ORIGINAL ARTICLE

CONTENTS

Histological and immunohistochemical features of the placenta associated with COVID-19: a systematic review and meta-analysis

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ABSTRACT

Aim: To make a systematic review and meta-analysis of published data on the study of histological and immunohistochemical features of the placenta in women who had acute coronavirus infection associated with SARS-CoV-2 ("Covid" placentas) during pregnancy.

Materials and Methods: The search for literature data is based on the PRISMA methodology); the MEDLINE database (PubMed®) was searched using Medical Subject Headings terms from January 2020 to July 2023. The project was registered in the Open Sience Frame (Project Identifier: DOI 10.17605/OSF.IO/GDR3S, Registration DOI: https://doi.org/10.17605/OSF.IO/H2KPU). Preference was given to studies in which the description of placentas met the requirements of the Amsterdam Placental Workshop Group Consensus Statement.

Results: A total of 31 studies were included; the number of participants whose morphological and histological description of the placentas could be subjected to meta-analysis was 2401, respectively, in the group with a "Covid" history and 1910 – conditionally healthy pregnant women. Pathological changes in the placental complex were not detected in 42±19.62% of pregnant women with a history of Covid. Immunohistochemical examination of placentas preferably focuses on the detection of SARS-CoV-2 spike protein or ACE2. According to currently available studies, in the placentas of women who have had COVID-19 during pregnancy, there are no pathognomic histological patterns specific to this infection and direct damage to the placenta is rarely observed. Histological patterns in "covid" placentas are isolated, most often a combination of lesions in both the maternal and fetal malperfusion.

Conclusions: According to currently available studies, in the placentas of women who have had COVID-19 during pregnancy, there are no pathognomic histological patterns specific to this infection and direct damage to the placenta is rarely observed. The probability of infection of the intrauterine fetus by the transplacental hematogenous route is the lowest compared to other routes, which, in our opinion, is a possible explanation for the high frequency of MVM without subsequent infection of the fetus.

KEY WORDS: Pregnancy, maternal/fetal vascular malperfusion, SARS-CoV-2, morphological features of the placenta

Wiad Lek. 2024;77(7):1434-1455. doi: 10.36740/WLek202407120 DOI

INTRODUCTION

Coronavirus disease (COVID-19) pandemic during 2019-2022. has become one of the most important medical and social problems of the society due to high contagiousness, rapid spread and high mortality rate. Due to the natural physiological immunodeficiency state of the body, pregnant women are among the most vulnerable groups of the population exposed to the adverse effects of infectious agents. This raised concerns in the medical community about the spread of COVID-19 among this cohort of patients [1, 2]. First observations showed asymptomatic or mild clinical course of the disease among pregnant women [3, 4], serious complications in this group were rarely observed. Also, there was no reliable confirmation of infection vertical transmission - from mother to fetus, so that was similar to previous coronavirus diseases (severe acute respiratory syndrome - SARS, Middle East respiratory syndrome - MERS) and other RNA respiratory viruses infections [5, 6].

As the pandemic spread and involved more and more people in the Western Hemisphere, Europe and the Middle East, cases of severe pneumonia and multiple organ failure syndrome began to be reported among pregnant women, with a natural increase for intensive care and mechanical ventilation; cases of maternal mortality began to be reported [7, 8].

Publications also began to appear on the possibility of vertical transmission of SARS-CoV-2-associated coronavirus infection from mother to fetus and morbidity in newborns [9, 10, 11, 12,13]. But there is currently insufficient information on the impact of the SARS-CoV-2 virus on the placenta and newborn to obtain convincing evidence [14-16].

In accordance with the physiology of pregnancy, the placenta plays the role of an important multifunctional mediator in the interaction between the organisms of mother and intrauterine fetus. During gestation, various organs of the fetus gradually take over all the functions of the placenta, including the lungs, liver, intestines, kidneys and endocrine glands, but the main function of the placenta - to ensure optimal metabolism and perfusion in the maternal-fetal bloodstream is retained. Optimal perfusion is ensured by structural remodeling of the uterine arteries and the formation of a large contact area between the placenta and the thin interhemal membrane separating the maternal and fetal circulation. Various maternal conditions leading to morphological and metabolic changes at the maternal-fetal interface can affect placental function [17, 18].

Information about the absence of a significant impact of COVID-19 on the course of pregnancy and perinatal outcomes [19, 20, 21], as well as information about the low probability of vertical transmission of infection and damage to the fetus [22, 23], does not exclude the possibility that the placenta may be infected with a virus and have certain histopathological features.

So, according to Şahin O. et al. (2022), the placenta of women with asymptomatic COVID-19 is characterized by the presence of parietal hypertrophy of arteriolar membranes [24]. In severe cases of SARS-CoV-2, an associated infection in "Covid" placentas, other authors have identified varying degrees of histiocytic intervillositis, perivillous deposition of fibrin and trophoblast necrosis, as well as cases of fetal vascular malperfusion (FVM) [25].

Based on Schwartz DA et al. data (2022), a characteristic feature of SARS-CoV-2-associated placentitis is increased fibrin deposition and necrosis of trophoblast villous tissue, as well as chronic histiocytic intervillositis. The authors note that an average of about 77.7% of the placental tissue is involved in the inflammatory destructive process [26].

In another work, Schwartz DA et al. (2022), when analyzing cases of stillbirth in pregnant women with COVID-19, note that infection and destruction of the placenta can be observed in the absence of proven infection in the fetus. It is assumed that the development of SARS-CoV-2-associated placentitis may be the result of viremia and have both an infectious and immunological basis. It is also emphasized that in all registered cases of stillbirth and neonatal losses with subsequent verification of placentitis, the mothers were not vaccinated [27].

There is evidence of the absence of any SARS-CoV-2-specific histopathological changes in the placenta, despite vascular malperfusion in the maternal and/or fetal bloodstream, inflammatory changes and other patterns. The authors consider direct infection of the placenta by the SARS-CoV-2 virus to be a rare event [28].

Currently, most histological and immunohistochemical studies of "Covid" placentas are devoted to confirming infection of the placenta with the SARS-CoV-2 virus [28, 29, 30, 31, 32] and studying directly in the placenta the expression of angiotensin-converting factor receptors (ACE2), through which one of the main damaging effects of SARS-CoV-2 is realized [33, 34, 35]. It is believed that the vertical transmission of SARS-CoV-2 is critically dependent on the presence of the ACE2 receptor in the placenta [36, 37].

Usually, not all placentas require routine histological examination; indications are justified by concomitant mother's diseases or complications of pregnancy, when this particular study can provide insight into the likely (and unlikely) causes of prenatal and intrapartum problems and prognostic information for the mother and child. Lack of information, relevant studies, lack of follow-up period, different inclusion standards and limitations of systematic reviews make it difficult to accurately interpret the data [14, 38-41].

AIM

The purpose of this work: to make a systematic review and meta-analysis of published data on the study of histological and immunohistochemical features of the placenta in women who had acute coronavirus infection associated with SARS-CoV-2 ("Covid" placentas) during pregnancy.

MATERIALS AND METHODS

The systematic literature review project was registered in Open Science Frame (Project Identifier: DOI 10.17605/OSF.IO/GDR3S, Registration DOI: https://doi.org/10.17605/OSF.IO/H2KPU), inclusion and exclusion criteria for studies are presented in Suppl.1 (OSF Registries | COVID-19 in Pregnancy and morphological and histological features of the placenta: a preliminary review | Files) .

The literature search was based on the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) methodology [42]; the MEDLINE database (PubMed®) was searched using combinations of the relevant Medical Subject Headings terms (MeSH), key words, and word variants for "COVID-19 and pregnancy," COVID-19 and placenta," "SARS- CoV-2 and the placenta" and "COVID-19 and histology of the placenta", "COVID-19 and immunohistochemistry of the placenta" (Suppl. 2. OSF Registries | COVID-19 in Pregnancy and morphological and histological features of the placenta: a preliminary review | Files). Papers in English were se-

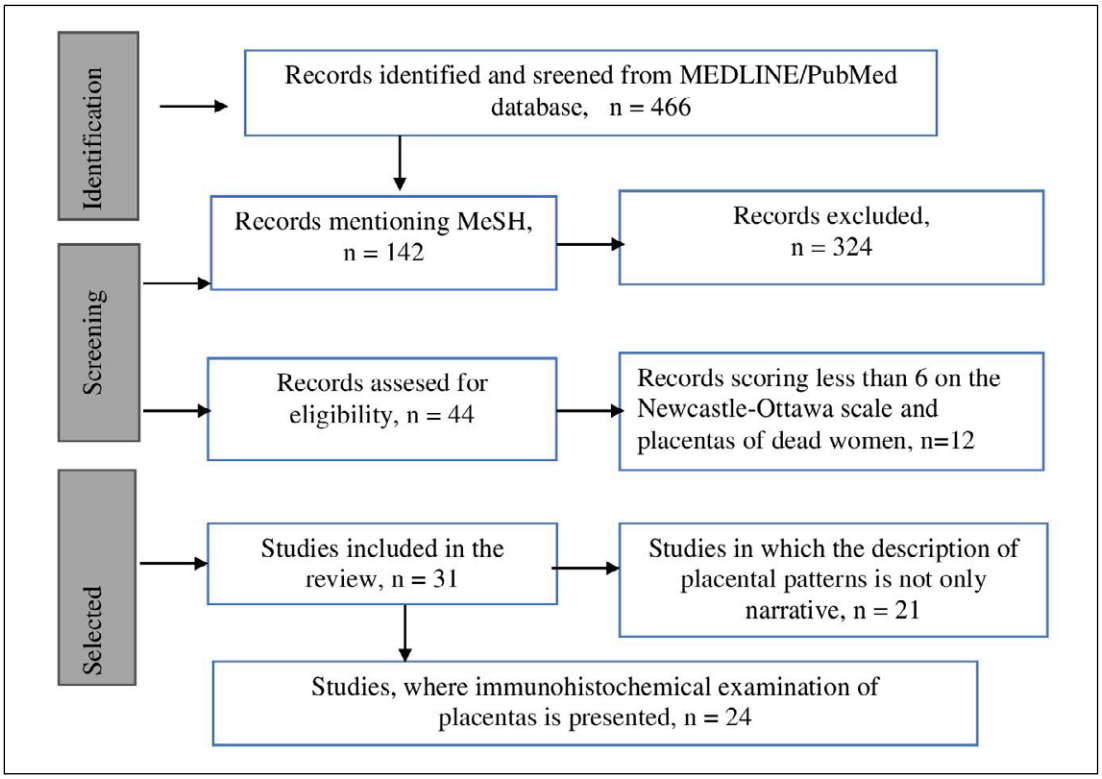

Fig. 1. PRISMA flow chart of database search.

lected for analysis in 3 stages (identification of relevant studies, selection and final selection) based on MeSH/ abstracts; in the case of lack of access to the full text or lack of information on the morphological-histological and immunohistochemical examination of placentas, the works were excluded from further analysis (Fig. 1).

Preference was given to studies that described placentas in accordance with the Amsterdam Placental Workshop Group Consensus Statement (APWGCS, 2016); which contained information not only of a descriptive nature about data such as Maternal vascular malperfusion (MVM), Fetal vascular malperfusion (FVM), Acute and Chronic inflammatory pathology (AIP, CIP) and other criteria [43]. All search results for the period January 2020 - July 2023, taking into account the recommendations of The Joanna Briggs Institute [44], were checked by two independent experts from different Ukrainian institutions and different cities (Fig. 1), the potential significance of the studies and the final selection were agreed upon during the discussion.

