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Histopathological evaluation of placentas after diagnosis of maternal SARS-CoV-2 infection.

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Histopathologic evaluation of placentas after diagnosis of maternal severe acute respiratory syndrome coronavirus 2 infection

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BACKGROUND: The impact of maternal severe acute respiratory syndrome coronavirus 2 infection on placental histopathology is not well known.

OBJECTIVE: To determine if any significant placental histopathologic changes occur after the diagnosis of severe acute respiratory syndrome coronavirus 2 infection during pregnancy and whether these changes are correlated with the presence or absence of symptoms associated with the infection.

STUDY DESIGN: A retrospective cohort study of women diagnosed as having severe acute respiratory syndrome coronavirus 2 infection who delivered at a single center from April 9, 2020 to April 27, 2020, and had placental specimens reviewed by the Department of Pathology. Women with singleton gestations and laboratory-confirmed severe acute respiratory syndrome coronavirus 2 infection were eligible for inclusion. Historical controls selected from a cohort of women who delivered 6 months before the study period were matched in a 1:1 fashion by weeks of gestation at delivery. Histopathologic characteristics were evaluated in each placenta, and the incidence of these findings was compared between placentas of those who received a diagnosis of maternal severe acute respiratory syndrome coronavirus 2 infection and historical controls, and between placentas from patients with or without typical symptoms related to the infection. Statistical analyses included the use of Wilcoxon rank-sum test and Fisher's exact test for the comparison of categorical and continuous variables. Statistical significance was defined as a *P* value of $<.05$.

RESULTS: A total of 50 placentas after the diagnosis of maternal severe acute respiratory syndrome coronavirus 2 infection and 50 historical controls were analyzed. Among the placentas from patients diagnosed with severe acute respiratory syndrome coronavirus 2 infection, 3 (6%) were preterm (33 3/7, 34 6/7, and 36 6/7 weeks of gestation), 16 (32%) were from patients with typical symptoms related to the infection, and 34 (68%) were from patients without typical symptoms related to the infection. All patients had received a diagnosis of severe acute respiratory syndrome coronavirus 2 infection in the third trimester. Decidual vasculopathy was not visualized in any of the placentas from patients diagnosed as having severe acute respiratory syndrome coronavirus 2 infection. There was no statistically significant difference in placental histopathologic characteristics between the groups. Severe acute respiratory syndrome coronavirus 2 test results for all neonates at 24 hours of life were negative.

CONCLUSION: Based on the results of this study, there are no significant placental histopathologic changes that occur after the diagnosis of severe acute respiratory syndrome coronavirus 2 infection in women during the third trimester of pregnancy compared with a gestational age—matched historical control group. Similar incidences of histopathologic findings were also discovered when comparing placentas from patients with severe acute respiratory syndrome coronavirus 2 infection with or without the presence of symptoms typically related to the infection.

Key words: coronavirus, coronavirus disease 2019, decidual vasculopathy, fetal vascular malperfusion, histopathology, maternal vascular malperfusion, placental pathology, thrombosis, thrombotic vasculopathy, thrombus

Introduction

Since the World Health Organization declared the outbreak of the novel coronavirus (severe acute respiratory distress syndrome coronavirus 2 [SARS-CoV-2]) a global pandemic, there have been approximately 7 million confirmed infections and 400,000 deaths worldwide.[1] Contemporaneous with the rapid rate of increase in infections, rigorous research efforts exploring the impact of this novel virus in pregnancy have been initiated. Several adverse pregnancy outcomes in women with SARS-CoV-2 infection have been reported thus far, including miscarriage,[2,3] intrauterine fetal demise,[4] preeclampsia,[5,6] preterm delivery,[7–9] maternal critical illness[7–10] and death,[4] and neonatal death.[11,12] Evidence regarding the occurrence of antepartum or peripartum vertical transmission has been conflicting to date.[13–17]

The placenta represents a highly specialized organ that is crucial for maintaining an optimal environment for fetal development.[18,19] Placental evaluation after delivery provides useful information such as the identification of disease processes in the mother or infant that require attention or diagnoses that provide a specific explanation for an adverse outcome.[20] Characteristic histopathologic findings in placentas from mothers with viral infections have been reported.[21–24] However, reports on placental evaluation in women with SARS-CoV-2 infection have been limited to a few case series,[25–28] and the association between infection and abnormal placental findings are not well known. Therefore, the objective of this study was to determine if any significant placental histopathologic changes occur after the diagnosis of SARS-CoV-2 infection in pregnancy and whether these changes are correlated with the presence or absence of symptoms typically related to the infection.

