Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Vertical transmission of coronavirus disease 2019: a systematic review and meta-analysis

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OBJECTIVE: This study aimed to conduct a systematic review of the current literature to determine estimates of vertical transmission of coronavirus disease 2019 based on early RNA detection of severe acute respiratory syndrome coronavirus 2 after birth from various neonatal or fetal sources and neonatal serology.

DATA SOURCES: Eligible studies published until May 28, 2020, were retrieved from PubMed, EMBASE, medRxiv, and bioRxiv collection databases.

STUDY ELIGIBILITY CRITERIA: This systematic review included cohort studies, case series, and case reports of pregnant women who received a coronavirus disease 2019 diagnosis using severe acute respiratory syndrome coronavirus 2 viral RNA test and had reported data regarding the testing of neonates or fetuses for severe acute respiratory syndrome coronavirus 2 immediately after birth and within 48 hours of birth. A total of 30 eligible case reports describing 43 tested neonates and 38 cohort or case series studies describing 936 tested neonates were included.

STUDY APPRAISAL AND SYNTHESIS METHODS: The methodological quality of all included studies was evaluated by a modified version of the Newcastle-Ottawa scale. Quantitative synthesis was performed on cohort or case series studies according to the neonatal biological specimen site to reach pooled proportions of vertical transmission.

RESULTS: Our quantitative synthesis revealed that of 936 neonates from mothers with coronavirus disease 2019, 27 neonates had a positive result for severe acute respiratory syndrome coronavirus 2 viral RNA test using nasopharyngeal swab, indicating a pooled proportion of 3.2% (95% confidence interval, 2.2—4.3) for vertical transmission. Of note, the pooled proportion of severe acute respiratory syndrome coronavirus 2 positivity in neonates by nasopharyngeal swab in studies from China was 2.0% (8/397), which was similar to the pooled proportion of 2.7% (14/517) in studies from outside of China. Severe acute respiratory syndrome coronavirus 2 viral RNA testing in neonatal cord blood was positive in 2.9% of samples (1/34), 7.7% of placenta samples (2/26), 0% of amniotic fluid (0/51), 0% of urine samples (0/17), and 9.7% of fecal or rectal swabs (3/31). Neonatal serology was positive in 3 of 82 samples (3.7%) (based on the presence of immunoglobulin M).

CONCLUSION: Vertical transmission of severe acute respiratory syndrome coronavirus 2 is possible and seems to occur in a minority of cases of maternal coronavirus disease 2019 infection in the third trimester. The rates of infection are similar to those of other pathogens that cause congenital infections. However, given the paucity of early trimester data, no assessment can yet be made regarding the rates of vertical transmission in early pregnancy and potential risk for consequent fetal morbidity and mortality.

Key words: COVID-19, SARS-CoV-2, transplacental transmission, vertical transmission

Introduction

The coronavirus disease 2019 (COVID-19) has spread from isolated cases of pneumonia in Wuhan, Hubei province, China, to become a worldwide pandemic as declared by the World Health Organization on March 11, 2020.[1] As of June 1, 2020, there have been more than 6,300,000 confirmed cases and more than 370,000 deaths worldwide. Coronaviruses are single-stranded RNA viruses. Although there are many coronaviruses, the particular coronavirus that is responsible for this pandemic is the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[2] After 2 to 7 days of incubation, most symptomatic patients typically experience fever, cough, or loss of taste or smell, with some cases developing into life-threatening pneumonia and acute respiratory distress syndrome.[3,4] Case fatality rates range from 1% to 2%, which is substantially less than the case fatality rates for other coronavirus infections including the severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) (10% and 35%, respectively).[5]

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The presence of COVID-19 infection in a pregnant patient raises concerns given that infections with other coronaviruses such as SARS and MERS have been associated with severe maternal and neonatal morbidity and mortality and adverse pregnancy outcomes including miscarriage, preterm birth, and stillbirth.[6] However, the effects of COVID-19 on pregnancy and the fetus are still largely unknown because of the recent nature of the outbreak. Pregnant patients are a potentially vulnerable group to COVID-19 infection. The first and third trimesters of pregnancy can be considered periods of increased

AJOG at a Glance

Why was this study conducted?

Coronavirus disease 2019 (COVID-19) is a pandemic that has and will continue to affect many pregnant women. Knowledge regarding the possible risk of vertical transmission is very limited but is crucial for guiding patient counseling regarding COVID-19–related pregnancy risks and obstetrical care for women with COVID-19.

Key findings

The vertical transmission of COVID-19 in the third trimester is approximately 3.2% (22/936) by infant nasopharyngeal swab testing, with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA positivity in other test sites ranging from 0% (0/51) in amniotic fluid and urine (0/17), 3.6% (1/28) in the cord blood, 7.7% (2/26) by placental sample analysis, 9.7% (3/31) by rectal or anal swab, and 3.7% (3/81) by serology.

What does this add to what is known?

There is evidence of SARS-CoV-2 vertical transmission when the infection occurs in the third trimester of pregnancy.

inflammatory activity, whereas the second trimester is a period of overall decreased immune activity.[7,8] Although initial reports of pregnant women infected with COVID-19 in the third trimester raised a concern for an increased risk for premature delivery,[9,10] recent larger cohorts of 116 women in China and 427 women in the United Kingdom suggest that pregnant women are not at an increased risk of spontaneous abortion or spontaneous preterm birth but have higher rates of cesarean delivery (CD).[11,12]

Vertical transmission is defined as the transmission of the infectious pathogen from the mother to the fetus during the antepartum and intrapartum periods, or to the neonate during the postpartum period via the placenta in utero, body fluid contact during childbirth, or through direct contact owing to breastfeeding after birth. Although multiple infectious vectors have been shown to be capable of vertical transmission, the possibility of vertical transmission of SARS-CoV-2 from the infected mother to the fetus or neonate has been a point of a recent debate with previous systematic reviews, albeit with a limited number of studies, concluding that there is no evidence of vertical transmission.[13–16] No known cases of vertical transmission have been noted with similar coronaviruses such as SARS and MERS, although the number of cases has been limited.[17,18] COVID-19 shares 50% and 79% sequence homology with SARS and MERS, respectively; despite this homology, a similar lack of vertical transmission cannot be assumed.[6]

A concern over vertical transmission in the case of COVID-19 exists for several reasons. First is the known tissue tropism of COVID-19. The main receptor that COVID-19 binds to enter a cell is the angiotensin-converting enzyme 2 (ACE2) receptor. ACE2 is expressed in the placenta[19] and is found in the syncytiotrophoblast, cytotrophoblast, endothelium, and vascular smooth muscle from both primary and secondary villi.[20] A recent systematic review also found evidence that ACE2 is expressed in gynecologic organs such as the ovary, uterus, and vagina.[21] Overall, ACE2 expression is seen in numerous tissues that are in direct communication with a developing pregnancy. These data were further bolstered by a recent single-cell RNA sequencing analysis that found ACE2 expression in stromal, perivascular, placental, and decidual cells at the maternal-fetal interface.[22] However, a single-cell RNA sequencing analysis looking at the coexpression of ACE2 and the transmembrane serine protein for virus spike (S) protein priming, transmembrane serine protease 2 (TMPRSS2), showed that only a minimal number of placental cells express both proteins in any trimester. Furthermore, this group showed that chorioamniotic membranes from the third trimester exhibit minimal coexpression of both proteins. Nonetheless, the authors suggested that viral entry into placenta cells may still occur using a combination of ACE2 and a noncanonical cell-entry mediator.[23] In addition, animal data indicated that oronasal inoculation of pregnant mice with mouse hepatitis virus (MHV), which is part of the Coronaviridae family, led to the dissemination of the virus to the fetus in each trimester. However, the dissemination was dependent on the strain of MHV and the strain of mice, with BALB/cByJ mice being the most susceptible.[24] In addition to this biological plausibility, there are several lines of clinical evidence concerning vertical transmission. Initial reports from China have documented immunoglobulin M (IgM) antibodies in neonates born to mothers who had positive results for COVID-19,[25,26] raising concerns for in utero transmission because IgM cannot cross the placenta. Moreover, several recent case reports provided evidence that COVID-19 can infect the placenta as confirmed by the presence of SARS-CoV-2 viral RNA and protein in the placenta and evidence of virions found within the syncytiotrophoblast.[27–30]