Taking into account the requirements for non-randomized studies, a questionnaire was developed for selection and methodological assessment of the quality of published works - the Newcastle-Ottawa Scale (NOS) [45], which included information about the diagnosis of Covid-19 in pregnant women, histological and immunohistochemical examination of placentas as one of the diagnostic methods for this diagnosis, information about the comorbid status of patients, the course of pregnancy, and perinatal outcomes (Table 1)

Studies were required to contain information on confirmation of SARS-CoV-2 infection by PCR (polymerase chain reaction); in the description of placentas, the presence of macroscopic examination, electron microscopy of placenta samples with hematoxylin and eosin staining, and immunohistochemical studies aimed at identifying inflammatory, immune-mediated and other changes in the placenta were taken into account.

STATISTICAL ANALYSIS

The statistical analysis was performed using the online software https://www.socscistatistics.com/tests. After determining the normality of the distribution with the use of the Kolmogorov-Smirnov test, a comparative analysis of the data was carried out. For the descriptive analysis of the study group, categorical variables were summarized as percentages and continuous variables as means or medians with the corresponding standard deviation (SD). Categorical variables were compared between groups using T-test calculator for 2 independent means and the Relative Risk (RR) and Odds Ratio (OR) calculator. The threshold for statistical significance was set at 0.05.

RESULTS

The total number of studies that generally met the stated selection criteria was 30 of the initially identified 466 studies (Table 2).

Table 1. The Newcastle-Ottawa Scale -NOS)

№	Author	Pregnant women with COVID-19 (PCR)	Histological examination of the placenta	IHC examination of the placenta (for ACE 1-2 and other)	Healthy pregnant women (control group)	Comorbid status	pregnancy complications	Perinatal outcomes	Gestational age	IHC examination of the placenta for COVID-19
1.	Adam A.M. [12].	*	*	*	*	*	*	*	*	NP
2.	Bertero L. [49].	*	*	NP	*	*	*	*	*	*
3.	Boyraz B. [67.	*	*	*	*	-	*	-	*	*
4.	C. Tasca C. [22].	*	*	*	*	*	*	*	*	*
5.	Celik E. [13].	*	*	*	NP	*	*	*	*	*
6.	Corbetta-Rastelli C.M. [23].	*	*	NP	NP	*	*	*	*	NP
7.	Damman E. [30].	*	*	*		*	*	*	*	*
8.	Di Girolamo R. [40].	*	*	*	*	NP	*	*	NP	*
9.	Edlow A.G. [36].	*	*	*	*	NP	*	*	NP	*
10.	Facchetti F. [39].	*	*	*	*	NP	NP	*	*	*
11.	Ferraz T. [51].	*	*	NP	*	*	*	*	*	*
12.	Gao L. [29].	*	*	*	NP	*	*	*	*	*
13.	Giordano G. [66].	*	*	*	NP	*	*	*	*	*
14.	Glynn S.M. [58].	*	*	*	*	*	*	*	*	*
15.	Gychka S.G. [15].	*	*	*	*	*	NP	*	*	*
16.	Horn L.C. [67].	*	*	*	NP	*	*	*	*	*
17.	Hsu A.L. [41].	*	*	*	NP	*	*	*	*	*
18.	Husen M.F. [69].	*	*	*	NP	*	*	*	*	*
19.	Jaiswal N. [71].	*	*	NP	*	NP	*	*	*	*
20.	Kosič N. [16].	*	*	*	NP	*	*	*	*	*
21.	Levitan D. [28].	*	*	*	*	*	*	*	*	*
22.	Linehan L. [31].	*	*	*	NP	*	*	*	*	*
23.	Marton T. [72].	*	*	*	NP	NP	NP	*	*	*
24.	Rakheja D. [46].	*	*	*	NP	NP	NP	NP	*	*
25.	Rebutini PZ. [59].	*	*	*	*	*	*	*	*	*
26.	Şahin O. [24]	*	*	NP	*	*	*	*	*	NP
27.	Sharps M.C. [60].	*	*	*	*	*	*	*	*	*
28.	Smithgall M.C. [32].	*	*	*	*	*	*	*	*	*
29.	Surekha M.V. [47].	*	*	NP	*	*	*	*	*	NP
30.	Taglauera E.S. [35].	*	*	*	*	*	*	*	*	*
31.	Watkins J.C [25].	*	*	*	NP	*	*	*	*	*

Note: Authors - only the first author is listed; (-) – absent; ACE - angiotensin converting enzyme; NP - not presented; IHC – Immunohistochemical; PCR - polymerase chain reaction.

Of the 30 studies, 9 described the placentas in a narrative manner and, thus, 21 studies were selected for meta-analysis in which the pathological patterns of "Covid" placentas were not only descriptive in nature, but could also be assessed statistically and allowed for a meta-analysis . It should be noted that not all of these works described placentas fully complied with the requirements of APWGCS; information on the number of studies with this or that characteristic of histological patterns is presented in Fig. 2.

Taking into account the peculiarities of COVID-19 pathogenesis, the prevalence of thrombotic compli-

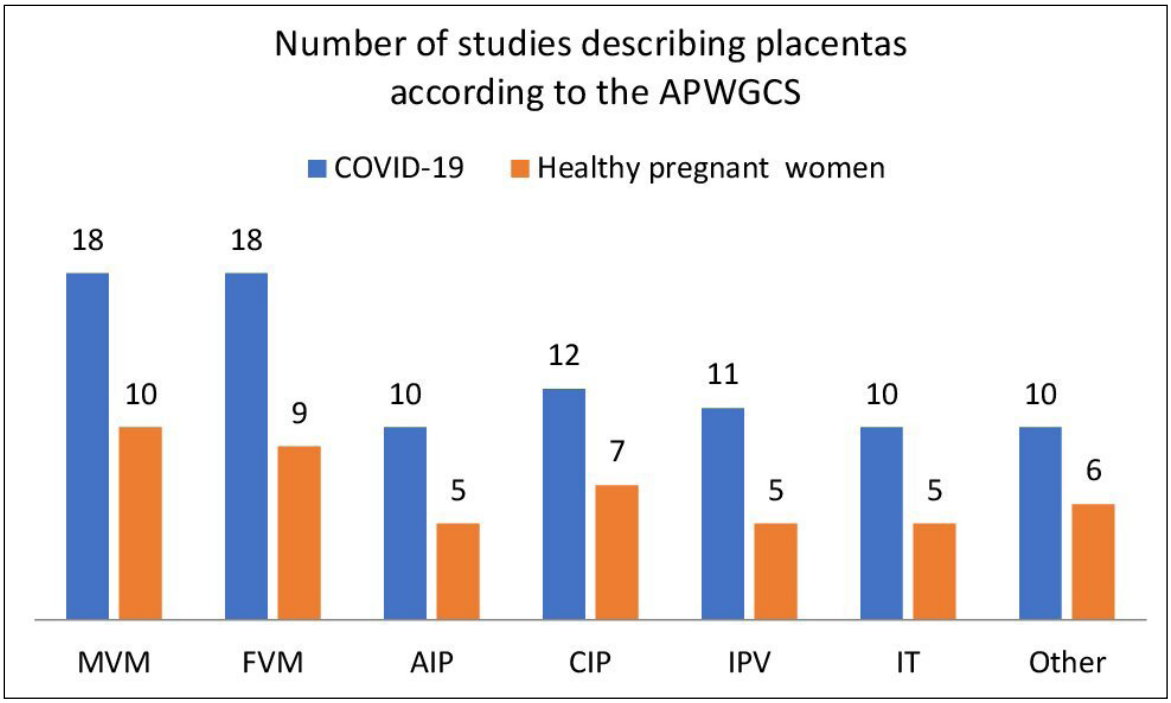

Fig. 2. Number of studies describing placentas according to the Amsterdam Placental Workshop Group Consensus Statement.
Note: MVM – maternal vascular malperfusion, including central villous infarction, peripheral villous infarction, villous agglutination, accelerated villous maturation, decidual arteriopathy (any atherosis and fibrinoid necrosis, mural hypertrophy of membrane arterioles, or absence of spiral artery remodeling), or retroplacental hematoma; FVM – fetal vascular malperfusion, including clustered avascular villi, fetal vessel mural fibrin, delayed villous maturation, hypercoiled umbilical cord, or chorioangiosis; AIP – acute inflammatory process, including maternal or fetal inflammatory response; CIP – chronic inflammatory process, including chronic villitis or low-grade chronic deciduitis with plasma cells; IPV – Increased perivillous fibrin; IT – Intervillous thrombosis. OTHER – including umbilical cord abnormalities, chorangiosis, hypertrophic arteriolopathy, subchorionic thrombus, a basal plate with attached myometrial fibers, microscopic accretism, villous edema, increased circulating nucleated red blood cells, or membranes with hemorrhage.

cations in the mechanisms of formation of multiple organ failure syndrome, such variants of the pathohistological characteristics of the placental complex as maternal vascular malperfusion (MVM), fetal vascular malperfusion (FVM), severe perivillous fibrin deposition (IPV) were identified for analysis, intervillous thrombus formation (IT). The category "other" - "OTHER" included umbilical cord anomalies, chorangiosis, hypertrophic arteriolopathy, edema of the villous space, hemorrhage into the fetal membranes, etc. Separately, inflammatory changes in the placental complex were described, which reflect the inflammatory response of the maternal body and intrauterine fetus (chorioamnionitis, chronic deciduitis, chronic villitis, etc.).

As for the results of immunohistochemical studies of "covid" placentas, they were presented in 24 of the 30 full-text papers selected for analysis (see Flowchart).

The main group of women who had COVID-19 during this pregnancy (pregnant women with a "Covid" history) consisted of 2581 participants; the control group included 2033 apparently healthy pregnant women who did not have any indication of SARS-CoV-2-associated acute respiratory viral infection (ARVI) or placentas that were studied before the COVID-19 pandemic.

The number of participants whose placentas were described "quantitatively", i.e. those where morphological and histological changes are described as a percentage, respectively, for the main and control groups were 2401 and 1910 (Table 3)

The distribution of the number of studies by type of study is presented in Table 4.

The most common pathological histological patterns of the placenta in the group of women with a "covid history" include, according to most of the studies presented, maternal vascular malperfusion (MVM) of the placental complex, the most recognizable pattern of placental damage associated with altered uterine and intervillous blood flow (Table 5).

