood vessels, which is prolonged in time and due to the duration and change of phases of the inflammatory process, explains the formation of chronic placental insufficiency, which can manifest itself clinically and become the cause of intrauterine hypoxia of the fetus precisely with the increase in the duration of the post-COVID interval.

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