Answering the question of vertical transmission is crucial for guiding patient counseling regarding COVID-19–related risks before and during pregnancy and obstetrical care for women infected with COVID-19. Therefore, we conducted this systematic review to summarize the available evidence regarding the risk of vertical transmission.

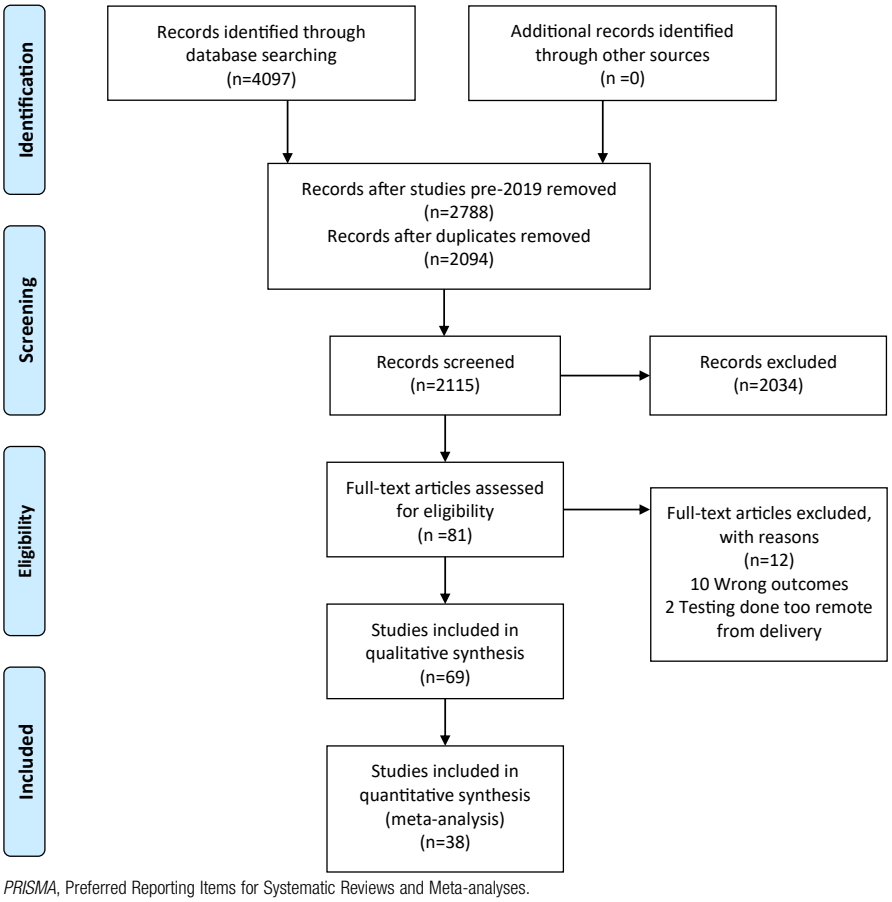
Methods

Search strategy, study selection, and data extraction

A medical librarian conducted a systematic search of the literature from Cochrane Library, DisasterLit, Ovid Embase, Ovid Medline, Google Scholar, LitCovid, MedRxiv, Pubmed, Scopus,

and Web of Science Core Collection databases to find relevant articles published from inception of the database to May 28, 2020, to identify cohort studies, case series, and case reports of pregnant women with COVID-19 that include information regarding fetal or neonatal COVID-19 testing. The study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines for the reporting of systematic reviews and meta-analyses and was registered in the International Prospective Register of Systematic Reviews (CRD42020190885). The databases were searched using a combination of controlled vocabulary and free-text terms for SARS-CoV-2, COVID-19, coronavirus, Coronaviridae, pregnancy, fetus, infant, mother-to-child, mother-to-infant, maternal-fetal, virus transmission, disease transmission, and vertical transmission (the full search strategy is provided in the Supplemental Figure). The search results were limited to English-language abstracts. Foreign-language articles were included only if a translation was available given the time-sensitive nature of this review. Bibliographies were cross-referenced to identify additional relevant studies. Studies were included if they were English-language articles that focused on the development of COVID-19 infection in fetuses and neonates. Citations from all databases were imported into an EndNote X9 library. Duplicates were removed from the EndNote, reducing the initial list of 4907 citations to 2904 citations. The database of 2904 citations was entered into Covidence, which is a screening and data extraction tool. Two independent screeners (A.K. and O.G.) performed a title abstract review and resolved conflicts by consensus between the 2 screeners. The screeners selected a total of 81 records for full-text review and included 68 studies that fulfilled the eligibility criteria in the qualitative synthesis (Figure 1). Cohort studies and case series (defined as having 5 or more patients) were selected for quantitative synthesis. Case series were defined as having 5 or more patients, consistent with the recommendations according to the study by Abu-Zidan et al[31] showing that case reports have a median number of 4 patients. Data were extracted from the article texts and tables and organized into tables in a systematic manner. The following information was extracted: author name; country; publication date; number of pregnant women; number of eligible neonates; gestational age (at onset of testing); mode of delivery; neonatal SARS-CoV-2 reverse transcription—polymerase chain reaction (RT-PCR) testing results from nasopharyngeal (NP) swab, placenta, cord blood, amniotic fluid, and any other fetal or neonatal sources; placental histology; and neonatal serology.

FIGURE 1
PRISMA flowchart outlining study selection



PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.

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Eligibility criteria

Studies were included in this systematic review if they met the following criteria: (1) the study population included women who had COVID-19 infection during pregnancy confirmed by positive viral SARS-CoV-2 RNA testing; (2) the study described results of viral RNA testing for SARS-CoV-2 infection in fetuses or neonates; (3) testing for SARS-CoV-2 infection was performed within 48 hours of delivery; and (4) any study design (cohort, case series, case report). Articles that focused on the transmission of COVID-19 outside of the perinatal period were excluded given that this was deemed out of scope for this article.

Methodological quality assessment

Each cohort or case series study selected for final inclusion in the quantitative synthesis was scored by the researchers (A.C. and R.T.) using the modified Newcastle-Ottawa scale, as previously

described (Supplemental Table).[32] Items that relate to comparability and adjustment are not relevant and were removed, whereas items that focused on the selection and representativeness of cases and ascertainment of outcome and exposure were maintained. This resulted in 5 items regarding the study quality characteristics: (1) representativeness of the exposed cohort, (2) exposure assessment, (3) outcome assessment, (4) adequacy of the length of time before follow-up, and (5) adequacy of the follow-up of cohorts. We considered the quality of the report good (low risk of bias) when all 5 criteria were fulfilled, moderate when 4 were fulfilled, and poor (high risk of bias) when 3 or fewer were fulfilled.