Thus, MVM was detected 1.7 times more often ($t = 2.72766$, $p = .000447$, $RR = 5.29$, $OR = 7.98$.) than in healthy women; indications of these histological findings in placentas were described in 18 studies for the COVID-19 group, and in 10 studies for the control group. Significantly more often, 1.8 times ($t = 2.19492$, $p = .019041$), there was increased deposition of fibrinoid in the villous, perivillous and intervillous space of the placenta - (IPV - increased

Table 2 . General characteristics of the studies included in the systematic review

Author	Country	Study design	COVID-19 group	Control group	Conclusion
Adam A.M. et al.	Romania, 2023	**PCCS**	26	26	IHC analysis failed to demonstrate positivity for CD19, CD3, CD4, CD8, and CD56 markers. Immunophenotyping analysis could be useful for risk stratification of pregnant patients, while further studies are needed to determine the extent of immunological decidual response in patients with various forms of COVID-19.
Bertero L. et al.	Italy, 2021	**CCS**	11	58	Inflammatory and thrombo-hemorrhagic alterations were the most frequent and peculiar pathological changes we observed in our series compared to control samples, but only chronic villitis/VUE and accelerated villous maturation retained statistical significance after restricting the analysis to placentas delivered after a previous CS.
Boyraz B. et al.	USA, 2022	**RS**	67	126 GBS-colonized	Cases of COVID19 are covered patients' placentas and found no placentas with SARS-CoV-2 placentitis or evidence for viral infection by IHC. ... exposure to SARS-CoV-2 during pregnancy is associated with increased MVM and a trend toward associated increased FVM pathologies, which suggests that SARS-CoV-2 viral infection during pregnancy, even cleared, can have lasting effects on the placenta.
C. Tasca et al.	Italy, 2021	**PMCCS**	64	64	The presented evidence suggests that SARS-CoV-2 infection during the third trimester does not affect placental histology and morphology, nor causes obstetrical or fetal adverse outcomes.
Celik E. et al.	Turkey, 21	**PMCS**	31; 22 (73%) asymptomatic/ mild; 8 (27%) -moderate to severe/critical disease	NP	Placental inflammation can occur in mothers with SARS-CoV-2 infection. The disease severity is associated with ischemic placental pathology which may result in adverse pregnancy outcomes such as PTL and IGR. A high maternal inflammatory state is possibly contributing to placental insufficiency. The frequency of placental abnormalities is correlated with the severity of disease.
Corbetta-Rastelli C.M. et al.	CA, 2023	**DRCS**	131; mild - 60%.	138; 8 - twins	There was a higher frequency of placental features associated with response to infection before 20 weeks of gestation than that from infections after 20 weeks of gestation (P=.001). ... features of severe MVM were only found in the placentas of patients with SARS-CoV-2 infection in the 2d and 3d trimesters of pregnancy, not in the placentas of patients with COVID-19 in the 1st trimester. Placentas from patients with COVID-19 showed no specific pathologic feature, regardless of the timing or severity of the disease. There was a higher proportion of placentas from patients with COVID-19–positive tests in earlier gestations with evidence of placental infection–associated features.
Damman E. et al.	France, 2023	**RS**	96	NP	Traditional risk factors such as diabetes and obesity were not associated with severe placental damage. However, our results show that severe placental damage was significantly associated with IUGR, maternal hypofibrinogenemia and thrombocytopenia.
Edlow A.G. et al.	Boston, USA. 2020	**PCS**	44	44	This report of maternal viral load, transplacental antibody transmission, and placental pathology in 127 pregnancies during the SARS-CoV-2 pandemic provides needed data about maternal viral control, reduced transplacental transfer of anti–SARS-CoV-2 antibodies, and lack of vertical transmission in mother-neonate dyads.
Facchetti F. et al.	Italy, 2020	**CSS**	15	34	The detection of SARS-CoV-2 in the placenta of COVID-19, distributed in multiple fetal cell types, including circulating cells, combined with the failure to reveal SARS-CoV-2 S-protein expression, establishes the infrequent occurrence of mother-to-fetus SARS-Cov-2 transmission with adverse effects on the newborn.
Ferraz T. et al.	Canada, 2023 - 13 studies from 13 countries	**SR**	500	301	Maternal obesity and antenatal infection with SARS-CoV-2 influence placental health and together, could lead to worse outcomes for babies.
Gao L. et al.	China, 2021	**CSS**	8	NP	We found no evidence of vertical transmission and adverse maternal-fetal outcomes in the placentas of third trimester COVID-19 pregnancy women, which provided further information for the clinical management of those women in the third trimester. However, further studies are still needed for patients with infections in different stage of gestation, especially in first and second trimester.

Table 2. continuation

Giordano G. et al.	Italy	**CR**	5	Yes	Placental patterns in pregnancy due to COVID-19 in the late stage of gestation indicate no evidence of vertical trans-placental SARS-CoV-2 transmission or a significant impact on the perinatal outcome of newborns, in both mild and more severe cases.
Girolamo R. et al.	Italy, 2021	**SR** &**MA** (56 studies)	1008	Yes	...A large proportion of pregnancies complicated by SARSCoV-2 infection present placental histopathologic abnormalities consistent with placental inflammation and hypoperfusion, whereas approximately 17.5% of these pregnancies did not show any placental anomalies. Subgroup analyses according to the presence of maternal symptoms or high-risk pregnancy showed similar results with most placentas from women with SARS-CoV-2 infection in pregnancy
Glynn S.M. et al.	USA, 2022	**PCS**	90 Nonacute SARS-CoV-2 (N = 64); Acute SARS-CoV-2 (N = 26)	188	The frequency of FVM lesions is significantly higher among the placentas from women with acute SARS-CoV-2 infection compared with women with nonacute SARS-CoV-2 infection at delivery. These findings raise new questions regarding the etiology, clinical consequences, and potential downstream effects of FVM lesions in the setting of acute SARS-CoV-2 infection.
Gychka S.G. et al.	Ukraine, 2022	**CCS**	85; 68% - mild disease; 32% - severe disease	126	Placental vascular walls thickened and the lumen narrowed in women who gave live birth but contracted COVID-19 during pregnancy. Smooth muscle proliferation and collagen fiber deposition appear to play major roles in the development of placental vascular remodeling. Elucidating the mechanism of these events should help provide new therapeutic targets to combat COVID-19, and prevent stillbirth and premature birth, as well as alterations of child development.
Horn L.C. et al.	Germany, 2022	**CR**	2	NP	Sudden intrauterine death may occur in mothers who are oligosymptomatic for COVID-19. Acute placental failure is responsible for SIUD, demonstrated by massive perivillous fibrin deposits and extensive necroses of the villous trophoblast with SARS-CoV-2-positivity based on IHC staining and RT-PCR.
Hsu A.L. et al.	USA, 2021	**CR**	1	NP	This is the 1st report of placental COVID-19 despite mild COVID-19 disease in pregnancy: SARS-CoV-2 was found in the placenta, but the newborn was COVID-19 negative. Our case shows maternal vascular malperfusion, with no features of fetal vascular malperfusion. Evidence of placental COVID-19 raises concern for placental vasculopathy and potential vertical transmission.
Husen M.F. et al.	The Netherlands, 2021	**PMCS**	36 (33/3 twins); Active COVID-19 (N = 17) Resolved COVID-19 (N = 19);	NP	We described a unique placental signature with a specific presence of CD20+ B-cells clustering around the necrotic syncytiotrophoblast combined with chronic intervillositis and perivillous fibrin depositions, in pregnant patients with COVID-19 not seen in historic controls. We assume foetal well-being can potentially be threatened by an increased risk of histopathologic placental abnormalities resulting from a localised immunological response triggered by the presence of SARS-CoV-2 in the placenta. …We recommend SARS-CoV-2 PCR of maternal blood and vaginal fornix, to identify women at risk of placental infection with SARS-CoV-2 and to prevent negative pregnancy outcomes due to COVID-19.
Jaiswal N. et al.	India, 2021	**PAS**	27	27	Asymptomatic or mildly symptomatic SARS-CoV-2 positive pregnant women, with otherwise uncomplicated pregnancies, show evidence of placental injury at a microscopic level. The features of MVM, FVM and other features of placental inflammation are found more in the SARS-CoV-2 affected women when compared to controls. Although this dysfunction does not seem to result in poor fetal outcomes but may have adverse long term effects. This is an evidence that can't be ignored. A systemic nature of the disease and its ability to trigger a procoagulant state in the body may be responsible for the placental injury.
Kosič N,	Slovenia, 2023	**CR**	1	NP	Based on clinical, pathological, and microbiological correlation supported by specific histological findings and IHC staining, we conclude that the cause of fetal death in a woman with mild Covid-19 disease was acute placental failure triggered by SARS-CoV-2 infection.
Levitan D. et al.	USA, 2021	**CSS**	65	85	Our study results and a literature review suggest that there is no characteristic histopathology in most placentas from women with SARS-CoV-2 infection. Likewise, direct placental involvement by SARS-CoV-2 is a rare event.

Table 2. continuation

Linehan L. et al.	Ireland, 2021	**CR**	1	5	We present a case of third trimester pregnancy complicated by SARS-CoV-2 infection and subsequent reduced fetal movements, resulting in emergency CD with demonstrable placental SARS-CoV-2 placentitis. SARS-CoV-2 placentitis therefore appears to be an uncommon but distinctive complication of maternal COVID-19 infection and appears to have the potential to cause significant placental injury, potentially resulting in fetal compromise.
Marton T. et al.	UK, Birmingem, 2021	**CR**	1	NP	This case report supports maternal- fetal vertical transmission of SARS-CoV-2 virus. Our case gives insight in the morphology of SARS-CoV-2 placentitis that is observed in the most severe COVID-19 related pregnancy complication leading to intrauterine fetal death. The main components of SARS-CoV-2 placentitis are MPFD and CHI. IHC and ISH proved the vertical transmission of the virus infecting the chorionic epithelium of the placenta.
Rakheja D. et al.	USA, 2022	**CSS**	9	NP	We have described an IHC assay for SARS-CoV-2 nucleocapsid protein that is highly sensitive, specific, and robust, allowing routine use in placental pathology practice.
Rebutini PZ. et al	Brazil, 2021	**PCCS**	19 (10 - asymptomatic, 9 - symptomatic)	19 (gave birth before the pandemic)	Pregnant women with symptomatic SARS-CoV-2 infection are more likely to exhibit an adverse fetal outcome, with slightly more frequent histopathologic findings of MVM and FVM, and CHI. The morphometric changes found in the placentas of the COVID-19 group do not seem to be different from those observed in the Control group... Only the deposition of villous fibrin could be more accentuated in the COVID-19 group ($p = 0.08$ borderline)
Şahin O. et al.	Turkey, 2022	**PCCS**	30 - with asymptomatic COVID-19	30	The results demonstrated that asymptomatic COVID-19 had no significant effect on pregnancy and neonatal complications. However, mural hypertrophy in the placenta was found at a significantly higher rate in pregnant women with asymptomatic COVID-19. Although concerns about placental vasculopathy increase in COVID-19-positive pregnant women...
Sharps M.C. et al.	United Kingdom, 2022	**CCS**	28: 8-activ COVID-19; 20 – post-COVID-19	16	…There was no specific placental pathology associated with maternal SARS-CoV-2 infection during pregnancy. The observed increase in the number of placental macrophages warrants further investigation to see if these cells are responding to any possible maternal hypoxia affecting the placenta (which increases cytokine release from placental tissue).
Smithgall MC,	USA, 2020	**CSS**	51	25	In our limited study of 51 placentas from SARS-CoV-2-positive women in the third trimester, ISH and IHC showed no definite evidence of SARS-CoV-2 in the placentas, and we noted non-specific histomorphologic changes suggestive of maternal–fetal vascular malperfusion. All neonates tested negative for SARS-CoV-2, and all women recovered clinically. Further studies, including more sensitive techniques for viral infection (e.g. RT-PCR), are warranted.
Surekha M.V. et al.	India, 2023	**CSS**	122 -seropositive for SARS-CoV-2 IgG, but none reported COVID-19 history	90 (of the 212, 63.2% (n=134) women were anemic)	Although the prevalence of anemia was high in the present study, its effects on placentae were less prominent than that of SARS-CoV-2. The most intriguing and novel finding of the study was strong evidences that of maternal COVID-19 infection, which was otherwise asymptomatic, was being associated with increased placental damage, indicating histopathological features of placental hypoxia and thus possibilities of intrauterine fetal hypoxia.
Taglauera E.S. et al.	USA, 2021	**CCS**	16	8	These data suggest that in acute maternal SARS-CoV-2 infections, decreased placental ACE-2 protein may be the result of ACE-2 shedding. Overall, this work highlights the importance of ACE-2 for ongoing studies on SARS-CoV-2 responses at the maternal-fetal interface.
Watkins J.C. et al.	USA, 2021	**RS**	7 (6 from live-born neonates; 1- stillbirth.	NP	SARS-CoV-2 placentitis is defined by the triad of histiocytic intervillositis, perivillous fibrin deposition, and trophoblast necrosis. The features may occur in cases without confirmed transplacental transmission. The damage caused by SARS-CoV-2 placentitis is likely mediated by complement activation.

