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# Pathomorphological ultrastructural changes in the placenta in coronavirus disease 2019 (COVID-19) during pregnancy: a literature review

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article

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COVID-19, SARS-CoV-2, pregnancy, placenta, chorionic villi, telocytes.

**Ключові слова:**
COVID-19, SARS-CoV-2, вагітність, плацента, ворсини хоріона, телоцити.

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**Aim.** Based on the analysis of literature data, to investigate the pathomorphological and ultrastructural changes in the placenta associated with COVID-19 during pregnancy, with the identification of critical periods for fetal development.

**Materials and methods.** A search for original research articles was conducted in the scientometric databases PubMed, Web of Science, Scopus, and Google Scholar published between 2017 and 2025. The following search terms were used: COVID-19, SARS-CoV-2, placenta, pregnancy, chorionic villi, and placental telocytes. A total of 44 publications were selected to summarize current knowledge on the issue.

**Results.** According to the literature, during the acute phase of COVID-19 in pregnant women, 100 % of cases showed placentitis, signs of endothelial dysfunction, damage to the microcirculatory bed, edema of the chorionic villi stroma, nuclear apoptosis, narrowing of the vascular lumen, and destructive changes in telocytes. As the post-COVID interval lengthened, manifestations of placentitis decreased and vascular lumens were restored (in cases of COVID-19 during the third trimester). In contrast, cases of infection in the second trimester were characterized by arteriolosclerosis, stromal fibrosis of the villi, and delayed chorionic maturation.

**Conclusions.** Vertical transmission of SARS-CoV-2 from infected pregnant women to their fetuses has been demonstrated, with no established correlation between the severity of maternal illness and the extent of placental or fetal impairment. The SARS-CoV-2 virus causes endothelial dysfunction, microcirculatory disturbances, edema, and placentitis, acting as a morphogenetic factor in chorionic remodeling. The degree of placental pathomorphological changes and the consequences for the fetus were determined by the gestational age at which maternal infection occurs. The loss of regulatory control by structurally damaged telocytes over angiogenesis, vascular tone regulation, and apoptosis constitutes one of the mechanisms underlying the development of placental insufficiency.

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## Патоморфологічні ультраструктурні зміни плаценти при коронавірусній хворобі 2019 (COVID-19) під час вагітності: огляд літератури

**Т. В. Савчук, І. В. Лещенко**

**Мета роботи –** на підставі аналізу даних наукової літератури дослідити патоморфологічні й ультраструктурні зміни плаценти при COVID-19 під час вагітності з визначенням критичних періодів для плода.

**Матеріали і методи.** Здійснено пошук оригінальних статей у наукометричних базах даних PubMed, Web of Science, Scopus та сервісі Google Scholar, опублікованих за період з 2017 до 2025 року. Використано такі пошукові терміни: COVID-19, SARS-CoV-2, placenta, pregnancy, chorionic villi, placental telocytes. Для узагальнення відомостей про проблему обрано 44 публікації.

**Результати.** Згідно з даними фахової літератури, у гострому періоді COVID-19 під час вагітності в 100 % випадків виявляли плацентит, ознаки дисфункції ендотелію, пошкодження мікроциркуляторного русла, набряк строми ворсин хоріона, апоптоз ядер, звуження просвіту судин, деструктивні зміни телоцитів. Зі збільшенням тривалості постковідного інтервалу симптоми плацентиту зменшувалися, просвіт судин відновлювався (COVID-19 у третьому триместрі вагітності), або виявляли артеріосклероз, фіброз строми ворсин, затримку дозрівання хоріона (COVID-19 у другому триместрі гестації).

**Висновки.** Доведено вертикальну передачу SARS-CoV-2 від інфікованих вагітних жінок до плодів, при цьому не виявлено кореляції між тяжкістю захворювання матері та порушенням стану плаценти і плода. Дія вірусу SARS-CoV-2 спричиняла дисфункцію ендотелію, порушення мікроциркуляції, набряк, плацентит та ставала морфогенетичним чинником ремоделювання хоріона. Вираженість патоморфологічних змін

плаценти та наслідки для плода зумовлені терміном інфікування вагітних. Втрата контролю деструктивно змінених телоцитів над ангіогенезом, регуляцією тонусу судин та апоптозом є одним із механізмів формування плацентарної недостатності.