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AJOG MFM at a Glance

Why was this study conducted?

The association between maternal severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and placental histopathology is not well known. This study aimed to determine if any significant placental histopathologic changes occur after the diagnosis of the SARS-CoV-2 infection during pregnancy and whether these changes are correlated with the presence or absence of symptoms typically related to the infection.

Key findings

Our study did not reveal significant placental histopathologic changes that occur after the diagnosis of SARS-CoV-2 infection in women during the third trimester of pregnancy compared with a gestational age—matched historical control group. There was no difference in the placental histopathologic findings when placentas from the patients were compared after the diagnosis of SARS-CoV-2 infection with or without the presence of symptoms typically related to the infection.

What does this add to what is known?

The results of this study add to the limited existing literature regarding placental histopathologic changes associated with SARS-CoV-2 infection and suggest that pregnancy with maternal SARS-CoV-2 infection may be managed based on the clinical findings alone, whereas findings from placental pathology warranting increased or different surveillance were not indicated.

Methods

This was a retrospective cohort study with historical controls. Cases included placentas from women who were diagnosed as having SARS-CoV-2 infection and delivered at a single center (Long Island Jewish Medical Center, Northwell Health, Queens, NY) from April 9, 2020 to April 27, 2020 (during the peak of the pandemic in New York). The Northwell Health Institutional Review Board approved this study as minimal-risk research using data collected for routine clinical practice and waived the requirement for informed consent. Women with singleton gestations who had received a laboratory-confirmed diagnosis of SARS-CoV-2 infection during their pregnancy were eligible for inclusion. The diagnosis of SARS-CoV-2 infection was confirmed using a qualitative real-time polymerase chain reaction (PCR) on maternal nasopharyngeal swab specimens. Before the study period, universal testing for SARS-CoV-2 infection had been implemented for all obstetrical patients admitted to labor and delivery. After delivery, the placentas were submitted to the Department of Pathology for evaluation. Placentas from women with high clinical suspicion for placenta accreta diagnosed during the antepartum period on either ultrasound or magnetic resonance imaging were excluded. Placental specimens from cases with accreta had a morbidly adherent uterus. Therefore, several gross examination characteristics, such as placental weight, could not be obtained, and standardized sampling of each placenta for the histologic evaluation would not be consistent with that of other placentas in the study.

Historical controls were selected from a cohort of women who had placentas submitted to the Department of Pathology (including specimens obtained from delivery at North Shore University Hospital, Northwell Health) during November 2019—at least 3 months before the first reported case of SARS-CoV-2 infection in New York. The decision for pathologic examination at that time was at the discretion of the delivery physician. However, the suggested criteria provided by the Department of Pathology were generally consistent with the College of American Pathologists guidelines.[29] Historical controls were used because placentas from patients who received negative test results for SARS-CoV-2 infection during the study period may not have represented an appropriate control group owing to the reported high false-negative rates.[30] Controls were matched in a 1:1 fashion by weeks of gestation at delivery. Gestational age at delivery was selected as the matching variable given its significance as a possible confounder, because there is a direct correlation of placental development with advancing gestation.[18,19]