Note: ACE – angiotensin converting enzyme; CHI – Chronic Histiocytic Intervillositis; CR – case report studies; CCS – case control studies; CD – caesarean delivery; CSS – cross-sectional studies; DRCS – descriptive retrospective cohort study; FVM – fetal vascular malperfusion; GBS-colonized – group B streptococcus colonized; IGR –intrauterine growth retardation; IHC – immunohistochemical analysis; ISH - in-situ hybridization; MPFD – Massive Perivillous Fibrin Deposition; MVM - maternal vascular malperfusion; NP – not presented; PAS – prospective analytical study; PCS – prospective cohort study; PCCS – prospective, case-control study; PMCS – Prospective multicentre cohort study; RS – retrospective study; PTL – preterm labor; RT-PCR – Real-time polymerase chain reaction; SR – systematic review; SR&MA – systematic review and meta-analysis.

Table 3. Morphro-histological patterns of placentas in women whore covered from COVID-19 during pregnancy and in apparently healthy women (studies with a "quantitative" description of morphological and histological changes in the placenta)

Authors	Number of placentas examined		MVM, n / %		FVM, n / %		AIP, n / %		CIP, n / %		IPV (Increased perivillous fibrin), n / %		IT (Intervillous thrombosis), n / %		OTHER, n / %		NO patjology, n / %	
	COVID-19	Control	COVID-19	Control	COVID-19	Control	COVID-19	Control	COVID-19	Control	COVID-19	Control	COVID-19	Control	COVID-19	Control	COVID-19	Control
Boyraz B. et al.	67	126	(-)	(-)	11 /16,4%	(-)	(-)	(-)	14/20,9%	(-)	(-)	(-)	7/10.4%	(-)	4 /6%		NP	NP
C. Tasca C. et al.	64	64	17/26,6%	11 /17,2%	5 /7,8%	12 /18,8%	2/3,1%	1 / 1,6%	10/15,6%	7/10,9%	(-)	(-)	(-)	(-)	(-)	(-)	21/ 32.8%	27/42.2%
Corbetta-Rastelli C.M. et al.	131	0	83 /64%	(-)	16 /12%	(-)	37 /28%	(-)	19 /15%	(-)	(-)	(-)	(-)	(-)	(-)	(-)	30/ 23%	NP
Damman E. et al.	96	0	29 /15,5%	(-)	5 /2,4%	(-)	32 /16,7%)	(-)	16 /8,3%	(-)	(-)	(-)	(-)	(-)	(-)	(-)	101 /53,5%	NP
Edlow A.G. et al.	44	44	16 / 36%	8 / 18%	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	28 / 64%	NP
Ferraz T. et al.	500	301	314/ 62,85%	(-)	244 /48,7%	(-)	(-)	(-)	426 /85,2%	(-)	430 /86%	(-)	(-)	(-)	(+)	(-)	NP	NP
Gao L. et al.	8	0	8 / 100%	(-)	(-)	(-)	(-)	(-)	2 / 25%	(-)	7 /87,5%	(-)	(-)	(-)	2 /25%	(-)	NP	NI
Giordano G. et al.	**5**	0	4 /80%	(-)	4 /80%	(-)	1 /20%	(-)	5 /100%	(-)	(-)	(-)	3 /60%	(-)	(-)	NP	NP	NP
Girolamo R. et al.	**1008**	895	309 /30,7%	(-)	273 /27,08%	%	(-)	(-)	258 /25,65%	(-)	329 /32,7%	(-)	147 /14,6%	(-)	378 /37,5%	(-)	176 /17,5%	NP
Glynn S.M. et al.	**90**	188	25 /27,95%	45 / 24,1%	32 /36,05%	25 /13,2%	9 /9,71 %	12 /6,38%	9 /9,71%	13 / 6,9%	(-)	(-)	19 /21,5%	27 /14,4%	4 /4,45%	16 /8,35%	NP	NP
Horn L.C. et al.	**2**	0	(-)	(-)	(-)	(-)	(-)	(-)	2 /100%	(-)	2 /100%	(-)	(-)	(-)	(-)	(-)	NP	NP
Husen M.F. et al.	36	0	5 /12,82%	(-)	4 /10,26%	(-)	6 /15,38%	(-)	4 /10,26%	(-)	4 /10%	(-)	(-)	(-)	4 /10,26%	(-)	14 /39%	NP
Jaiswal N. et al.	**27**	27	10 /36,68%	3 /12,58%	7 /24,67%	2 /7,4%	8 /29,6%	3 /11,1%	(-)	(-)	26 /96,2%	6 /22%	3 /11,1%	(-)	5 /18,5%	1 /3,7%	NP	NP
Kosič N. et al.	**1**	0	(+)	(-)	(+)	(-)	(+)	(-)	(-)	(-)	(+)	(-)	(+)	(-)	(+)	(-)	(-)	NP
Levitan D. et al.	**65**	85	23 /35%	31 /36%	6 /9%	16 /19%	(-)	(-)	23 /35%	29 /34%	10 /15%	17 /20%	15 /23%	19 /22%	16 /25%	32 /38%	NP	NP
Rebutini PZ. et al	**19**	19	11 /56,6%	3 /15,7%	15 /78,9%	5 /26,31%	(-)	(-)	16 /84,21%	17 /89,5%	7 /36,8%	1 /5,26%	6 /31,05%	1 /5,26%	15 /78,9%	14 /73,7%	NP	NP
Şahin O. et al.	**30**	30	25 /83,3%	9 /30%	13 /43,3%	8 /26,7%	1 /3,3%	2 /6,7%	(-)	(-)	23 /76,7%	17 /56,7%	2 /6,7%	1 /3,3%	6 /20%	5 /16,7%	NP	NP
Sharps M.C. et al.	**28**	16	16 /57%	6 /34,5%	6 /21,4%	4 /25,5%	2 /6%	(-)	(-)	1 /6%	(-)	(-)	(-)	(-)	(-)	(-)	NP	NP
Smithgall M.C. et al.	**51**	25	17 /33,3%	9 /36%	9 /17,7%	3 /12%	(-)	(-)	2 /3,9%	2 /8%	(-)	(-)	8 /15,7%	7 /28%	14 /28%	2 /8%	NP	NP
Surekha M.V. et al.	122	90	47 /38,55%	14 /15,95%	68 /55,4%	38 /42,3%	77 /63,3%	36 /39,6%	17/14,25%	2 /2,75%	49 /40,3%	33 /36,3%	NP	NP	NP	NP	NP	NP
Watkins J.C. et al.	**7**	0	2 /28,57%	(-)	3 /42,85%	(-)	1 /14,28%	(-)	6 /85,7%	(-)	6 /85,7%	(-)	1 /14,28%	(-)	(-)	NP	NP	NP
Total	2401	1910	961 / 38,51%	139 / 7,27%	721 / 28,9%	113 / 5,91%	176 / 7,05%	54 / 2,82%	829 / 33,22%	71 / 3,71%	893 / 35,79%	74 / 3,87%	211 / 8,45%	55 / 2,87%	448 / 17,95%	70 / 3,66%	376 / 15,07%	27/ 42.2%

Note: AIP – including acute maternal or fetal inflammatory response; CIP – including chronic villitis or low-grade chronic deciduitis with plasma cells; IPV – increased perivillous fibrin; IT – intervillous thrombosis; MVM – maternal vascular malperfusion, including central villous infarction, peripheral villous infarction, villous agglutination, accelerated villous maturation, decidual arteriopathy (any atherosis and fibrinoid necrosis, mural hypertrophy of membrane arterioles, or absence of spiral artery remodeling), or retroplacental hematoma; FVM – fetal vascular malperfusion including clustered avascular villi, fetal vessel mural fibrin, delayed villous maturation, hypercoiled umbilical cord, or chorioangiosis; OTHER – including umbilical cord abnormalities, chorangiosis, hypertrophic arteriolopathy, SCT - subchorionic thrombus, a basal plate with attached myometrial fibers, microscopic accretism, villous edema, increased circulating nucleated red blood cells,or membranes with hemorrhage; NP - not presented; (+) – the description is narrative, signs are present; (-) – narrative description, no signs.

Table 4. Distribution of participants by type of study

Type of study	Number of study	Participants	
		COVID-19, n / %	Control, n / %
Case control study	4	141 / 5.9%	129 /6.75%
Case report	3	8 / 0.33%	0/
Cross sectional study	4	246 / 10.24%	200 / 10.47%
Descriptive retrospective cohort study	1	131 / 5.45%	0
Prospective analitycal study	1	27/ 1.12%	27 / 1.41%
Prospective cohort study	3	170 / 7.08%	232 / 12.14%
Retrospective study	3	170 / 7.08%	126 /6.59%
Systematic review	2	1508 / 62.8%	1196 / 62.61%
Total	21	2401	1910

Table 5. Comparative frequency of pathological histological patterns of the placenta in pregnant women who have recovered from COVID-19 and in healthy pregnant women.