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The placenta (chorion) is a temporary organ with dual blood circulation that acts as an intermediary between the mother and the fetus throughout pregnancy [1]. The morphological structure of the chorion varies depending on gestational age [2]. Timely maturation of chorionic villi ensures adequate placental function in accordance with fetal needs [3,4]. A cotyledon represents the structural unit of the term placenta and consists of the branching of a single stem villus into mature intermediate and terminal chorionic villi [5]. The latter give rise to vasculosyncytial membranes (composed of the endothelial cell, basement membrane, and syncytiotrophoblast cytoplasm), which are specialized structures responsible for diffusion exchange [6,7]. Adequate placental perfusion, which ensures satisfactory fetal condition, depends on sufficient vascularization of terminal chorionic villi and a patent intervillous space (IVS) [8,9]. Due to the absence of innervation in the placenta, the regulation of vascular smooth muscle tone and intercellular communication is attributed to telocytes (interstitial cells of Cajal) [10,11,12].

SARS-CoV-2, the causative agent of coronavirus disease (COVID-19), binds to the angiotensin-converting enzyme 2 (ACE2) receptor [13,14], which is expressed in cells of various organs [15]. In the placenta, the level of ACE2 activity and protein concentration contribute to protection against vertical viral transmission [16]. Nevertheless, cases of intrauterine infection, fetal demise, placental abruption, and preterm birth associated with COVID-19 have been reported [17,18]. Activation of endothelial cells disrupts blood rheology and microcirculation [19], leading to both fetal and maternal malperfusion [20].

## Aim

Based on the analysis of literature data, to investigate the pathomorphological and ultrastructural changes in the placenta associated with COVID-19 during pregnancy, with the identification of critical periods for fetal development.

## Materials and methods

A search for original research articles was conducted in scientometric databases, including PubMed, Web of Science, Scopus, and Google Scholar, covering publications from 2017 to 2025. The following search terms were used: COVID-19, SARS-CoV-2, placenta, pregnancy, chorionic villi, and placental telocytes. The search included both Ukrainian and international scientific literature. After reviewing article abstracts and analyzing full-text results, a total of 44 publications were selected to summarize the available data on the topic.

## Results

Researchers examined the pathomorphological changes in the placenta of pregnant women with confirmed COVID-19 infection, verified by a positive PCR test (detection of SARS-CoV-2 RNA) at various stages of gestation [16,17,21]. Direct placental SARS-CoV-2 expression was studied by two methods – nucleocapsid protein expression by immunohistochemistry, and RNA expression by in situ hybridization [22]. Researchers have reported that the SARS-CoV-2 spike protein was detected in individual cases within the syncytiotrophoblast of the placenta in mothers with COVID-19 when the newborn tested PCR-positive. In contrast, the spike protein was absent in the placentas of mothers with a positive PCR result whose newborns tested negative by PCR. Notably, none of the infants exhibited clinical manifestations of infection [23]. The severity of the maternal disease and the fetal condition at birth (assessed using the Apgar score) were taken into account. Vertical transmission of SARS-CoV-2 was detected only in isolated cases (3 %) [14,21,24,25,26].

In the majority of observations, during the acute phase of the disease in term pregnancies, regardless of the severity of clinical manifestations in the mother, newborns tested negative for COVID-19 by PCR and had Apgar scores of 8–9 [21]. No statistically significant correlation was found between the severity of maternal illness and the neonatal condition at birth [18]. Similarly, researchers reported no association between the degree of COVID-19-induced pathomorphological changes in the placenta and the severity of maternal disease [22,27]. Placentitis was described even in cases of mild disease [28], while minimal placental pathology was observed in severe cases accompanied by pneumonia [18]. However, the neonatal condition at birth consistently correlated with the extent of placental alterations [29].

Most studies focused on placental changes during the third trimester of pregnancy in the acute phase of COVID-19 [27,28,30]. Macroscopic examination of placentas during acute infection revealed pronounced circulatory disturbances, including hyperemia and hemorrhages [31], as well as the presence of white infarctions [32]. In cases of COVID-19 infection during the second trimester, the placenta appeared mottled due to numerous white infarctions and demonstrated a firm consistency. Pale coloration and flaccid consistency were characteristic of placentas associated with antenatal fetal death [33].

Microscopic examination of placentas from pregnant women with COVID-19 revealed vascular thrombosis, chorangiosis of terminal villi, stromal edema, and placentitis (chorioamnionitis and basal deciduitis) [14,27]. Researchers reported the presence of intervillositis both in cases with live births and in cases of antenatal fetal asphyxia [34,35]. In the latter, generalized intervillositis was observed in women infected with COVID-19 during the first and second trimesters of gestation [36]. The presence of macrophages, detected using CD-68, indicated chronic intervillous inflammation, which was observed in full-term pregnancies and was focal in nature [14,36].