Statistical analysis

We evaluated the positive rates of each of the explored SARS-CoV-2 testing outcomes (RT-PCR of NP swab, placenta, cord blood, rectal or anal, urine, amniotic fluid, and IgM serology). Pooled proportions of these categorical variables were calculated with percentages and 95% confidence intervals (CIs). Calculations were performed using the MedCalc Statistical Software version 19.3.1 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2020). The Cochran Q test was used to determine whether to use the fixed effects model or the random effects model ($P<.1$: random effects model). A Freeman-Tukey transformation (arcsine square root transformation)[33] was used to calculate the weighted summary proportion under the fixed and random effects models.[34] The random effects model was preferred because it is more conservative.

Results

Search results

A total of 81 records were selected for full-text review, and 69 studies fulfilled the eligibility criteria and were included in the qualitative synthesis. There were 30 case reports. Their characteristics and test findings are summarized in Table 1. A total of 39 additional studies were cohort studies or case series (defined as having 5 or more patients) and were selected for quantitative synthesis. The characteristics and test findings of these cohort or case series studies are summarized in Tables 2 and 3. These were divided into reports from China (Table 2) and reports from the rest of the world (Table 3) because evidence indicates that earlier Asian viral samples were completely dominated by the original Wuhan D614 form through mid-March, and subsequently, in countries outside of China and across the globe, a different form (G614) was expanding and dominating.[91] The flow diagram of the study selection strategy is presented in Figure 1. The methodological quality assessment of the cohort or case series studies included in the quantitative synthesis showed that 13 studies were of high quality, 16 studies were of moderate quality, and 10 studies were of low quality (Supplemental Figure).

Systematic review

This systematic review included 30 eligible case reports describing a total of 44 SARS-CoV-2–positive pregnant women with outcomes available for 43 neonates (Table 1) and 39 cohort or case series studies describing a total of 936 tested neonates born to SARS-CoV-2–positive pregnant women (Tables 2 and 3). Data in this review were limited to pregnant women who had laboratory-confirmed SARS-CoV-2 infection diagnosed by RT-PCR in an NP swab specimen, which is considered the gold standard for the diagnosis of COVID-19.

Because of the recent onset of the pandemic, the vast majority of data came from pregnant women in their third trimester, whereas the greatest paucity of reports involved patients in the earlier stages of pregnancy. Of the 30 case reports, 29 reports described neonatal outcomes of women in their third trimester, whereas only 2 case reports described outcomes of women in their second trimester.[13,18,25,27–30,35–50,51–58,66] To date, no reports are available describing the assessment for the presence of SARS-CoV-2 in products of conception of a first-trimester pregnancy. Most women in case report studies (32/44) underwent CD with a resultant CD rate of 73%. Similarly, 73% of women (659/901) in cohort or case series studies delivered via CD.

This systematic review identified 2 case reports of second-trimester fetal SARS-CoV-2 testing. Baud et al[28] reported a case of a patient at 19 weeks' gestation with a positive result from a SARS-CoV-2 NP swab who had a miscarriage delivering a stillborn infant. Fetal axillary, oral, meconium, and blood samples all tested negative for SARS-CoV-2 RNA. However, placental swabs from the fetal side taken immediately after expulsion were positive for SARS-CoV-2 by RT-PCR. In another case report by Hosier et al,[27] a COVID-19–positive patient delivered at 22 weeks' gestation because of early-onset preeclampsia with severe features. Quantitative RT-PCR tests of placental and umbilical cord samples were positive for SARS-CoV-2 RNA, and viral capsids were found within the trophoblast cells by electron microscopy, confirming infection of the fetal side of the placenta by this novel coronavirus. Although these cases do not provide evidence that placental COVID-19 infection was the cause of these adverse pregnancy outcomes, they lend support to the possibility of in utero maternal-to-fetal transmission.

Overall, the majority of COVID-19 cases of pregnant women with fetal or neonatal outcomes reported thus far involved patients in their third trimester of pregnancy. Given the plethora of studies of patients in the third trimester, we analyzed them according to the study type (case report vs cohort or case series study) and site of SARS-CoV-2 testing. Because selection bias is more likely in case reports than in cohort or case series studies, we focused our quantitative synthesis on the case series and cohort studies to reach pooled proportions regarding various parameters indicative of vertical transmission.

Severe acute respiratory syndrome coronavirus 2 reverse transcription–polymerase chain reaction testing of nasopharyngeal swab. In our review, 38 of 39 cohort or case series studies of pregnant women with COVID-19 infection had information on

TABLE 1
Case reports

Author (country)	Number of women	Number of eligible neonates	GA at onset of Sx or diagnosis (range)	Mode of delivery	RT-PCR for SARS-CoV-2					Neonatal serology	Placental histology or EM
					Neonatal NP swab	Placenta	Cord blood	Amniotic fluid	Other fetal sites or tests		
Alzamora et al (Peru)[35]	1	1	33 wk	CD	1/1	None	None	None	None	IgG (0/1), IgM (0/1)	None
Chen et al (China)[36]	3	3	35 wk—38 wk 6 d	CD 3/3	0/3	0/3	None	None	None	None	Chorionic hemangioma (1/3), fibrin deposits in villi interstitium and around the villi (3/3), multifocal infarction (1/3)
Dong et al (China)[25]	1	1	34 wk 2 d	CD	0/1	None	None	None	None	IgG and IgM elevated on delivery day and 13 d later (1/1)	None
Fan et al (China)[13]	2	2	36—37 wk	CD 2/2	0/2	0/2	0/2	0/2	None	None	None
Kalafat et al (Turkey)[37]	1	1	35 wk 3 d	CD	0/1	0/1	0/1	None	None	None	None
Khan et al (China)[38]	3	3	34 wk 6 d —39 wk 1 d	VD 3/3	0/3	None	None	None	None	None	None
Li et al (China)[39]	1	1	35 wk	CD	0/1	0/1	0/1	0/1	None	None	None
Liu et al (China)[40]	3	3	37—40 wk	VD 1/3; CD 2/3	0/3	None	0/3	None	0/3	None	None
Lowe and Bopp (Australia)[41]	1	1	40 wk 3 d	VD	0/1	None	None	None	None	None	None
Lu et al (China)[42]	1	1	38 wk	CD	0/1	None	0/1	None	None	None	None
Peng et al (China)[43]	1	1	34 wk 3 d	CD	0/1	0/1	0/1	0/1	Anal (0/1), serum (0/1), sputum (0/1), urine (0/1), BAL fluid (0/1)	None	None
Schnettler et al (United States)[44]	1	1	30 wk 3 d	CD	0/1	None	None	0/1	None	None	None
Wang et al (China)[45]	1	1	40 wk	CD	1/1	0/1	0/1	None	None	None	None

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(continued)