Group / Indicator	COVID-19 group	Control group	P value (at p < .05)	CI
MVM, M ± m (SD), %, size 18 – 10	50.32 ± 25.29	30 ± 24.87	t = 2.72766. p =.00447	t = 4732, 95% CI 2869.86 - 6594.14
FVM, M ± m (SD), %, size 18 – 9	39.29 ± 26.84	28.28 ± 21.76	t = 1.4791 p = .072893	t = 1101, 95% CI-1028.38 - 3230.38
AIP, M ± m (SD), %, size 10 – 5	23.63 ± 20.83	30.1 ± 26.45	t = -0.72423 p=.237578	t = 2062, 95% CI -624.98 - 4748.98.
CIP, M ± m (SD), %, size 12 – 7	45.65 ± 33.67	35.38 ± 38.04	t = 0.83874 p =.203737	t = 1027, 95% CI -2374.63 - 4428.63
IPV, M ± m (SD), %, size 11 – 5	58.5 ± 29.43	33.12 ± 20.83	t = 2.19492 p =.019041	t = 2727, 95% CI -425.45 - 5879.45
IT, M ± m (SD), %, size 10 – 5	29.89 ± 22.66	21 ± 12.79	t = 1.03104 p=.156401	t = 777, 95% CI -1606.71 - 3160.71
Other, M ± m (SD), %, size 10 – 6	30.12 ± 25.91	35.55 ± 30.31	t = -0.50656. p = .308367	t = 543, 95% CI -2509.69 - 3595.69

Note: MVM – maternal vascular malperfusion, including central villous infarction, peripheral villous infarction, villous agglutination, accelerated villous maturation, decidual arteriopathy (any atherosis and fibrinoid necrosis, mural hypertrophy of membrane arterioles, or absence of spiral artery remodeling), or retroplacental hematoma; FVM – fetal vascular malperfusion, including clustered avascular villi, fetal vessel mural fibrin, delayed villous maturation, hypercoiled umbilical cord, or chorioangiosis; AIP – acute inflammatory process, including maternal or fetal inflammatory response; CIP – chronic inflammatory process, including chronic villitis or low-grade chronic deciduitis with plasma cells; IPV – Increased perivillous fibrin; IT – Intervillous thrombosis. OTHER – including umbilical cord abnormalities, chorangiosis, hypertrophic arteriolopathy, a basal plate with attached myometrial fibers, microscopic accretism, villous edema, increased circulating nucleated red blood cells, or membranes with hemorrhage. Size – number of studies that quantify placental patterns in pregnant women who have recovered from COVID-19 and in pregnant controls.

perivillous fibrin or fibrinoid), which may be due to hypercoagulation or degenerative processes. According to characteristics such as FVM, i.e. placental lesions associated with reduced or absent perfusion of the villous parenchyma of the fetus, as well as the frequency of intervillous thrombosis (IVT - Intervillous thrombosis), associated with the leakage of fetal blood into the intervillous space and further blood clotting, there were no significant differences between the groups. However, analysis of the probability and chance of developing FVM (RR = 4.88, OR = 6.46), acute (RR = 2.5,

Table 6. Course of pregnancy, perinatal outcomes and results of immunohistochemical study of "COVID-19" placentas.

Author	COVID-19 gruop	Control group	Maternal outcomes	Fetal outcomes	Gestational age at delivery	Comorbiduty	Complications of pregnancy	Immunohistochemical analysis of placenta
Adam A.M. et al.	26	26	PTL - 5 (19.2%) vs 2 (7.7%); OR 0.98 (0.96–1.00) p 0.22	Weight, g - 3151.92 ± 564.70 vs 3189.23 ± 406.08; AS - 5 min - 8.38 ± 0.63 vs 8.88 ± 0.58, OR 4.11 (1.211–13.974), p - 0.005; NICU -1 (3.8%) vs 0 (0%) OR 1.01 (0.98–1.05) 0.31	38.19 ± 1.91; 38.53 ± 1.10	DM- 1- 3,8% vs 0%, p - 0.31; Thrombophilia 4 (15.4%) VS 2 (7.7%), p-0.38; Lower limb varicose veins- 2 (7.7%) VS 1 (3.8%), p- 0.55	IGR 4 (15.4%) vs 2 (7.7%) OR 0.32 (0.03–3.12) p - 0.38	IHC demonstrate positivity for CD19, CD3, CD4, CD8, and CD56 markers
Bertero L. et al.	11	58	NP	1 neonatal nasopharyngeal swab was positive for the virus	4 - PTL, 6 - full-term, 1-twins (35 (30–38)	β-thalassemia - 2; CH -1, severe obesity (BMI: 50)-1, GD-1,	Polyhydramnios -1; Intrahepatic cholestasis of pregnancy -1	NP
Boyraz B. et al.	67	126- GBS-colonized	20 (29.8%) including tight/ wrapped nuchal cord, shoulder dystocia, and failure to progress; GBS.	Weight, g, 993-4555; 3202.1 ± 538.7	34.0 to 41.5 (mean = 39.0 weeks)	33 (49.2%) - GH, GDM, GBS infection, obesity, breast cancer, acute kidney injury, anemia, Coxsackie virus infection, Zika virus exposure, depression		SARS-CoV-2 spike (S) protein expression placentas
C. Tasca C. et al.	64	64	VD - 42 (65.6%) 35 (54.7%), CD - 20 (31.2%) 26 (40.6%), Vacuum-assisted VD - 2 (3.1%) 3 (4.7%)	Weight (g) - 3160.6 ± 449.4 3237.4 ± 479.5 0.309 AS at 5 minutes <7 0 (0%) 0 (0%) 1; NICU admission 1 (1.6%) 3 (4.7%) 0.310	≥34 weeks	ICP, GH, thyroid diseases, GDM	IUGR, PTL, PPH	NP
Celik E. et al.	31; 22 asymptomatic/ mild; 8 -moderate to severe/critical disease	NP	NP	AS - 5' less than 7, n (%) 1 (5)vs 2 (25); CNAO, , n (%) 2 (9)vs 3 (37) 0.09; SGA , n(%) 1vs 2; NICU admission, n(%) 3 (14) 4 (50) 0.06; Prematurity (CPAP), n(%) – 2 (25)	38.6 (37.9–38.8) vs 38.1 (31.8–38.8) 0.37	Comorbid conditions, 3 -(13.6%) vs 5 (62.5) p 0.02*;DM 1 vs1; Hypothyroidism 1vs 2; Asthma – 0 vs1;Epilepsy – 0 0vs1;	GDM - n (%) 2 (9) vs 2 (25); GH, n (%) – 0 vs 2 (25); GC, n (%) 1 (5) vs 0;	SARS-CoV-2 spike (S) protein expression placentas
Corbetta-Rastelli C.M. et al.	131	138, 8 -twins	CD - 54 (41.0); PTL - (<37 wk), n (%) 131 35 (27.0); Required blood transfusion-7 (5.3%); PA - 2 (1.5%); Umbilical cord or placental anomalies - 5 (3.8);	NICU admission, n (%) 135 47 (35.0); Composite neonatal morbidity, n (%) - 139 - 51 (37.0%); 10% - FGR; 9% - clinical CA; SGA n (%) 136 - 11 (8.0%);	38.6 (37.0–39.0)	BMI of >30 kg/m2 (n=55 [50%]), asthma (n=20 [15%]); CKD - 1 (0.8); IVF pregnancy-7 (5.3);	GH- 21, PE without severe features, 7- PE with severe features-15 , GDM - 20	NP
Damman E. et al.	96	NP	CD -mild covid - 28 (33%) vs severy- 8 (67%); PTL - 15 (18%) vs 11 (92%) <0.001; IUFD 1 (1.2%) vs4 (33%) <0.001; IUGR 7 (8.3%) 5 (42%) <0.01;	13 neonates (13.5%) had IUGR and 26 (27%)- PTL; 5 cases of IUFD. 24 neonates (25.0%) - NICU;	36 + 6 days	BMI - 25.8 (±6.0) kg/m2 and 18 patients (18.8%) had obesity.	14- (14.6%) - GD; PE 2 (2.4%); Anemia mild COVID - 51 (67%) vs severy - 4 (33%);	IHC - with anti-SARS-CoV-2 NcP performed in all 12 cases of severe placental damage; SARS-CoV-2 PCR tests - on extracted RNA in 9/12 cases and were all positive.
Edlow A.G. et al.	44	44	Composite morbidity - 2 (3) vs 9 (14) p=.03; CD - 39 (62)vs 21 (37); PPL - 5 (8) vs10 (18) .11; Spontaneous 2 (40) vs 3 (30) NA;	Composite morbidity - 5 (8) vs 14 (25) p=.01; FGR -1 (2) vs 4 (6) .06; ND -0 vs 2 (4), p= .16;	39.1 (38.3-39.7) 39 (37.4-40.1) .14;	CH- 1 (2) vs 3 (5), p .32; DM or GDM - 12 (19) vs 11 (17) .79; BMI >30 18 (29) 26 (41) .15; Asthma 8 (13) 7 (11).76; Thyroid disease 4 (6) 13 (21) .02; Cancer 2 (3) 2 (3) .99;	PE/ GH: 13 (21) vs 15 (26)	Placenta examined for expression of the SARS-CoV-2 receptor (ACE2) and the TMPRSS2; identified membranous syncytiotrophoblastic ACE2 expression.

Table 6. continuation

Facchetti F. et al.	15	34	Labor Induction - 5; TCP--1, PPH-2, PPP- -1, ARDS-2,CA - 1	NICU - 4; Severe neonatal morbidity: RDS - 1, HMD -2, . NEC - 1, NI-2, PI - 1. CH	32+6 - 41+3	HYT, CHB - chronic HBV hepatitis, OB - 4, ATH --1, HbC - 1; COL: cholestasis -1, CH -1	NP	IHC for the SARS-CoV-2 S-protein; for the inflammatory cells, Hofbauer cells, platelets and megakariocytes. Very few lymphoid T-cells (A, immunostain for CD3), B-cells (B, for CD20) occurred in the placenta.
Ferraz T. et al. -	CS -7 (participants -49); Cohort Series – 6 (participants - 451 COV+; 301 - COV-;	451	NP	Only weght	At term	Obesity-BMI ≥ 25.0 kg/m2 before conception	NP	NP
Gao L. et al.	8	NP	CD - 7; Indication for delivery - SARS-CoV-2;	AS -8-10; wegth - 2,17-3,55	3+6 -40+1	no	NP	IHC for inflammatory cells and Hofbauer cells, (SARS) CoV-2 RNA FISH and SARS-CoV-2 NcP. The list of primary antibodies was as follows: anti-CD3, anti-CD20, anti-CD163, anti-CD68, anti-CD138.
Giordano G. et al.	5	yes	At term	None of the newborns had signs or symptoms related to COVID-19, stayed with their mother (rooming-in), receiving breast milk, and were discharged on the 3rd day of life	Late pregnancy	GDM 1, HYT - 2.	(+)	Anti-CD3, anti-CD8, anti-CD20, anti-CD68 antibodies and CD15
Girolamo R. et al.	1008	да	NP	(+)	NP	Subanalyses of symptomatic women only and those with a high-risk pregnancy	(+)	(+)
Glynn S.M. et al.	97 - 90 placentas; Nonacute SARS-CoV-2 (N = 64); Acute SARS-CoV-2 (N = 26)	SARS-CoV-2 Negative (N = 188)	CD 20 (31.2%); 8 (30.8%); 95 (50.5%)	SGA, n (%) 11 (17.2); 2 (7.69); p= 0.333 37 (19.7);p=0.328; Weight, (g) 3082 ± 627 3190 ± 631 0.457 3048 ± 680 0.595; 5-minute AS, median (IQR) 9.00 [9.00-9.00] 9.00 [9.00-9.00] 0.604	37+2 - 39+6	DM, n (%) 2 (3.12); 0 (0.00);p >0.99; 8 (4.26);p= 0.880;	PE/GH, n (%) 5 (7.81) 3 (11.5) 0.686 33 (17.6) 0.132; GDM, 3 (4.69) 0 (0.00) 0.554 16 (8.51) 0.260; CA, 2 (3.12) 1 (3.85) >0.99 13 (6.91) 0.650;	SARS-CoV-2 spike NcP expression placentas
Gychka S.G. et al.	85	126.	68% - mild disease; 32% - severe disease accompanied by pneumonia	AS, 7.9 ± 0.4 7.7 ± 0.8	39+6	NP	Uncomplicated	Antibody against α-smooth muscle actin and Kv11.1 channel, was carried out.
Horn L.C. et al.	2	2- oligosymptomatic for COVID-19	NP	Sudden IUD in the 2-nd trimester; The female fetus of 730 g (20th percentile) and 24.4 cm crown-rump length (< 10th percentile). No malformations nor inflammatory changes were detected on autopsy.	15 + 2 and 27 + 3 weeks	NP	NP	IGH staining was strong and diffusely positive for SARS-CoV-2 in the villous trophoblast and rarely within the villous stromal cells. Placental SARS-CoV-2 infection was confirmed by RT-PCR.