In addition to inflammatory infiltration of the intervillous space, deposition of perivillous fibrin was noted [14,34,35], resulting in

a reduced proportion of free intervillous space [34,35]. Evidence suggests that the highest rate of pathomorphological alterations occurred in cases of COVID-19 infection during the third trimester (acute phase), characterized by chorangiosis, vascular thrombosis, fibrinoid necrosis, and pronounced placentitis [30,37]. The severity of these manifestations decreased with longer post-COVID intervals [30].

Changes were also noted in stem and intermediate chorionic villi, including fibrinoid deposition and proliferative alterations of the vascular wall leading to lumen narrowing during the acute phase, or vascular obliteration with increasing duration of the post-COVID interval [33]. Therefore, the reduction in the number of terminal villi in COVID-19 in the second trimester of gestation was explained by vascular remodeling and changes in the stroma of stem and semi-stem villi, which are the source for the formation of terminal villi [33,38].

Electron microscopy of placentas during the acute phase of maternal COVID-19 revealed aggregated erythrocytes within narrowed vessels [38]. Apoptotic nuclear changes and cytoplasmic swelling of endothelial cells were observed, accompanied by a reduction in cytoplasmic organelles, disruption of cellular membranes, mitochondrial homogenization, and stromal edema of the villi [30,38]. The latter resulted in an increased stromal-to-vascular ratio within the villi. With longer post-COVID intervals (infection during the second trimester), cytoplasmic swelling of endothelial cells and stromal edema diminished, and vascular lumens were restored [38]. The basal membrane of the syncytiotrophoblast was thickened. Syncytiotrophoblast cells covering the outer surface of the villi formed syncytial knots, the number of which increased during the acute phase of infection [29]. The nuclei of these cells displayed apoptotic changes, and most cytoplasmic organelles were destroyed, with numerous small vacuoles detected [28,30]. Microvilli on the surface of the syncytiotrophoblast were reduced in number [38].

Electron microscopy also revealed destructively altered telocytes (TCs) – interstitial cells with spindle-shaped nuclei and long cytoplasmic projections (telopodes) – located within the villous stroma and adjacent to vessels. With increasing duration of the post-COVID interval, numerous collagen fibers were found surrounding telocyte-like cells [14,38], indicating telocyte transformation into fibroblasts [10,11,12]. Stromal edema and fibrosis led to thickening of the vasculosyncytial membrane, while fetal vessels became more centrally located within terminal villi [39].

Electron-dense virion-like structures were identified within syncytiotrophoblasts [34]. Spherical, osmiophilic particles resembling viral particles were described in terminal villi, located externally near the plasma membranes of stromal fibroblasts [38]. The presence of extracellular viral particles indicated viral budding via endocytosis or exocytosis [40].

Immunohistochemical analysis of placentas from women with COVID-19 demonstrated a positive reaction to the SARS-CoV-2 spike protein. A slightly lower expression of ACE2 was observed, accompanied by significantly higher expression of TMPRSS2 ($4.76 \pm 1.37$ vs. $2.61 \pm 1.04$; $p < 0.001$) [27]. The apoptosis index in syncytiotrophoblast cells was significantly higher ($56.66 \pm 14.28$ vs. $38.92 \pm 13.71$; $p = 0.004$) [27]. Moreover, no correlation was found between the severity of maternal COVID-19 and the increase in apoptosis index or the intensity of placentitis.

In placentas of women infected with SARS-CoV-2, a marked decrease in VEGF-A expression was detected. VEGF-A promotes angiogenesis in the placenta and is normally expressed in syncytiotrophoblasts, cytotrophoblasts, and stromal cells of chorionic villi, with expression levels typically declining as gestation progresses [30].

## Discussion

The analyzed literature data concern placental remodeling in COVID-19–positive mothers at different gestational stages, both in cases of live birth and antenatal asphyxia. The condition of the fetus at birth correlated with the intensity of placental pathomorphological changes caused by SARS-CoV-2 ($p < 0.0001$) and depended on the gestational age at which maternal infection occurred [38]. Published studies provide conflicting evidence regarding the risk of vertical transmission of SARS-CoV-2 from infected pregnant women to fetuses [21,27,34]. Most researchers observed that infection during the third trimester did not affect neonatal condition. Newborns were PCR-negative and exhibited no signs of hypoxia [21,27,41]. This phenomenon has been attributed to decreased co-expression and concentration of angiotensin-converting enzyme 2 (ACE2) and transmembrane serine protease 2 (TMPRSS2), which serve as protective mechanisms against vertical viral transmission [15,16,17].