TABLE 1
Case reports *(continued)*

Author (country)	Number of women	Number of eligible neonates	GA at onset of Sx or diagnosis (range)	Mode of delivery	RT-PCR for SARS-CoV-2					Neonatal serology	Placental histology or EM
					Neonatal NP swab	Placenta	Cord blood	Amniotic fluid	Other fetal sites or tests		
Xiong et al (China)[46]	1	1	33 wk	VD	0/1	None	None	0/1	Rectal swab (0/1)	IgG (0/1), IgM (0/1)	No inflammation
Zamaniyan et al (Iran)[47]	1	1	32 wk	CD	0/1	0/1	0/1	1/1	None	None	None
Baud et al (Switzerland)[28]	1	1	19 wk	VD	0/1	1/1	None	0/1	Fetal blood, lung, liver, thymus biopsies (all 0/1)	None	Mixed inflammatory infiltrates composed of neutrophils and monocytes in the subchorial space and increased intervillous fibrin deposition (1/1), funisitis (1/1)
Blauvelt et al (United States)[48]	1	1	28 wk	CD	0/1	None	None	None	Rectal swab (0/1)	IgG and IgM drawn on day 5 were negative	Acute chorioamnionitis (1/1), no funisitis or histologic evidence of other placental infections
Buonsenso et al (Italy)[49]	4	2	17–38 wk	CD 2/2	0/2	None	0/2	None	None	None	None
Gidlöf et al (Sweden)[50]	1	2	36 wk	CD	0/2	None	None	None	None	None	None
Hosier et al (United States)[27]	1	1	22 wk	D&E	N/A	1/1	1/1	None	Fetal heart, lung, kidney (0/1)	None	Diffuse perivillous fibrin and inflammatory infiltrate in intervillous space showing histiocytic intervillositis, EM showing virions noted inside syncytiotrophoblast
Huang et al (China)[51]	1	1	35 wk	CD	0/1	0/1	0/1	0/1	None	None	None
Kirtsman et al (Canada)[29]	1	1	35 wk	CD	1/1	1/1	0/1	None	Plasma (1/1), stool (1/1)	None	Multiple areas of infiltration, extensive early infarction, consistent with chronic histiocytic intervillositis
Lang and Zhao (China)[52]	1	1	35 wk 2 d	CD	0/1	0/1	0/1	0/1	None	None	None
Lee et al (Republic of Korea)[53]	1	1	36 wk 2 d	CD	0/1	0/1	0/1	0/1	None	None	None
Lyra et al (Portugal)[54]	1	1	39 wk 4 d	CD	0/1	Collected for future analysis	None	Collected for future analysis	None	None	None

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(continued)

TABLE 1
Case reports *(continued)*

Author (country)	Number of women	Number of eligible neonates	GA at onset of Sx or diagnosis (range)	Mode of delivery	RT-PCR for SARS-CoV-2				Other fetal sites or tests	Neonatal serology	Placental histology or EM
					Neonatal NP swab	Placenta	Cord blood	Amniotic fluid			
Vallejo and Illagan (United States)[55]	1	1	36 wk	CD	0/1	None	None	None	None	None	Negative histopathologic findings
Yu et al (China)[56]	1	1	34 wk	VD	0/1	None	None	None	None	None	None
Algarroba et al (United States)[57]	1	1	28 wk	CD	0/1	None	None	None	None	None	Mature chorionic villi with focal villous edema, area of decidual vasculopathy, EM showing single virions invading a syncytiotrophoblast and also visualized in a microvillus and fibroblast processes
Vivanti et al (France)[58]	1	1	35 wk 2 d	CD	1/1	1/1	None	1/1	Rectal swab 1/1, neonatal blood 1/1	None	Diffuse perivillous fibrin deposition, infarction and acute and chronic intervillositis. SARS-CoV-2 N-protein seen within cytoplasm of perivillous trophoblastic cells

All papers are identified by author, country (unless otherwise specified), and citation number within the main text.

BAL, bronchoalveolar lavage; *CD*, cesarean delivery; *D&E*, dilation and evacuation; *EM*, electron microscopy; *GA*, gestational age; *IgG*, immunoglobulin G; *IgM*, immunoglobulin G; *N/A*, not available; *NP*, nasopharyngeal; *RT-PCR*, reverse transcription–polymerase chain reaction; *SARS-CoV-2*, severe acute respiratory syndrome coronavirus 2; *Sx*, symptoms; *VD*, vaginal delivery.

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neonatal NP swab testing results. There were 22 studies from China (Table 2) and 17 studies from countries outside of China (Italy, Spain, United Kingdom, and United States of America) (Table 3). In total, of 397 neonates born to mothers with COVID-19 infection in China, there were 8 who had a positive result for SARS-CoV-2 by NP swab resulting in a pooled proportion of 2.0% for vertical transmission.[8–11,26,56,59–71,72–75] The largest cohort study from China was by Yan et al,[11] in which 116 COVID-19–positive pregnant patients delivered 100 infants, of whom 86 underwent testing for SARS-CoV-2. None of the 86 infants had a positive result for COVID-19 via NP swab. Among studies from outside of China, the largest cohort study thus far came from the United Kingdom involving 427 pregnant women with COVID-19 including 244 neonates tested by NP swab, 12 of whom were positive for SARS-CoV-2 (12/244).[12] An analysis of 68 women from a hospital in New York City showed that of the 55 neonates born, 48 were tested at day 0 of life with none having a positive result for COVID-19 (0/48).[82] One Italian study that assessed 42 infants born via vaginal delivery and CD found 3 infants (3/42) who had positive results for SARS-CoV-2 via NP swabs within 48 hours after birth.[78] Pooling studies from outside of China revealed that 19 of 539 neonates born to mothers with COVID-19 infection had positive results for SARS-CoV-2 by NP swab, yielding a pooled proportion of 3.5%.[12,18,76–90] Combining all 38 cohort or case series studies in a meta-analysis, of all 936 neonates tested, 27 had positive results for SARS-CoV-2 RNA by NP swab either immediately after birth or within 48 hours of birth, yielding a pooled proportion of 3.2% (95% CI, 2.2–4.3) (Figures 2 and 3).

Placental analysis. In our review, we identified 8 cohort or case series studies that reported on the assessment of placentas for SARS-CoV-2 by RT-PCR, 2 from China and 6 from outside of China. The placental analysis yielded the second highest pooled rate of possible vertical transmission with 7.7% (2/26) of all