Table 6. continuation

Hsu A.L. et al.	1	VD	NP	Newborn course was uneventful; AS of 8 and 9 at 1 and 5 minutes; Weight -3521 g (66th percentile); discharged home at 36 hours of life,	40-4/7 weeks for labor induction	NP	Uncomplicated	IHC was performed with SARS-CoV-2 - NcP specific rabbit monoclonal antibody; To identify trophoblasts, IHC was performed using rabbit recombinant anti-cytokeratin 7 (CK7) monoclonal antibody
Husen M.F. et al.	36 (33/3 twins); Active COVID-19 (n = 17) Resolved COVID-19 (n = 19);	NP	Maternal condition for emergency CD - 5 (13.9); Labour by induction 10 (27.8%); Spontaneous labour 1 (2.8); CD - 22 (61.2); Vaginal instrumental 1 (2.8) .	Breech position 3 (8.3); FD 7 (19.4) - for CS; SGA (BW < 10th percentile) 9 (23.1); AS <7 at 5 min, n (%) 5 (12.8); pH < 7.10, n (%) 2 (5.1) ;	PTL, n (%) total- 11 (30.6%) 9 (52.9) 2 (10.5) 0.01;	Comorbidities, n = 34 (%); Autoimmune disease total- 3 (8.3%); 1 (5.9%); 2 (10.5%) 0.88; GD - 6 (16.7) 5 (29.4) 1 (5.3) 0.15; HD - 2 (5.6) 0 (0.0) 2 (10.5) 0.39; Smoking, n = 25 (%) 3 (8.3) 2 (11.8) 1 (5.3) 0.68; Pre-pregnancy BMI, kg/m2, median (IQR) 28.8 (10.4%);	no	IGH markers CD3), CD20 and CD68 to visualise the location of respective T-cells, B-cells and macrophages.
Jaiswal N. et al.	27	27	CD 9(33.3) 4(14.8)	Still born 4(14.8) 6(22.2); AS (at 5 min) - 8 11(40.8) 7(25.9); 9 7(25.9) 12((44.5); 10 5(18.5) 2(7.4).	In days, 265.0±18.1 268.48±15.9;	no	Anemia 8(29.6) 7(25.9);	(+)
Kosič N,	1	NP	Maternal vital signs were normal. The postpartum course was unremarkable.	FD, was normally developed, weighing 1190 g and the length of 42 cm.	29 4/7	Controlled HYT and GDM	Uneventful until 28 2/7 weeks	SARS-CoV-2 spike (S) NcP expression placentas
Levitan D. et al.	65	85	PTL 12 (18%), 27 (32%), CD 20 (30%); 36 (42%). 59 (91%) - asymptomatic/ mild/moderate disease, and 6 (9%) had severe/ critical disease. CD (5 of 6 in critical disease). CD - asymptomatic/ mild/moderate SARS-CoV-2 infection (15 of 59).	IUFD occurred in both group	PTL - 12 (18%), 27 (32%),	DM - 2 (3%), 11 (13%). Obesity -34 (52%), 46 (54%)	PE - 9 (14%); 12 (14%).ICP - 5 (8%); P = .01	64 of the placentas IHC staining for SARS-CoV-2 NcP.
Linehan L. et al.	1	5	Emergency CD - distress	(+)	36+4 weeks	Stable HYT	No befor COVID	IGH: CD 68, CD3, CD20, CD138, RTU B-A38), Sars-CoV-2 (Covid-19) Spike Antibody.
Marton T. et al.	1	NP	23-year-old patient with high temperature and reduced fetal movements	Fetal death	25 + 5/40 weeks	Did not have other comorbidities	No befor COVID	CD68 positive histiocytes in the intervillous spaces and the villous trophoblast was positive for the COVID-19 spike protein
Rebutini PZ. et al	19 (10 - asymptomatic, 9 - symptomatic)	19 (birth before the pandemic)	PTL- 10, Term - 9; In the 2-d trimester, 2 woman died due to COVID-19 (1- with her infant 2d trimester)	Infant death - 3 - were positive for SARS-CoV-2 RNA in nasopharyngeal swab or umbilical cord blood samples	33,6 (23–38)	GH - 3, HYT - 4, GD - 4, obesity - 4, bipolar disorder -1, syphilis-1, Hyperthyroidism-1. Situs inversus totalis with metallic stent-1	(+)	To quantify Hofbauer cells (HC), the number of villi and CD68+ cells in those villi were counted in 30 high-power random fields

Table 6. continuation

Şahin O. et al.	30 - with asymptomatic COVID-19	30	CD - 24 (80,0%) vs 15 (50%), p=0,015; NICU - 7 (23.3%) vs 2 (6,7%), p=0,145; uterine atony - 1 (3,3%)vs 0; Maternal nasal O2 requirement 6 (20%) vs 0, p= 0.024	AS <7- 9 (15%), >7 - 51 (85%) vs 2 (6,7%) vs 28 (93,3), p= 0,071;	38+2 weeks	No comorbiduty	GDM - 1 (16,7%); Polyhydramnios 1 (3.3%); PRoM - 1 (3.3%).	NP
Sharps M.C. et al.	28: 8-activ COVID; 20 – post-COVID	16	CD - 4(50%), 11 (55%); control - 13 (81%).	Weight of the infants between groups: 3240 vs 3237 vs 3384 g. 1- recurrent reduced fetal movements; 1- in the control group RFM.	273-274 day	1 - DM, 1 - CH, 1 - HYT,	1- GDM	For the SARS-CoV-2 spike protein, CD163 for macrophages, CD3 for T lymphocytes, CD20 for B lymphocytes or CD31 for endothelial cells.
Smithgall MC,	51	25	CD- 25 (49.0) vs 15 (60.0), VD- 26 (51.0) vs10 (40.0), p= 0.47. Ascending IUI: Maternal response 17 (33.3) vs 9 (36.0), p= 1.00;	IUI: Fetal response 9 (17.7) vs 3 (12.0),p=0.74, no deaths	<37 10 (19.6) vs 4 (16.0), ≥37 41 (80.4) 21 (84.0), p=1,00	Yes - 21 (41.2) vs 12 (48.0), p=0.63; No -30 (58.8) 13 (52.0).	no	IHC with the monoclonal SARS-CoV-2 spike antibody 1A9 for placental evaluation.
Surekha M.V. et al.	122 -seropositive for SARS-CoV-2 IgG, but none reported COVID-19 history	90 (Of the 212, 63.2% (n=134) women were anemic)	Post-dated pregnancy (n=12), cephalopelvic disproportion (n=12), PROM (n=22), , Rh-ve pregnancy (n=8), meconium-stained liquor (MSL) (n=5)	Of 212 case - 3 cases of still births and 7 cases of spontaneous abortions. AS 1 min - 122 (6.20 ± 3.01) 92 (6.21± 3.11) 0.99; AS 5 min - 100 (9.43 ± 0.68) 74 (9.51± 0.58) 0.39	102 (38.22 ± 1.05) vs 78 (38.73 ± 5.82) 0.38	Overweight category (65.5 vs. 76.7%)	134 - anemia, PE (n=3), oligohydramnios (n=51), post-dated pregnancy (n=12), GH (n=2); placenta previa (n=1),	NP
Taglauera E.S. et al.	16	8	Maternal COVID severity – N (%) Hospitalized ICU-N/A 00 vs 1- 3d trim (12.5%)	3353 (459)vs 3453 (327) vs 3446 (411) 0.86; 5-minute APGAR – median (IQR)9 [8.75- 9.00] vs 9 [9- 9]vs 9 [9 - 9], p= 0.12; Required NICU admission – N (%) 1 (12.5%) vs 1 (12.5%) vs 0, p= 1	38.6 (0.9) 39.9 (1.1) 40.0 (1.9) 0.09	Maternal chronic health conditions – N (%)- 5 control (62.5%) vs 3 (37.5%) 2d COVID vs 4 (50%) 3d COVID, p= 0.87	Pregnancy complicationsb – N (%) - 5 (62.5%) vs 7 (87.5%)vs 8 (100%), p= 0.27.	ACE-2 expression, ADAM17 activity and serum ACE-2 abundance in a cohort of matched villous placental and maternal serum samples
Watkins J.C. et al.	7	NP	2 VD, 3 CD; indications spontaneous labor (1 case), PA (1 case).	Fdistress - (2 cases), 1 case - stillbirth. One neonate - complications of prematurity, all remaining neonates were well.	32 weeks - 39+2	Obesity - 1, GH - 1	Abruption -1	Expression of CD4, CD68

Note: ACE – angiotensin converting enzyme, AS – Apgar score, ATH - autoimmune thyroiditis, BMI – body mass index, CA – chorioamnionitis, CD – cesarean delivery, CH – chronic hypertension, CHB - chronic HBV hepatitis, CKD - chronic kidney disease, CNAO - composite neonatal adverse outcomes, COL – cholestasis, CS – case series, FD - foetal distress, FGR - fetal growth restriction, FISH - fluorescence In-Situ Hybridization, GBS – group B- Streptococc, GD – gestational diabetes, GCOL -gestational cholestasis, GDM – gestational diabetes melitus, GH – gestational hypertension, HbC - congenital Hemoglobinopathy, HD - Hypertensive disordersHMD - hyaline membrane disease, HYT - hypothyroidism; ICP – Intrahepatic Cholestasis of Pregnancy, IGH - Immunohistochemical analysis, ISH - in situ hybridization, IUFD – intrauterine fetal death, IUGR – Intrauterine Growth Restriction, IUI – intrauterine infection, NcP - nucleocapsid protein, ND - Neonatal death, NEC – necrotizing enterocolitis, NI – neonatal infection, NICU – Need for intensive care unit, PA – Placental abruption, PE – Preeclampsia, , PPH – postpartum hemorrhage, PPP- post-partum PE, PRoM - Premature rupture of membranes, PTL – preterm labor,RDS – respiratory distress syndrome, SGA – Small for gestational age, TCP- thrombocytopenia, TMPRSS2 - spike transmembrane serine protease 2, VD – Vaginal delivery.

OR = 2.61) and chronic (RR = 8.94, OR = 12.89) inflammatory process in the placenta, as well as the probability of fibrinoid deposition (RR = 9.24, OR = 13.83) and the formation of thrombosis in the intervillous space (RR = 2.94, OR = 3.12) were significantly higher in patients of the main group.

No pathological changes in the placental complex were found in 42±19.62142% of patients in the main group.

Information on perinatal outcomes and the main results of immunohistochemical studies of "covid" placentas is presented in Table 6.