Other studies demonstrated that SARS-CoV-2 infection may cause intrauterine fetal death during the first and second trimesters [28]. To assess potential placental transmission, electron microscopy identified coronavirus virions invading syncytiotrophoblasts of the chorionic villi [32,34]. Viral particles were detected both in acute and prolonged post-COVID periods, particularly in cases of second-trimester infection, suggesting viral persistence [34]. However, even in the absence of direct viral invasion, activation of maternal inflammation and immune response may adversely affect fetal condition [14].

Both the direct cytopathic action of SARS-CoV-2 and the maternal immune response (“cytokine storm”) contribute to endothelial activation, which has been associated with the development of a preeclampsia-like syndrome in pregnant women with COVID-19 [41,42,43]. Unlike true preeclampsia, the clinical and pathomorphological manifestations of this syndrome regress following maternal recovery. Moreover, the biomarker ratio of soluble fms-like tyrosine kinase-1 (sFlt-1) to placental growth factor (PlGF) remains within normal limits (sFlt-1/PlGF ≤38), distinguishing it from preeclampsia [44]. Despite pathogenetic differences between preeclampsia and COVID-19, similar placental alterations have been reported, including microcirculatory disturbances and an increased number of syncytial knots as a compensatory response to decreased maternal perfusion [29]. Placental changes in moderate-to-severe preeclampsia – such as infarctions, arteriolosclerosis, and delayed maturation – resembled those seen in COVID-19 during the second trimester [38].

Placental pathomorphological changes described in the literature – thrombosis, endothelial cytoplasmic swelling, membrane rupture, and stromal edema of the chorionic villi – indicate endothelial dysfunction [27]. Stromal edema

contributes to thickening of the vasculosyncytial membrane, leading to malperfusion [20]. The thickened membrane, in turn, triggers endothelial activation, and the resulting mediators promote microcirculatory disturbances, vasoconstriction, stromal edema, hypoxia, and fibroblast activation, ultimately leading to stromal fibrosis [38].

Adequate maternal perfusion depends on the integrity of maternal perfusion, defined as a three-dimensional network of channels between chorionic villi [20,29]. In COVID-19, fibrinoid deposition, intervillositis, hemorrhage, and edema of terminal villi reduce the perfusion area. The increased number of syncytial knots described in areas of closely apposed villi or fibrinoid encasement is considered a compensatory mechanism to restore microcirculation by increasing the intervillous distance – thus serving as a marker of malperfusion [20]. Alternatively, excessive syncytial knot formation may reflect the loss of telocyte control over apoptosis due to destructive changes [10].

An elevated apoptotic index is indicative of energy deficiency that activates fibroblasts, explaining stromal fibrosis of the chorionic villi. The loss of telocytic regulation of fibroblast activity, observed both in COVID-19 and preeclampsia, may further contribute to fibrosis [10]. Telocytes also regulate angiogenesis, vascular tone, and terminal villi growth; therefore, their injury leads to vasoconstriction and impaired chorionic growth in COVID-19-positive mothers infected during the second trimester [11,12,38].

The intensity of placentitis in COVID-19 correlated with the timing of infection and the duration of the post-COVID interval [38]. The generalized pattern of intervillositis was attributed to immaturity of placental defense mechanisms [29]. Pronounced basal deciduitis and subchorionic intervillositis exceeding the degree of inflammation in the amniotic membranes in cases of antenatal fetal death indicated vertical viral transmission [29].

The aggregate placental pathomorphological alterations observed in COVID-19 during pregnancy lead to maternal and fetal malperfusion, manifesting as placental dysfunction [20].

## Conclusions

1. Vertical transmission from infected pregnant women to fetuses has been demonstrated; however, no correlation was found between the severity of maternal disease and placental or fetal impairment.

2. The action of the SARS-CoV-2 virus induced endothelial dysfunction, microcirculatory disturbances, edema, and placentitis, acting as a morphogenetic factor in chorionic remodeling. The severity of placental pathomorphological changes and fetal outcomes depended on the gestational age at which maternal infection occurred.

3. The loss of control by destructively altered telocytes over angiogenesis, vascular tone regulation, and apoptosis represents one of the key mechanisms underlying the development of placental insufficiency.

**Perspectives for further research.** Data from the literature and our own analysis indicate the absence of a clear correlation between the severity of maternal disease and placental pathology. This finding underscores the need for further studies to better understand the mechanisms of SARS-CoV-2 infection in pregnancy and to evaluate potential long-term consequences for children born to mothers infected with COVID-19 during gestation.

**Ethical approval**
The study was approved by the Bioethics Committee of Bogomolets National Medical University (Protocol No. 144, dated March 29, 2021).

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