TABLE 2
Cohort or case series studies from China

Author	Number of women	Number of eligible neonates	GA at onset of Sx or diagnosis (range)	Mode of delivery	RT-PCR for SARS-CoV-2					Neonatal serology	Placental histology
					Neonatal NP swab	Placenta	Cord blood	Amniotic fluid	Other fetal sites or tests		
Cao et al[59]	10	5	GA at admission: 33 wk 6 d–40 wk 5 d	VD 2; CD 8	0/5	None	None	None	None	None	None
Chen et al[10]	9	6	GA at admission: 36 wk–39 wk 4 d	CD 9	0/6	None	0/6	0/6	None	None	None
Hu et al[60]	7	7	37–40 wk	VD 1; CD 6	1/7 (subsequent swabs were negative for that positive neonate)	None	None	0/7 positive	Fetal blood (0/7), feces (0/7), urine (0/7)	None	None
Khan et al[61]	17	17	Date of admission: 35–41 wk	CD 17	2/17	None	None	None	None	None	None
Liu et al[62]	19	19	36 wk 3 d–41 wk 2 d	CD 19	0/19	None	0/10	0/10	Urine (0/10), anal swabs (0/10)	None	None
Nie et al[63]	33	28	3 women in the second trimester (17–26 wk), rest in the third trimester	VD 5, CD 22	1/28	0/1	0/1	None	None	1/28	None
Qiancheng et al[64]	28	23	Median GA on admission=38 wk (IQR, 36.5–39)	VD 5, CD 17	0/23	None	None	None	None	None	None
Yan et al[11]	116	100	37 wk 3 d–39 wk 4 d	CD 85, VD 14	0/86	None	0/10	0/10	None	None	None
Yang et al[65]	7	7	36–38 wk	CD 7	0/5	None	0/5	0/5	None	None	None
Yin et al[66]	31	17	N/A	VD 4, CD 13, TAB 3	0/17	0/2	None	0/2	Rectal swab (0/5)	None	None
Yu et al[56]	7	7	37 wk–41 wk 5 d	CD 7	1/3	None	None	None	None	None	None
Zeng et al[26]	6	6	N/A	CD 6	0/6	None	None	None	Fetal blood	Elevated IgM (2/6), elevated IgG (3/6)	None
Zeng et al[67]	33	33	31 wk 2 d–41 wk 4 d	VD 7, CD 26	3/33	None	None	None	Anal swab (3/33)	None	None
Zhu et al[9]	9	10	33 wk 6 d–39 wk	VD 2, CD 7	0/9	None	None	None	None	None	None

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(continued)

TABLE 2
Cohort or case series studies from China *(continued)*

Author	Number of women	Number of eligible neonates	GA at onset of Sx or diagnosis (range)	Mode of delivery	RT-PCR for SARS-CoV-2					Neonatal serology	Placental histology
					Neonatal NP swab	Placenta	Cord blood	Amniotic fluid	Other fetal sites or tests		
Chen et al[68]	5	5	38–41 wk	VD 3, CD 2	0/5	None	None	None	None	None	No placental infarction and chorionic amniotic inflammation
Chen et al[69]	17	17	3<37 wk, 14>37 wk	CD 17	0/17	None	None	None	None	None	None
Liao et al[70]	88	10	36–40 wk	VD 10	0/7	None	None	None	None	None	None
Liu et al[71]	51	51	GA at delivery: 35 wk 1 d–41 wk 2 d	VD 3, CD 48	0/51 (5 were considered false positive)	None	None	None	None	IgM and IgG (0/51)	None
Wu et al[72]	13	5	5–38 wk	VD 1, CD 4	0/5	None	None	None	Anal (0/4)	None	None
Wu et al[73]	23	21 (1 case of twins)	First trimester (6–12 wk), third trimester (31 wk 5 d–40 wk)	VD 2, CD 18	0/5 (5 negative by RT-PCR, 17 negative by clinical criteria)	None	None	None	None	None	None
Yang et al[74]	55	57 (2 cases of twins)	Average GA: 38 wk	VD 16, CD 39	0/20	None	None	None	None	None	None
Yang et al[75]	27	24 (1 case of twins)	3 women in the first trimester, rest in the third trimester (30–40 wk)	VD 5, CD 18	0/23	None	None	None	None	IgM and IgG (1/1), other 23 not tested	None

All papers are identified by author, country (unless otherwise specified), and citation number within the main text.

BAL, bronchoalveolar lavage; *CD*, cesarean delivery; *EM*, electron microscopy; *GA*, gestational age; *IgG*, immunoglobulin G; *IgM*, immunoglobulin G; *IQR*, interquartile range; *N/A*, not available; *NP*, nasopharyngeal; *RT-PCR*, reverse transcription–polymerase chain reaction; *SARS-CoV-2*, severe acute respiratory syndrome coronavirus 2; *Sx*, symptoms; *TAB*, therapeutic abortion; *VD*, vaginal delivery.

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TABLE 3
Cohort or case series studies from outside of China

Author (country)	Number of women	Number of eligible neonates	GA at onset of Sx or diagnosis (range)	Mode of delivery	RT-PCR for SARS-CoV-2					Neonatal serology	Placental histology
					Neonatal NP swab results	Placenta	Cord blood	Amniotic fluid	Other fetal sites or tests		
Breslin et al (United States)[76]	43	18	Median GA 37 wk (IQR, 32 wk 4 d—38 wk 6 d)	VD 10, CD 8	0/18 positive	None	None	None	None	None	None
Breslin et al (United States)[77]	7	2	26 wk 3 d—37 wk 5 d	CD 2	0/2 positive	None	None	None	None	None	None
Ferrazzi et al (Italy)[78]	42	42	Third trimester, 30 women >37 wk, 12 women <37 wk	VD 24, CD 18	3/42	None	None	None	None	None	None
Penfield et al (United States)[79]	32	10	26 wk 4 d—41 wk 2 d	VD 7, CD 4	0/10	1/1	None	None	Fetal membranes (2/10)	None	None
Pierce-Williams et al (United States)[80]	64	33 (1 set of twins)	16 wk 1 d—39 wk 1 d	VD 8/32, CD 24/32	1/33	None	None	None	None	None	None
Lokken et al (United States)[81]	46	8	33 wk 0 d—38 wk 6 d	VD 3, CD 5,	0/8	0/1 (stillbirth)	None	None	Fetal autopsy sites (0/1)	None	Severe chronic villitis but no viral inclusions (1/1)
London et al (United States)[82]	68	48	3 in the second trimester (17 wk, 25 wk, 26 wk), the rest in the third trimester	VD 33, CD 22	0/48	None	None	None	None	None	None
Mulvey et al (United States)[83]	5	5	38—40 wk	VD 4/5, CD 1/5	N/A	0/5	None	None	None	None	Fetal vascular malperfusion (5/5), thrombosis (5/5), intramural fibrin deposition (4/5), meconium (3/5), avascular villi (1/5), villous stromal-vascular karyorrhexis (1/5)
Baergen and Heller (United States)[84]	20	21 (1 pair of twins)	32—40 wk	VD 15/20, CD 5/20	0/21	None	None	None	None	None	Fetal vascular malperfusion (9/20), intramural fibrin deposition (3/20), meconium macrophages (6/20), lesions of maternal vascular malperfusion (5/20), ascending infection with acute chorioamnionitis and acute funisitis (1/20), chronic villitis (4/20)

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(continued)