Placentas were routinely transported to the Department of Pathology within 24 hours of delivery. All placentas were examined according to a standardized protocol. This included storage at 4°C after delivery, fixation in formalin (added within 2 hours of specimen receipt, with a duration of up to 48—72 hours, from women after the diagnosis of SARS-CoV-2 infection), gross examination with weight and measurements after fixation, sectioning with processing in paraffin blocks and staining the cut tissue (4 μm) on glass slides using the hematoxylin and eosin stain, and, finally, microscopic examination of the cut sections. There were between 5 and 12 microscopic sections examined per placenta, which represented at least 2 from the umbilical cord, 1 from free membranes, and 2 full-thickness sections of placental disc including fetal and maternal surfaces. If visible lesions were present, the representative samples of such lesions were obtained and examined. Placentas were not tested for SARS-CoV-2 infection. Histopathologic characteristics evaluated for each placenta included the presence or absence of maternal vascular malperfusion such as accelerated villous maturation, decidual vasculopathy, distal villous hypoplasia, excessive infarction, and old hemorrhage in membranes. Additional characteristics evaluated included the presence or absence of chorionitis, amnionitis, umbilical vasculitis, villitis, intervillous thrombi, fetal vascular malperfusion, increased perivillous fibrin, delayed villous maturation, retroplacental thrombus, chorangiosis, and meconium

staining. All examinations were reviewed by an experienced perinatal and pediatric pathology subspecialist (K.A.M.) who utilized a standardized set of criteria for sampling and defining placental lesions,[31] and was not blinded to the patient's clinical history or diagnosis of SARS-CoV-2 infection.

Maternal and neonatal characteristics collected from each medical record included maternal age, race or ethnicity, parity, gestational age at diagnosis of SARS-CoV-2 infection, presence or absence of symptoms typically related to SARS-CoV-2 infection (ie, fever or chills, cough, dyspnea, myalgias, nausea and vomiting, diarrhea, headache, anosmia or ageusia), gestational age at delivery, the time interval from diagnosis of infection to delivery, mode of delivery, neonatal birthweight, and neonatal SARS-CoV-2 test at 24 hours of life. Maternal disease severity was further classified based on the defined criteria from the United States National Institutes of Health.[32] Mild cases were defined as those who have symptoms typically related to SARS-CoV-2 infection, but without dyspnea or abnormal imaging. Moderate cases were defined as those who had evidence of lower respiratory disease by clinical assessment or imaging and a blood oxygen saturation of >93% on room air. Severe cases were defined as those with a respiratory rate ≥30 breaths per minute, blood oxygen saturation of ≤93% on room air, partial pressure of arterial oxygen to fraction of inspired oxygen of <300 mm Hg, and lung infiltrates of >50%. Critical cases were defined as those who exhibited respiratory failure, septic shock, or multiple organ dysfunction or failure.

A total of 2 comparative analyses evaluating the histopathologic characteristics of placentas were performed. The first comparison was between placentas from women after the diagnosis of SARS-CoV-2 infection and gestational age–matched historical controls. The second comparison was between placentas from women after the diagnosis of SARS-CoV-2 infection who had typical symptoms related to the infection and those who did not have such typical symptoms. Statistical analysis included the use of the Wilcoxon rank-sum test and Fisher's exact test for comparison of categorical and continuous variables. Statistical significance was defined as a P value of <.05.

TABLE 1
Characteristics of the study cohort at baseline

Characteristic	Patients with SARS-CoV-2 infection (n=50)	Historical controls (n=50)	P value
Maternal age (y), median (IQR)	30 (24.25–33.75)	30 (27.00–33.75)	.57
Race or ethnic group, n (%)			
Non-Hispanic black	12 (24)	16 (32)	.23
Non-Hispanic white	14 (28)	16 (32)	
Asian	7 (14)	10 (20)	
Hispanic	9 (18)	2 (4)	
Other or multiracial	6 (12)	3 (6)	
Unknown	2 (4)	3 (6)	
Nulliparous, n (%)	24 (48)	20 (40)	.55
Gestational age at delivery (wk), median (IQR)	39.3 (38.45–40.10)	39.3 (38.40–40.25)	.86
Antepartum or intrapartum complications, n (%)			
Pregestational diabetes	1 (2)	1 (2)	1
Gestational diabetes	1 (2)	7 (14)	.059
Gestational hypertension	3 (6)	1 (2)	.62
Chronic hypertension	0	1 (2)	1
Preeclampsia with severe features	4 (8)	6 (12)	.74
Preeclampsia without severe features	1 (2)	1 (2)	1
Fetal growth restriction	2 (4)	5 (10)	.44
Intrahepatic cholestasis of pregnancy	3 (6)	2 (4)	1
Oligohydramnios	1 (2)	2 (4)	1
Placental abruption	0	1 (2)	1
Intrapartum fever	6 (12)	8 (16)	.77
Vaginal delivery, n (%)	38 (76)	28 (56)	.057
Birthweight (g), median (IQR)	3213 (2771–3435)	3353 (2766–3635)	.44

Data are presented as number (percentage) or median (IQR).