Most of these works reflect a "simple" (conditionally) description of the search for the expression of the SARS-CoV-2 spike protein in placental tissue - 14 (58.33%) studies; 2 (8.33%) papers presented the results of a search for ACE2 receptors, as well as T and B cells of the immune system; 9 works (37.5%) studied the expression of immunocompetent killer cells (CD3, CD4, CD8, CD15, CD19, CD20, CD56, CD68, CD138, CD163. In addition, there are works (5 - 20.83%) that present search data for such cells of the inflammatory process, such as Hofbauer cells, platelets, megakaryocytes; as well as antibodies against alpha smooth muscle cells and cells encoding potassium channels (Kv11) (1 - 4.16%), T and B lymphocytes and macrophages (1 - 4.16%), ADAM-17 (1 – 4.16%)

DISCUSSION

The COVID-19 coronavirus disease pandemic, which began in 2019 in China, affected the entire world and the population of pregnant women involved in the pandemic was no exception, as pregnancy complications and negative perinatal outcomes were not uncommon [47, 48].

Due to the body's aggressive immune response to viral infection in the form of a potentially lethal massive "cytokine storm," COVID-19 is characterized by damage to a wide range of organs and tissues, which leads to various clinical conditions and multiple organ failure [49], incl. endothelial dysfunction and imbalance of pro- and anticoagulation potential of the blood. Within the wide range of pathological manifestations of COVID-19, the high probability of involvement of the utero-placental-fetal complex in the systemic process has attracted special attention. But no clear pathognomic signs were obtained during histopathological evaluation of placentas from women with SARS-CoV-2 viral infection [50].

Based on the results of this systematic review, we conducted a meta-analysis, which allowed us to describe the frequency of histological patterns of the placental complex, taking into account the recommendations of the Amsterdam Placental Workshop Group Consensus Statement (APWGCS, 2016).

MATERNAL VASCULAR MALPERFUSION OF THE PLACENTAL BED IN SARS-COV-2 INFECTION

Common findings most typical of MVM include placental hypoplasia, infarctions, and retroplacental hemorrhage. Microscopic signs include abnormalities in villous development in the form of distal villous hypoplasia or accelerated villous maturation. In most cases, etihistological patterns are not isolated [43]. Our meta-analysis showed that MVM is one of the significantly more frequent events in pregnant women with a "covid history" compared to the control group (38.5% vs7.27%; $F < 0.00001$, $p < .05$).

The information available in the literature regarding the frequency of MVM is extremely conflicting. Thus, according to Tasca S. etal., (2021), the frequency of MVM is only 6%: COVID-19 in the 3rd trimester does not affect the morphology of the placenta and does not cause adverse outcomes for the mother or fetus [22]. Gao L. et al. (2021), despite the presence of signs of MVM in 100% of cases (8 cases with a "covid history" in the 3rd trimester), found no evidence of vertical transmission and adverse outcomes for the mother and fetus [29]. Systematic review on the study of perinatal outcomes in pregnant women with impaired fat metabolism and Sars-CoV-2 infection, which was carried out by Ferraz T. etal. (2023), showed that MVM is observed in 62.85% of women and can lead to negative perinatal outcomes for the fetus. Levitan D. et al. (2021), when ascertaining MVM in the placental complex in 35% and 36% of women, respectively, in the main and control groups, they concluded that direct damage to the placenta is rare, and no pathognomic histological changes specific to COVID-19 infection were found in the placentas [28].

It is known that for most viral infections, overcoming the placental barrier and the development of a generalized inflammatory process with clinical and morphological manifestations is quite characteristic. The main barrier line for vertical transmission of infection is the layer of syncytiotrophoblasts.

The primary receptor of SARS-CoV-2 is angiotensin converting enzyme 2 (ACE2), which ensures the penetration of the virus into the cell and the implementation of its effects. The expression of ACE2 in the cells of the maternal-fetal interface is extremely pronounced: these are syncytiotrophoblast cells, cytotrophoblasts, endothelial cells and smooth muscle cells of the vessels of the primary and secondary villi, but the frequency of vertical transmission of infection, on the contrary, is low. A number of studies have shown the presence of the Sars-CoV-2 virus directly in the syncytiotrophoblast, but the fruits are not infected.

To assess the potential for non-respiratory transmission of SARS-CoV-2 coronavirus infection, Wang W.

et al. (2020), tested samples of bronchoalveolar fluid, sputum, feces, blood and urine of patients for viral RNA and found the following. The frequency of viremia in adults with symptoms of COVID-19 is only 1%, and the SARS-CoV-2 coronavirus is most often detected in fluid bronchoalveolar lavage (93%), sputum (72%), nasal (63%) and pharyngeal swabs (32%). This information highlights the importance and uniqueness of the placental barrier, where maternal and fetal bloodstreams meet and do not mix. between themselves. That is, the probability of infection of the intrauterine fetus by the transplacental hematogenous route is the lowest compared to other routes, which, in our opinion, is a possible explanation for the high frequency of MVM without subsequent infection of the fetus.

FETAL VASCULAR MALPERFUSION IN SARS-COV-2 INFECTION

The main features of FVM include thrombosis, segmental avascular villi, and villous stromal karyorrhexis; Intramural deposition of fibrin in vessels, obliteration of stem vessels, fibromuscular sclerosis and vascular ectasia are also possible. FVM may be segmental due to thrombotic occlusion of chorionic or truncal villous vessels or obliteration of truncal vessels. In global FVM, there is partial obstruction of umbilical blood flow with venous ectasia, intramural fibrin deposition in large vessels, and/or small foci of avascular or karyorectic villi. Obstruction in this case is partial or intermittent, but lesions can spread to most of the placenta up to intrauterine fetal death [43].

According to our review, the frequency of detection of FVM in "covid" placentas ranges from 2.4% (Damman E. et al., 2023) to 78.9% (Rebutini P Z. et al., 2021). If we talk about a comparative analysis of the placentas of a population of healthy women who gave birth (control group) and women who had COVID-19 during pregnancy, FVM was detected in 5.91% (113 cases) vs 28.9% (721 cases) respectively. ($F<0.00001$, $p<.05$).

The results of a number of cohort studies show the following frequency of FVM according to the groups: Glunn S.M. et al. (2022) – 13.2% vs 36.05%, Jaiswal N. et al. (2021) – 7.4% vs 24.67%, Surekha M.V. et al. (2023) – 42.3% vs 55.4%, Sharps M.C. et al. (2022) – 25.5% vs 21.4%. Glunn S. M. notes a higher incidence of fetal vascular lesions in women with symptomatic COVID-19 compared to women with a non-acute form of the disease; according to the authors, this only raises new questions regarding the mechanisms of etiology and clinical consequences of the disease.

According to Rebutini P. Z. et al. (2021), signs of FVM in pregnant women with symptomatic COVID-19 are detected 3 times more often than in women with asymptomatic coronavirus infection (78.9% vs26.31%), but at the same time, compared with the control group of healthy women, morphometric changes there were no pronounced differences in the placenta. Only a significant difference was noted in the frequency of fibrinoid deposition in placental tissues.

Sharps O. et al. (2022) determined the frequency of FVM to be 21.4% and 25.5%, respectively, in the COVID-19 group and the group of healthy postpartum women and concluded that there are no specific Sars-CoV-2-associated changes in the placenta, and the observed increase in the number of placental macrophages may be their response to any possible maternal hypoxia, which increases the release of cytokines in the placental tissue.

Data from our meta-analysis show that FVM is almost 4 times more common in the population of pregnant women with coronavirus infection than in women without a "covid" history, but there is no significant difference between the main and control groups. We emphasize that the histological patterns in the studied placentas are not isolated; in most cases, there is a combination of lesions in both the maternal and fetal bloodstreams.

FVM is a term coined in 2015 by the Amsterdam International Consensus Placenta Pathology Group to characterize a group of non-acute vascular lesions in the placental-fetal circulation [34]. These include various variants of vasculopathies in the fetus of polyetiological origin (parietal and occlusive thrombi, extensive areas of avascular villi, hemorrhagic endovasculitis, thrombosclerosis, fibrinous vasculosis, etc.), which were described in the literature in connection with significant clinical morbidity and mortality of intrauterine fetuses. It is likely to assume that in the conditions of SARS-CoV-2 - associated DIC syndrome, the risk of involvement of the fetal bloodstream in the inflammatory process due to blood stasis, hypercoagulation and endotheliopathy may be a natural process. It is likely that this particular histological pattern of placental changes in pregnant women with a "covid" history may explain the frequency of intrauterine fetal death in these women.

Thus, the high frequency of FVM in its "classical" manifestations in the population of women with coronavirus COVID-19 infection, which our meta-analysis showed, despite the lack of any specificity, is reliable ($F<0.00001$, $P<.05$). However, further research is needed to identify possible specific disorders of coagulation potential and endothelial dysfunction specifically in pregnant women with SARS-CoV-2-associated acute respiratory viral infection.

INFLAMMATORY FINDINGS IN "COVID-19" PLACENTA AS PART OF MATERNAL / FETAL VASCULAR MALPERFUSION

Inflammatory pathological patterns of the placenta or, according to APWGCS, ascending intrauterine infection are of important clinical significance, and its correct documentation is a necessary characteristic of clinical pathology. Histological chorioamnionitis may not be equivalent to clinical chorioamnionitis. The topography and chronicity of the inflammation focus is important, since negative perinatal outcomes are most often associated with the inflammatory reaction of the fetus [43]. Currently, the histological description of acute inflammation in the placenta, extraplacental membranes and umbilical cord is recommended to be designated as acute chorioamnionitis (or acute chorionitis) with or without fetal inflammatory reaction in the chorionic vessels, umbilical vein and/or umbilical artery. Some pathologists may prefer to use the terms "maternal".

In a systematic review that was presented by Hessami K. et al. (2022), it was shown that there are no significant differences in the frequency of maternal (maternal inflammatory response - MIR - OR: 0.66, 95% CI: 0.29–1.52) or fetal inflammatory response - FIR (OR: 0.85, 95% CI: 0.44–1.63), as well as chronic inflammatory lesions (CILs - OR: 0.97, 95% CI: 0.55–1.72) in the placentas of pregnant women with symptomatic or asymptomatic COVID-19.

According to Giordano G. et al. (2022), a report on a series of cases of COVID-19 in pregnant women showed that inflammatory lesions in the form of an acute process (chorioamnionitis) were observed in 20%, and chronic villitis in 100%. It is the chronic aspect of the inflammatory process that is emphasized, but this was not accompanied by vertical transmission of the virus and a significant effect on perinatal outcomes. Horn L.C. et al. (2022), when studying placentas in 2 cases of sudden intrauterine fetal death, revealed a picture of a chronic inflammatory process, despite the asymptomatic course of COVID-19 in these patients. They also noted massive perivillous fibrin deposition and extensive trophoblast necrosis.

Levitan D. et al (2021) reported no differences in the frequency of signs of chronic inflammation in the group of pregnant women with COVID-19 (35%) and the control group (34%); they suggest that there is no direct involvement of the placenta in the systemic process in pregnant women with a "Covid" history [28]. Boyraz B. et al. (2022 – 9%), Damman E. et al. (2023 –– 8.3%), Husen M. F. (2021 – 10.26%) note signs of chronic inflammation in "covid" placentas ranging from 9% to 10.26% and these data did not have significant differences with the control group [30].