TABLE 3
Cohort or case series studies from outside of China *(continued)*

Author (country)	Number of women	Number of eligible neonates	GA at onset of Sx or diagnosis (range)	Mode of delivery	RT-PCR for SARS-CoV-2					Neonatal serology	Placental histology
					Neonatal NP swab results	Placenta	Cord blood	Amniotic fluid	Other fetal sites or tests		
Buonseno et al (Italy)[85]	7	2	8 wk–37 wk 3 d	CD 2/2	0/2, on d 15 positive (1/2)	1/2	1/2	0/2	Rectal swab (0/2)	IgM negative (0/1), IgG slightly positive (1/1)	None
Govind et al (United Kingdom)[86]	9	9	27–39 wk	VD 1/9, CD 8/9	1/9	0/9	None	0/9	None	None	None
Knight et al (United Kingdom)[12]	427	244	Median, 34 wk (IQR, 29–38), <22 wk (n=22), 22–27 wk (n=60), 28–31 wk (n=64), 32–36 wk (n=106), 37+ wk (n=142), peripartum (n=30), missing (n=3)	VD 101, CD 144	12/244 (6/244 tested positive <12 h, 6/244 tested positive >12 h)	None	None	None	None	None	None
Patanè et al (Italy)[30]	22	22	35–37 wk	VD 1/2, CD 1/2	2/22 (1 was negative at birth but turned positive at day 7 without contact with mother)	None	None	None	None	None	Chronic intervillositis in intervillous and the villous space (2/22)
Pereira et al (Spain)[87]	60	23	Median GA, 32 wk (range, 5–41 wk)	VD 18/23, CD 5/23	0/23	0/6	None	None	None	None	None
Shanes et al (United States)[88]	16	16	Second trimester (16 wk), third trimester (34–40 wk)	N/A	0/16	None	None	None	None	None	IUFD case pathology showed retroplacental hematoma and villous edema, maternal vascular malperfusion (12/15), central and peripheral villous infarctions (4/15), mural hypertrophy of membrane arterioles (5/15), accelerated villous maturation (2/15)

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TABLE 3
Cohort or case series studies from outside of China *(continued)*

Author (country)	Number of women	Number of eligible neonates	GA at onset of Sx or diagnosis (range)	Mode of delivery	RT-PCR for SARS-CoV-2				Other fetal sites or tests	Neonatal serology	Placental histology
					Neonatal NP swab results	Placenta	Cord blood	Amniotic fluid			
Qadri and Mariona (United States)[89]	16	12	22–40 wk	VD 8/12, CD 4/12	0/12	None	None	None	None	None	None
Vintzileos et al (United States)[90]	32	29	N/A	N/A	0/29	None	None	None	None	None	None

All papers are identified by author, country (unless otherwise specified), and citation number within the main text.

BAL, bronchoalveolar lavage; *CD*, cesarean delivery; *EM*, electron microscopy; *GA*, gestational age; *IgG*, immunoglobulin G; *IgM*, immunoglobulin G; *IQR*, interquartile range; *IUFD*, intrauterine fetal demise; *N/A*, not available; *NP*, nasopharyngeal; *RT-PCR*, reverse transcription–polymerase chain reaction; *SARS-CoV-2*, severe acute respiratory syndrome coronavirus 2; *Sx*, symptoms; *VD*, vaginal delivery.

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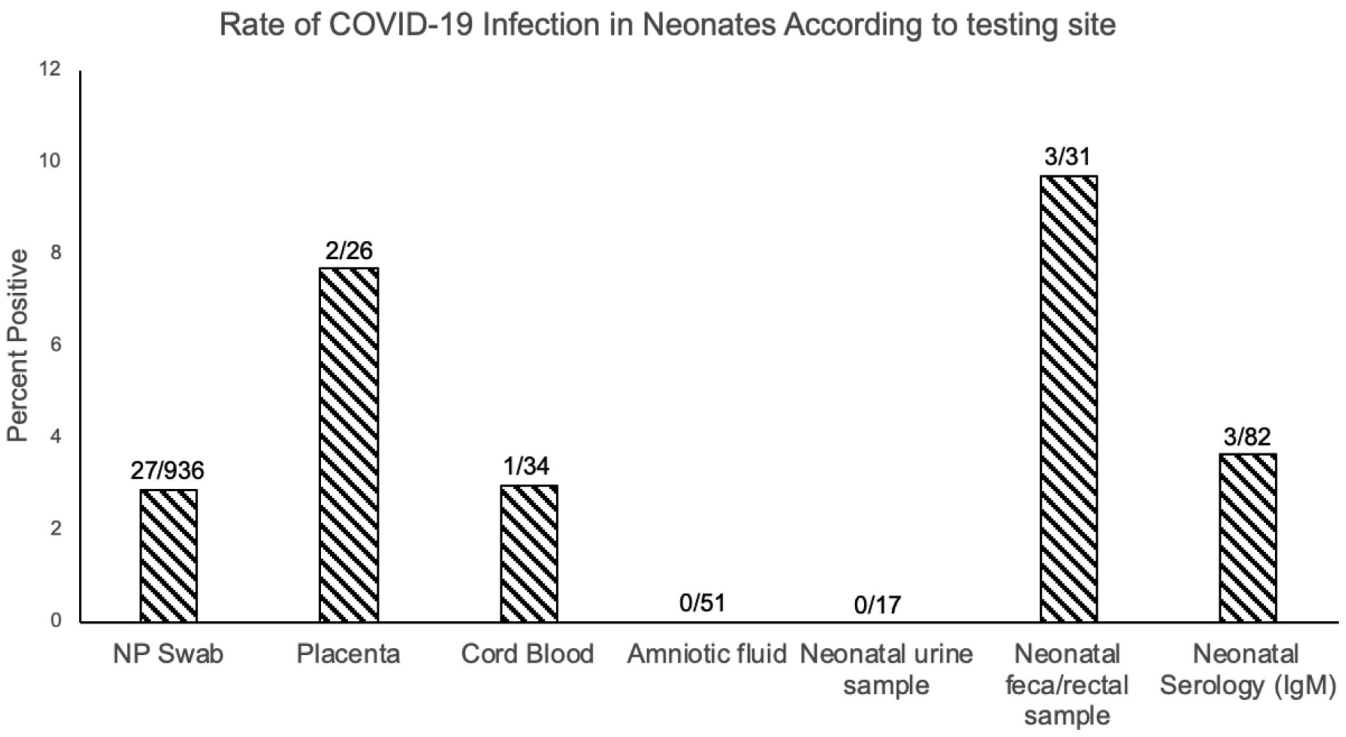
tested placentas of COVID-19–infected mothers having positive results for SARS-CoV-2 RNA (Figure 2). Among the case reports, 4 of 20 placentas tested for SARS-CoV-2 RNA had positive results. In 1 case, the placenta from a 19-week fetal demise had a positive result for SARS-CoV-2 RNA via PCR.[28] In another case mentioned earlier, a patient was diagnosed as having severe preterm preeclampsia complicated by placental abruption in the setting of COVID-19 at 22 weeks' gestation and underwent dilation and evacuation. Placental and fetal tissues were examined for the evidence of SARS-CoV-2 infection. Placenta and umbilical cord were positive for SARS-CoV-2 RNA tested by RT-PCR, whereas the fetal heart, lungs, and kidneys were negative. The sequencing of the virus isolated from the placenta confirmed it to be identical to the typical locally isolated SARS-CoV-2. Immunohistochemistry for the SARS-CoV-2 S protein and electron microscopy confirmed viral localization predominantly in the syncytiotrophoblast cells of the placenta.[27] The presence of SARS-CoV-2 virions in the fetal side of the placenta was similarly confirmed using electron microscopy in another case report of a woman who presented at 28 weeks' gestation and delivered by CD because of rapid maternal deterioration.[57] In this case, single virions were visible invading a syncytiotrophoblast, a single virion was also visualized in a microvillus, and virions were also noted in the mesenchymal core of terminal villus in the processes of the fibroblasts, but there was no evidence of fetal infection. In another case of a woman with a COVID-19 infection who delivered at 35 weeks' gestation by CD, placental viral testing had a positive result, which also correlated to the positive SARS-CoV-2 PCR testing of the newborn in NP, plasma, and stool samples, highly suggestive of in utero vertical transmission.[29] Another case of SARS-CoV-2 being detected in the placenta, which provides a particularly strong evidence for vertical transmission, was in a patient who delivered at 35 weeks and 5 days' gestation. In this case report, immunostaining of the perivillous

FIGURE 2
Rate of vertical transmission according to neonatal testing source



COVID-19, coronavirus disease 2019; *IgM*, immunoglobulin M; *NP*, nasopharyngeal.