IQR, interquartile range; *SARS-CoV-2*, severe acute respiratory syndrome coronavirus 2.

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Results

During the study period, a total of 52 placentas from singleton gestations diagnosed as having SARS-CoV-2 infection were submitted to the Department of Pathology. Of note, 2 cases with placenta accreta were excluded from the analysis. Therefore, the study cohort included 50 placentas after the diagnosis of maternal SARS-CoV-2 infection and 50 placentas as historical controls, which were further analyzed. Among placentas from the patients who were diagnosed as having SARS-CoV-2 infection, 3 (6%)

TABLE 2
Comparison of histopathologic characteristics of placentas from women after diagnosis of SARS-CoV-2 infection and gestational age–matched historical controls

	Patients with SARS-CoV-2 infection (n=50)	Historical Controls (n=50)	*P* value
Placental weight			
<10th percentile	7 (14)	10 (20)	.87
10th–90th percentile	40 (80)	37 (74)	
>90th percentile	3 (6)	3 (6)	
Maternal vascular malperfusion			
Accelerated villous maturation	0	1 (2)	1
Decidual vasculopathy	0	1 (2)	1
Distal villous hypoplasia	2 (4)	1 (2)	1
Excessive infarction	4 (8)	4 (8)	1
Old hemorrhage in membranes	1 (2)	2 (4)	1
Fetal vascular malperfusion	4 (8)	6 (12)	.74
Increased perivillous fibrin	6 (12)	7 (14)	1
Intervillous thrombus	13 (26)	8 (16)	.33
Delayed villous maturation	10 (20)	13 (26)	.64
Villitis	2 (4)	1 (2)	1
Chorionitis	11 (22)	8 (16)	.61
Amnionitis	9 (18)	4 (8)	.23
Umbilical vasculitis	7 (14)	8 (16)	1
Retroplacental thrombus	2 (4)	0	.5
Chorangiosis	3 (6)	1 (2)	.62
Chorangioma	0	1 (2)	1
Meconium staining	9 (18)	5 (10)	.39

Data are presented as number (percentage).

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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were preterm (33 3/7 weeks, 34 6/7 weeks, and 36 6/7 weeks), 16 (32%) were from patients who had typical symptoms related to infection, and 34 (68%) were from patients who did not have typical symptoms related to the infection. Disease severity for the 16 cases from patients with symptoms related to SARS-CoV-2 infection included 9 with mild disease, 3 with moderate disease, 2 with severe disease, and 1 with the critical disease. All patients had received a diagnosis of SARS-CoV-2 infection in the third trimester. There were 2 patients who had recovered from the infection and had negative SARS-CoV-2 test results at the time of delivery. The results of SARS-CoV-2 testing by means of PCR for all neonates at 24 hours of life were negative.

Maternal age, race or ethnicity, parity, gestational age at delivery, mode of delivery, neonatal birthweight, and the number of antepartum or intrapartum complications were similar between patients with SARS-CoV-2 infection and historical controls (Table 1). Histopathologic findings, such as accelerated villous maturation or decidual vasculopathy, were not visualized in any of the placentas from patients with SARS-CoV-2 infection. There was no statistically significant difference in maternal vascular malperfusion histopathologic characteristics, such as distal villous hypoplasia (4% vs 2%), excessive infarction (8% vs 8%), and old hemorrhage in membranes (2% vs 4%), between the 2 groups (Table 2). There were also no statistically significant difference in fetal vascular malperfusion (8% vs 12%), increased perivillous fibrin (12% vs 14%), intervillous thombi (26% vs 16%), chorangiosis (6% vs 2%), or the presence of meconium staining (18% vs 10%) between the 2 groups (Table 2).