There is also contrary information in the literature about the inflammatory component in "Covid" placentas. This is shown in the works of Ferraz T. et al. (2023), Rebutini P. Z. (2021 – 84.21%), Watkins J. C. (2021 – 85.7%), where the frequency of the inflammatory process is more than 80% [25].

According to our review and meta-analysis, signs of acute inflammatory damage to the placenta were found in 7.05% versus 2.82%, and chronic - in 33.22% versus 3.71% of women from the compared groups ($F<0.00001$, $p<.05$).

It should be noted that information about the acute inflammatory process in the placenta, in particular about chorioamnionitis, is extremely contradictory. Thus, the frequency of this pathology ranges from 3.1% (C. Tasca C., 2021) to 63.3% (Surekha M. C. et al., 2023) [22, 47].]. Research by Surekha M. C. (India, CSS) demonstrates a high incidence of acute inflammation in "Covid" placentas compared to a group of anemic pregnant women [37]. The authors note that even oligosymptomatic/asymptomatic maternal COVID-19 infection was associated with more frequent placental damage and this may indicate histopathological features of placental hypoxia and the likelihood of intrauterine fetal hypoxia [47].

We assume that with COVID-19, the placental-fetal complex is involved in the systemic inflammatory process to a greater or lesser extent, is nonspecific in nature, and depends on both the severity of SARS-CoV-2 infection and the comorbid status of the patient.

PERIVILLOUS FIBRIN DEPOSITION IN "COVID-19" PLACENTA AS PART OF FETAL VASCULAR MALPERFUSION

According to the APWGCS (2015) guidelines, fibrin deposition can be subendothelial or intramuscular (intramural) and is part or manifestation of global FVM. These deposits are not occlusive in nature, they are localized in the wall of large fetal vessels, and calcification is possible. The significance of detecting isolated intramural fibrin deposits remains unclear [43]. Small amounts of fibrin are usually detected in normal placenta during physiological pregnancy. The pathohistological picture is characterized by a diffuse increase in the amount of perivillous fibrin, which surrounds the terminal villi and the main stem. The basis of the architectonics of these disorders is the infiltration of placental tissue by maternal immune cells and a decrease in the area between the villous space, which can lead to a deterioration in the perfusion abilities of the placenta and gas exchange with the development of corresponding complications of pregnancy (IUGR,

preterm birth, oligohydramnios, neurological disorders and fetal death ch.).

The pathohistological pattern in the form of intervillous fibrin deposition in "covid" placentas, according to our review, is a significantly common occurrence and occurs in 35.79% of women with a "covid" history versus 3.87% in the control group (F<0.00001, p<.0.5).

According to the literature, the frequency of fibrin deposition in the placentas of women with a "covid" history ranges from 10% (HusenM.F. etal., 2021) to 96.2% (Jaiswal N.et al., 2021). Husen M. F. et al. (2021) identified a specific cluster deposition of CD20+ and B cells around necrotic syncytiotrophoblast in combination with chronic intervillositis and perivillous fibrin deposits in pregnant women with a "covid" history, which was not observed in historical control studies. The authors believe that this localized immunological response in the placental tissue may be due to the presence of SARS-CoV-2 in the placenta and poses a potential danger to the fetus.

There is evidence that the only pathological sign found in "Covid" placentas is an increase in perivillous fibrin deposition -PVFD. Sahin O. et al. (2022), when studying placentas in pregnant women with symptomatic and asymptomatic COVID-19, they determined the frequency of perivillous fibrin deposition as 76.7% vs 56.7%; parietal hypertrophy in placental tissue was found significantly more often in pregnant women with asymptomatic COVID-19 [24].

Watkins J.C. et al. (2021) during a retrospective study of placentas of women with a "Covid" history, incl. and a case of stillbirth, determined that SARS-CoV-2-associated placentitis is characterized by histiocytic intervillositis, perivillous fibrin deposition and trophoblast necrosis. The incidence of perivillous fibrin deposition was 85.7%. The authors believe that these placental features can occur in cases without confirmed transplacental transmission of coronavirus infection, and placental damage is likely mediated by complement activation [25].

INTERVILLOUS THROMBOSIS IN "COVID-19" PLACENTA AS PART OF MATERNAL / FETAL VASCULAR MALPERFUSION

Thrombosis of the intervillous space can be both arterial and venous, and also have different localization, which significantly affects the clinical picture of placental dysfunction [43].

As a result of our review and meta-analysis, we found that the frequency of thrombosis of the intervillous space in "covid" placentas is 6.7% (SahinO., 2022) – 60% (GiordanoG. etal., 2021), while in the group of women without "covid""Anamnesis ranges from 3.3% (SahinO., 2022) to 28% (Smithgall M.C. et al., 2020) [24, 32].

According to a systematic review by Giordano G. et al. (2021), thrombosis is detected in 60% of placental samples, but this pattern is not specific to COVID-19 and does not have a significant impact on perinatal outcomes [66]. Boyraz B. et al. (2022) found that thrombosis is detected in every tenth "covid" placenta (10.4%). There were no placentas with SARS-CoV-2-associated placentitis or evidence of viral infection by immunohistochemistry; the authors suggest that after eliminating the acute inflammatory reaction, persistent infection or chronicity of the process does not occur. However, there has been an increase in the incidence of MVM followed by fetal reaction and FVM with long-term consequences for the fetus. This suggests that the currently existing concept of "long COVID" may also have applied significance to SARS-CoV-2-associated pathology of the placenta.

As for the population frequency of intervillous thrombosis in placentas, according to our data, they are 3 times more likely to accompany a "covid" history in women who have given birth and amount to 8.45% (211 pregnant women) vs 2.87% (55 pregnant women) (F<0.00001, p<. 05).

Taking into account the pathogenetic mechanisms of the development of COVID-19 - the associated syndrome of multiple organ failure and, in particular, disturbances in the coagulation potential of the blood towards hypercoagulation, it is likely and logical to assume that the placenta should become a target for the SARS-CoV-2 virus. In reality, literature data do not support this assumption.

A possible explanation for this fact may be, firstly, the rare involvement of the placenta in the specific SARS-CoV-2 infectious process [28, 29]. Secondly, the placenta is an independent metabolic and hormonal unit of the body, a place of synthesis and implementation the effects of a huge number of enzymes, hormones, biologically active substances. So, for example, a peptidase was found in the placental cyto- and syncytiotrophoblast - aminopeptidase A (L-α-aspartyl-(L-α-glutamyl)-peptide hydrolase, angiotensinase A or glutamyl aminopeptidase, which was isolated biochemically, and its angiotensinase activity is confirmed. This enzyme converts angiotensin II into angiotensin III and its activity increases as pregnancy progresses, which may suggest its participation in reducing the vascular pressor response to angiotensin II in pregnant women. This suggests that angiotensinase A may be a specific counterfactor that promotes the conversion of angiotensin II into the less active metabolite angiotensin III, i.e., thus neutralizing the effect of the promoter of the

SARS-CoV-2 virus - ACE 2. This conclusion is an assumption and requires further research.

Considering that endothelial dysfunction is one of the known mechanisms for the implementation of SARS-CoV-2 - an associated systemic inflammatory response, it seems appropriate to study the interaction of such endothelium-dependent biological messengers of intercellular interaction as prostacyclin, nitric oxide (NO), etc., the synthesis of which is also carried out directly in the placenta; in particular, studies are presented on the role of nitric oxide in the pathogenesis and therapeutic direction of COVID-19.

The correlation between the severity of respiratory viral diseases and NO levels has been known since the H1N1 influenza pandemic, which has led to speculation about the possible effectiveness of NO in COVID-19. Studies have appeared that have confirmed this effectiveness. Possible mechanisms that can neutralize the pathogenic effect of the SARS-CoV-2 virus, incl. in the placenta, there may be vasodilating, direct antiviral and antithrombotic effects of NO.

Thus, we can say that a number of enzymes and biologically active messengers of intercellular interaction are synthesized directly in the placenta, in particular, angiotensinase A and nitric oxide, the activation of which can "strengthen" the placental barrier for the SARS-CoV-2 coronavirus.

OTHER FINDINGS IN "COVID-19" PLACENTA

According to the APWGCS, the concept of "other" pathological changes in the placenta includes an increase in fibrinoid islands with extravillous trophoblast (so-called X-cells), placental pseudocysts, chorionic pseudocysts and membranous decidual necrosis, which cannot be fully characterized as MVM due to the lack of sufficient evidence base [43], but, nevertheless, it is recommended to describe them, which may facilitate further research.

Some researchers have included in this category umbilical cord abnormalities, chorangiosis, hypertrophic arteriolopathy, changes in the basal plate with attached myometrial fibers, microscopic accretism, villous edema, increased circulating nucleated red blood cells or membranes with hemorrhage [28, 29, 32].

According to our meta-analysis, in the population of pregnant women with a "covid" history, the average frequency of detection of "other" placental damage was 17.95% vs 3.66% in the control group ($F<0.00001$, $p<.05$) with fluctuations from 6% (Boyraz B., 2022) up to 78.9% (Rebutini P.Z., 2021). In our opinion, such variability of this indicator emphasizes the lack of specific, pathognomic histological patterns in "Covid" placentas, as well as a unified approach to describing the identified histological patterns - APWGCS recommendations are not always taken into account, which significantly complicates the analysis and interpretation of the results obtained.

CONCLUSIONS

According to currently available studies, in the placentas of women who have had COVID-19 during pregnancy, there are no pathognomic histological patterns specific to this infection and direct damage to the placenta is rarely observed. The probability of infection of the intrauterine fetus by the transplacental hematogenous route is the lowest compared to other routes, which, in our opinion, is a possible explanation for the high frequency of MVM without subsequent infection of the fetus.

Histological patterns in "covid" placentas are not isolated; in most cases there is a combination of lesions in both the maternal and fetal bloodstreams.

The high frequency of FVM in its "classical" manifestations in the population of women with coronavirus COVID-19 infection, despite the lack of any specificity, is reliable. It is likely that the placental-fetal complex in COVID-19 is involved in the systemic inflammatory process to a greater or lesser extent, is nonspecific in nature, and depends on both the severity of SARS-CoV-2 infection and the comorbid status of the patient.

The currently existing concept of "long Covid" may also have applied significance to SARS-CoV-2, an associated pathology of the placenta. It is likely that the activation of a number of enzymes and biologically active messengers of intercellular interaction, in particular, angiotensinase A and nitric oxide, which are synthesized directly in the placenta, can help "strengthen" the placental barrier and prevent the penetration of the SARS-CoV-2 coronavirus.

The variability of various histological patterns in "Covid" placentas emphasizes their lack of specificity, and also reflects the lack of a unified approach to describing the identified histological patterns - APWGCS recommendations are not always taken into account or are not fully taken into account, which significantly complicates the analysis and interpretation of the results obtained.

Further research is needed to identify or deny specific pathohistological changes in the placenta in pregnant women with SARS-CoV-2 associated infection, which may possibly contribute to the development of certain directions for the prevention of pregnancy complications and improvement of perinatal outcomes.

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CONFLICT OF INTEREST
The Authors declare no conflict of interest

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A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval of the article

RECEIVED: 21.11.2023
ACCEPTED: 27.02.2024