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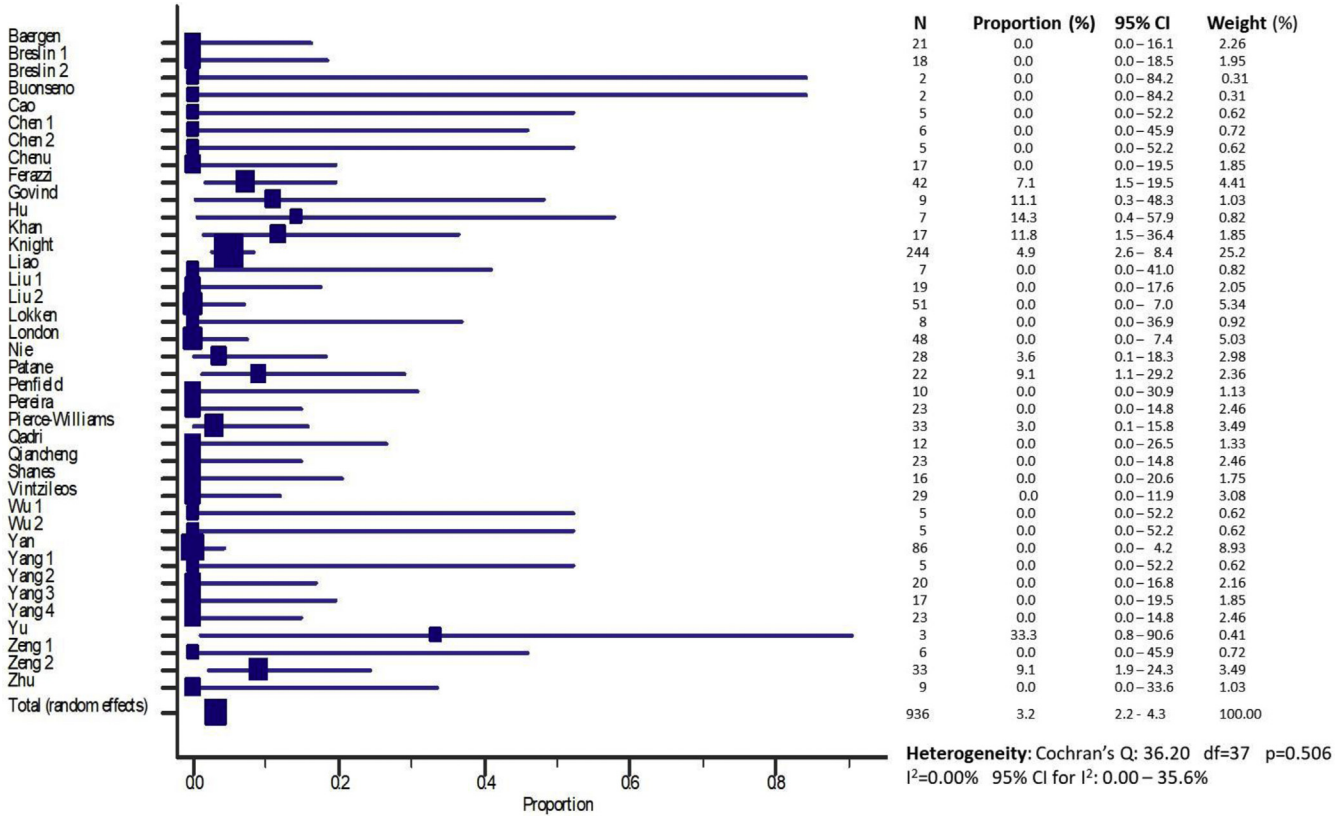
trophoblastic cells showed positivity for SARS-CoV-2 N-protein. Viral RNA was also detected in placental, amniotic fluid, and neonatal blood samples taken at birth, which is indicative of transplacental transmission of SARS-CoV-2.[58]

Placental histologic assessment from COVID-19—infected mothers was described in 6 cohort or case series studies showing various abnormalities that seem to have some common pathologic themes including vascular malperfusion, fibrin deposition, and chronic villitis or intervillositis. In a pathologic study of placentas from COVID-19—infected mothers, 12 of 15 placentas showed evidence of maternal vascular malperfusion, with 4 placentas demonstrating central and peripheral villous infarctions.[88] In addition, another series demonstrated the presence of placental vascular malperfusion in 10 of 20 placentas, with some showing intramural fibrin deposition (3/20) and chronic villitis (4/20).[84] In both of these studies, there was no evidence of neonatal SARS-CoV-2 infection by NP swab, and direct assessment of SARS-CoV-2 in the placenta was not performed. In another series of 5 COVID-19—positive mothers, all 5 placentas were negative for SARS-CoV-2 RNA but similarly exhibited fetal vascular malperfusion (5/5) and fibrin and complement deposition (4/5).[83] In a cohort of 8 COVID-19—positive patients who delivered, 1 stillborn fetus delivered at 38.7 weeks' gestation did not show any SARS-CoV-2 RNA in the placenta or in fetal tissues tested at autopsy, but the placenta demonstrated evidence of severe chronic villitis.[81] In another cohort study of 22 women with COVID-19, 2 neonates who were positive for SARS-CoV-2 by NP swab had placental histologic assessment revealing chronic intervillositis.[30] A similar evidence of chronic histiocytic intervillositis with intervillous inflammatory infiltrate consisting of mostly CD68+ macrophages and some T cells was also seen in other reports.[27,29,58]

Additional testing sites for severe acute respiratory syndrome coronavirus 2 by reverse transcription—polymerase chain reaction. Other neonatal sites have been tested for SARS-CoV-2 RNA. A total of 8 cohort or case series studies included in this systematic review had SARS-CoV-2 testing of the amniotic fluid (6 from China, 1 from the United Kingdom, and 1 from Italy). There were no positive cases among the 51 total amniotic fluid specimens tested (0/51) (Figure 2). However, we identified 2 case reports of positive amniotic fluid testing (Table 1). In the first case report, sterilely collected amniotic fluid (via syringe before rupturing the membranes) during a CD performed on a critically ill mother at 34 weeks' gestation was subjected to RT-PCR and had a positive result for SARS-CoV-2 RNA. The infant was immediately separated

FIGURE 3
Forest plot of meta-analysis of SARS-CoV-2 nasopharyngeal swab assessments of all case series and cohort studies



CI, confidence interval; *df*, degrees of freedom; *SARS-CoV-2*, severe acute respiratory syndrome coronavirus 2.