On subgroup analysis, maternal age, race or ethnicity, parity, gestational age at delivery, mode of delivery, neonatal birthweight, and the number of antepartum or intrapartum complications were similar between patients with SARS-CoV-2 infection who had typical symptoms related to the infection and those who did not have such typical symptoms (Table 3). The time interval from the diagnosis of SARS-CoV-2 infection to delivery was significantly higher among patients who had typical symptoms related to the SARS-CoV-2 infection than those who did not have such typical symptoms (12.5 days vs 0.5 days; $P<.001$). There was no statistically significant difference in maternal vascular malperfusion histologic characteristics such as distal villous hypoplasia (0% vs 5.9%), excessive infarction (18.8% vs 2.9%), and old hemorrhage in membranes (6.2% vs 0%) between the 2 groups (Table 4). There were also no statistically significant differences in fetal vascular malperfusion (6.2% vs 8.8%), increased perivillous fibrin (12.5% vs 11.8%), intervillous thombi (37.5% vs 20.6%), chorangiosis (6.2% vs 5.9%), or the presence of meconium staining (25% vs 14.7%) between the 2 groups (Table 4).

Discussion

Principal findings

The results of our study did not indicate significant placental histopathologic changes that occur after the diagnosis of

SARS-CoV-2 infection in women during the third trimester of pregnancy compared with a gestational age–matched historical control group with a similar incidence of antepartum or intrapartum complications. Moreover, there was no difference in placental histopathologic findings when placentas from the patients were compared after the diagnosis of SARS-CoV-2 infection with or without the presence of symptoms typically related to the infection.

Results

There is a paucity of data regarding placental pathology from patients with SARS-CoV-2 infection. Shanes et al[25] recently described histopathologic findings in placentas of 15 women with SARS-CoV-2 infection from 34 to 40 weeks of gestation and compared with either a historical control group of third-trimester placentas submitted for suggested clinical indications to the Department of Pathology for examination or because of a history of melanoma. Compared with all historical controls, placentas from women infected with SARS-CoV-2 in their cohort indicated a higher incidence of decidual arteriopathy (47% vs 16%; $P=.04$), delayed villous maturation (27% vs 4%; $P<.001$), chorangiosis (27% vs 5%; $P=.001$), and intervillous thrombi (40% vs 9%; $P<.001$).[25] The rates of delayed villous maturation, chorangiosis, and intervillous thrombi were lower in our cohort of placentas from pregnancies with SARS-CoV-2 infection, and decidual vasculopathy was not seen in any case. Baergen and Heller[26] have also recently reported placental findings from 20 cases of third-trimester maternal SARS-CoV-2 infection without a comparative group. With a gestational age range of cases from 32 2/7 to 40 4/7 weeks, including 1 twin pregnancy, they found incidences of low-grade fetal vascular malperfusion and maternal vascular malperfusion in 45% and 20% of cases, respectively.[26] Although disease severity based on the established criteria was not reported in either study by Shanes et al[25] and Baergen and Heller,[26] the incidence of cases without symptoms associated with the infection varied between 33.3% and 85%, respectively. Differences in case sample size, the nature of case selection, the rate of cases with symptoms related to infection, the severity of symptoms, the incidence of adverse pregnancy outcomes, variations in the degree of diversity in patient populations, and interobserver variability may have contributed to the differences in the placental findings reported by Shanes et al[25] and Baergen and Heller[26] compared with our study.

TABLE 3
Characteristics of patients with symptoms related to SARS-CoV-2 infection compared with those without such symptoms

Characteristic	Patients with symptoms related to SARS-CoV-2 infection (n=16)	Patients without symptoms related to SARS-CoV-2 infection (n=34)	*P* value
Maternal age (y), median (IQR)	31 (28.00–34.25)	29.5 (24–33)	.19
Race or ethnic group, n (%)			
Non-Hispanic black	2 (12.5)	10 (29.4)	.46
Non-Hispanic white	5 (31.25)	9 (26.5)	
Asian	2 (12.5)	5 (14.7)	
Hispanic	5 (31.25)	4 (11.8)	
Other or multiracial	2 (12.5)	4 (11.8)	
Unknown	0 (0)	2 (5.8)	
Nulliparous, n (%)	7 (43.8)	19 (55.9)	.55
Gestational age at delivery (wk), median (IQR)	39.1 (38.38–40.00)	39.3 (38.75–40.38)	.22
Time interval from diagnosis of infection to delivery (d), median (IQR)	12.5 (8.25–20.00)	0.5 (0–1)	<.001
Antepartum or intrapartum complications, n (%)			
Pregestational diabetes	1 (6.2)	0	.32
Gestational diabetes	0	1 (2.9)	1
Gestational hypertension	0	3 (8.8)	.54
Preeclampsia with severe features	1 (6.2)	3 (8.8)	1
Preeclampsia without severe features	1 (6.2)	0	.32
Fetal growth restriction	0	2 (5.9)	1
Intrahepatic cholestasis of pregnancy	1 (6.2)	2 (5.9)	1
Oligohydramnios	1 (6.2)	0	.32
Intrapartum fever	2 (12.5)	6 (17.6)	1
Vaginal delivery, n (%)	10 (62.5)	28 (82.4)	.16
Birthweight (g), median (IQR)	3180 (2699–3421)	3235 (2775–3450)	.44

Data are presented as number (percentage) or median (IQR).

IQR, interquartile range; *SARS-CoV-2*, severe acute respiratory syndrome coronavirus 2.

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Clinical implications

The typical course of SARS-CoV-2 infection and its clinical sequelae in humans is still being studied. Early reports have suggested an incubation

TABLE 4
Comparison of histopathologic characteristics between placentas from women after diagnosis of SARS-CoV-2 infection who had typical symptoms related to the infection and those without such typical symptoms

Histopathologic characteristic	Patients with symptoms related to SARS-CoV-2 infection (n=16)	Patients without symptoms related to SARS-CoV-2 infection (n=34)	*P* value
Placental weight			
<10th percentile	1 (6.2)	6 (17.6)	.32
10th–90th percentile	13 (81.2)	27 (79.4)	
>90th percentile	2 (12.5)	1 (2.9)	
Maternal vascular malperfusion			
Distal villous hypoplasia	0	2 (5.9)	1
Excessive infarction	3 (18.8)	1 (2.9)	.09
Old hemorrhage in membranes	1 (6.2)	0	.32
Fetal vascular malperfusion	1 (6.2)	3 (8.8)	1
Increased perivillous fibrin	2 (12.5)	4 (11.8)	1
Intervillous thrombus	6 (37.5)	7 (20.6)	.3
Delayed villous maturation	2 (12.5)	8 (23.5)	.47
Villitis	0	2 (5.9)	1
Chorionitis	2 (12.5)	9 (26.5)	.47
Amnionitis	2 (12.5)	7 (20.6)	.7
Umbilical vasculitis	2 (12.5)	5 (14.7)	1
Retroplacental thrombus	2 (12.5)	0	.1
Chorangiosis	1 (6.2)	2 (5.9)	1
Meconium staining	4 (25)	5 (14.7)	.44

Data are presented as number (percentage).

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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period of up to 14 days, with a median time of 4 to 5 days from exposure to symptom onset.[33–35] The illness severity ranges from asymptomatic carriers to critical with respiratory failure, shock, or multiorgan system dysfunction.[32–35] However, not all patients infected with the virus exhibit typical symptoms related to the infection, and the physiological effect of this presentation in pregnant women is unknown. Given the varying clinical presentations of infection, it is reasonable to consider that histopathologic changes in organs such as the placenta may result as a direct insult from the infection, or indirectly from maternal physiological changes. Whether this may impact antenatal surveillance remains to be seen. The results of this study suggest that pregnancy with maternal SARS-CoV-2 infection may be managed based on the clinical findings alone, because findings from placental pathology warranting increased or different surveillance were not indicated.

A particular point of interest regarding the physiological response to SARS-CoV-2 infection has been its associated prothrombotic state.[36,37] Thus far, evidence has not proven that pregnant women with infection are more likely to suffer from venous thromboembolism. On a recent evaluation by Mulvey et al[27] of 5 term placentas from women with SARS-CoV-2 infection who were classified as mostly without typical symptoms related to infection, all 5 indicated evidence of fetal vascular malperfusion with thrombosis. The rate of fetal vascular malperfusion in our study was relatively low and was similar in patients who presented with and without typical symptoms related to the infection. This was despite a significant difference in the time interval from the diagnosis of infection to delivery, which likely reflects the universal testing performed on women admitted for delivery at our institution. Whether such histopathologic findings were related to the time interval from infection to delivery or were a result of maternal immunologic response to infection requires further study, including identifying possible associated markers on a molecular level.

Research implications

Data regarding SARS-CoV-2 and its impact on pregnancy are rapidly evolving. To date, it remains unclear if vertical transmission—either intrauterine, intrapartum, or immediately postpartum—of SARS-CoV-2 occurs.[13–17] Further evidence concluding whether SARS-CoV-2 can infect the placenta, traverse the placental barrier or induce morphologic changes is needed. Reports have suggested that cell entry of SARS-CoV-2 is mediated through the angiotensin-converting enzyme 2 (ACE2) receptor.[38] Although ACE2 expression has been reported at the maternal-fetal interface of placentas,[39] the correlation between receptor expression, viral load, and associated histologic changes has not been studied. Our findings of no significant difference in placental histopathology after the third-trimester diagnosis of SARS-CoV-2 infection are reassuring. However, in the absence of placental SARS-CoV-2 testing and standardized serology testing for neonates, we cannot assume or refute vertical transmission. Furthermore, whether these pathologic findings would be similar after first or second-trimester SARS-CoV-2 infection and whether earlier infection increases the likelihood of vertical transmission is unknown and requires further study.

Strengths and limitations

There are several strengths to this study. This study reported a cohort of examined placentas from pregnancies with SARS-CoV-2 infection and the comparison of histopathologic findings in women with and without symptoms related to infection. Our control group was matched by gestational age and had the same median maternal age; thus, there were limited possible confounders. Our population was diversified in terms of demographics and was derived from New York, where the total number of novel coronavirus infections is among the highest worldwide. Finally, all placentas were reviewed by only 1 pathologist subsequent to the initial histopathologic examination, which reduced the impact of interobserver variability.

There are also several limitations to this study. The pathologist was not blinded to the clinical history or status of SARS-CoV-2 infection for each placenta examined, which may have introduced bias regarding interpretation. However, this is unlikely because no pattern of significant histopathologic changes were found. Despite a larger sample size of cases relative to other reports in the literature, several outcomes had relatively low frequencies. This may have limited the power to detect significant differences, particularly when histopathologic characteristics in placentas from infected patients with or without symptoms related to SARS-CoV-2 infection were compared. We also utilized a historical control group with several clinical diagnoses that may have contributed to the abnormal pathologic findings, because placentas are not routinely sent for examination at our institution. However, the rates of these diagnoses were similar between cases from infected pregnancies and controls. We did not test each placenta for the presence of SARS-CoV-2. Nevertheless, the test results of all neonates at 24 hours of life were negative for infection. The results of this study are only reflective of the third trimester SARS-CoV-2 infection. Whether significant placental histopathologic changes occur after the first or second-trimester infection is unknown. Finally, it is unknown whether our reported findings are directly related to placental infection or an indirect effect from maternal physiological or immune response to infection.

Conclusions

The results of this study add to the limited existing literature focused on placental histopathologic changes associated with SARS-CoV-2 infection and suggest that there is no increased risk of significant placental histopathologic changes that occur after the diagnosis of SARS-CoV-2 in the third trimester regardless of the presence or absence of symptoms typically related to infection. Future studies examining histopathologic changes associated with earlier infection and identifying key placental biological markers on a molecular level that may be directly affected by SARS-CoV-2 are needed to better understand the impact of this virus on placental physiology. ■

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