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from the mother, and initial testing was negative for SARS-CoV-2 RNA in the NP samples; however, the second neonatal NP swab was positive at 24 hours of life. Repeat throat swab from the neonate at 1 week of life remained positive.[47]

Six cohort or case series studies (5 from China and 1 from Italy) reported cord blood testing in 34 neonates with 1 positive test result resulting in a pooled vertical transmission rate of 2.9% (Figure 2).[85] In the aforementioned case report by Vivanti et al,[58] SARS-CoV-2 RNA was also detected in the amniotic fluid and NP swab of the neonate. Furthermore, SARS-CoV-2 RNA was also detected in bronchoalveolar lavage specimens and neonatal blood, showing the presence of neonatal viremia after transplacental transmission. Numerous case reports also assessed the cord blood for SARS-CoV-2 RNA. Of 16 case reports that tested the cord blood, none reported any positive cases (Table 1).

In adults, there has been evidence of the presence of SARS-CoV-2 in the gastrointestinal (GI) tract and persistent viral RNA identification in fecal specimens.[92,93] In our review, among 6 cohort or case series studies (5 from China, 1 from Italy), 9.7% of neonates (3/31) had positive results for SARS-CoV-2 in the GI tract through RT-PCR testing in anal or rectal swabs and feces (Figure 2). One case report demonstrated a positive stool sample 7 days after birth.[29] In another study, 3 neonates of mothers with COVID-19 had positive results for SARS-CoV-2 RNA on anal swabs at day 2 of life.[67] There have been only 2 cohort or case series studies from China describing results of SARS-CoV-2 RT-PCR testing of urine samples in neonates born to women with COVID-19 infection. Of a total of 17 neonates tested, the detection rate for SARS-CoV-2 was 0% (0/17) (Figure 2).

In addition, we reviewed the articles for the presence of SARS-CoV-2 RNA in maternal body fluids that may be responsible for vertical transmission before and after delivery. There were 2 studies from China that reported on SARS-CoV-2 RT-PCR testing in vaginal swabs, demonstrating a detection rate of 0% (0/19). Our review included 6 cohort or case series studies from China that assessed for the presence of SARS-CoV-2 in breast milk by RT-PCR, revealing a

positive rate of 4.2% (2/47) in the breast milk specimens tested.[29,72,85]

Serologic assessment. Serologic assessment was performed on neonates born to COVID-19–infected mothers in 4 cohort or case series studies from China and 1 from Italy.[26,71,75,85] Among the total number of neonates tested in those cohort or case series studies, 3.7% of tested infants (3/82) were positive for anti–SARS-CoV-2 IgM antibodies (Figure 2). In a case report, an otherwise healthy infant was born via CD to a 29-year-old woman with an RT-PCR–confirmed COVID-19 infection. This infant was immediately placed in isolation, and a blood sample at 2 hours of age was noted to show an elevated SARS-CoV-2 immunoglobulin G (IgG) and IgM. Although the IgG can be secondary to transplacental transfer, the infant's positivity for SARS-CoV-2 IgM cannot be explained by transplacental transfer.[25] Furthermore, IgM antibodies usually do not appear until 3 to 7 days after infection. Paradoxically, all 5 RT-PCR tests on the infant were negative for COVID-19.[25] Nonetheless, the antibody profile of this infant is suggestive of fetal exposure to COVID-19 in utero. A follow-up study conducted on 6 infants born to COVID-19–positive mothers showed positive IgM antibodies in 2 infants. However, all throat swabs and blood samples from the neonates similarly tested negative for the virus.[26] In one of the largest studies looking at neonatal serology, Liu et al[71] tested 51 infants for COVID-19 antibodies with none having a positive result for IgM and IgG. Yang et al[75] assessed 23 infants for COVID-19 infection; although none of them had positive NP swabs, 1 premature infant was found to have a positive result for anti–SARS-CoV-2 IgM within 2 hours after birth. Overall, the presence of IgM in these neonates immediately after birth is highly suggestive of in utero vertical transmission.

Comment

Main findings

In this systematic review, we aimed to summarize initial data regarding the risk of vertical transmission of COVID-19 to help inform counseling and care of women who are pregnant or contemplating pregnancy at this time. It included 39 cohort or case series studies in the quantitative synthesis summarizing data from a total of 936 SARS-CoV-2–tested neonates to pregnant women with COVID-19 infection, spanning the initial 6 months since the disease manifested (end of December 2019). Regarding the most common method of testing for SARS-CoV-2, that is, NP swab RT-PCR testing, we determined that maternal-to-fetal transmission of the virus may occur in approximately 3.2% of infected mothers in the third trimester. Interestingly, there is a striking similarity in NP swab SARS-CoV-2 pooled positivity rates between studies from China (2%) and studies outside of China (3.5%). This rate of SARS-CoV-2 RNA positivity was also in the same range as for placental (7.7%) and cord blood samples (2.9%). The fact that IgM serology was also in the same range (3.7%) provides further support to the notion that vertical transmission is occurring in the third trimester, albeit in a minority of pregnant women. Nonetheless, these are all indirect measures of possible vertical transmission. The best evidence to date for transplacental transmission of SARS-CoV-2 was seen in the case report by Vivanti et al[58] showing not only viral RNA and protein in the placenta but also viral RNA in the amniotic fluid and neonatal blood sampled at birth. Although these studies further strengthen the case for vertical transmission occurring in utero, fetal infection could only be conclusively determined by the direct demonstration of the presence of SARS-CoV-2 in fetal tissues.

Clinical implications

Because of the teratogenicity and fetal morbidity associated with other viral infections such as Zika and Rubella, vertical transmission remains a concern with COVID-19. Compared with other known viruses leading to congenital infections, the vertical transmission rates reported in this review are consistent with those for numerous pathogens. The transmission rates for these pathogens range from as low as 0.2% to 0.4% for cytomegalovirus and varicella zoster virus to as high as 17% to 33% for parvovirus B19.[94] Although the vast majority of infants delivered in these reports did not experience significant morbidity and mortality, nearly all of them were born in the third trimester.[94] For the aforementioned pathogens, the transplacental passage of infectious pathogens tends to occur with increasing frequency as gestational age increases, whereas detrimental effects on the fetus increase with decreasing gestational age. Therefore, we should assume that COVID-19 may also have similar detrimental effects when maternal infection occurs early in gestation.

In addition to direct fetal infection and subsequent teratogenicity, indirect fetal effects are also a major concern with the COVID-19 infection. It has recently been proposed that COVID-19 results in systemic endothelial damage that, in adults, predisposes to the development of or exacerbation of already existing hypertension and other cardiovascular diseases and results in a severe COVID-19 course.[95,96] In particular, COVID-19 frequently induces hypercoagulability with both microangiopathy and local thrombus formation.[97] Pregnant women present an especially vulnerable population given their hypercoagulable state, with associated unique conditions. Hypertensive disorders of pregnancy are a group of conditions, the pathogenesis of which is not well understood; however, systemic endothelial dysfunction, vascular malperfusion, and a systemic proinflammatory state have been implied as potential etiologies or components of the disease pathophysiology, especially in cases of preexisting hypertension, obesity, or diabetes.[98] Of note, our systematic review found several cohort studies and case reports describing an association between maternal COVID-19 infection and placental evidence of maternal vascular malperfusion, particularly maternal vessel injury and intervillous thrombi. One may speculate that COVID-19 may result in the activation of endothelial damage pathways predisposing to the development of hypertensive disorders

of pregnancy with associated adverse maternal and neonatal outcomes (ie, prematurity, growth restriction) over the long term. This is one of the many issues that remain open for study.

Research implications

The standard for detecting COVID-19 infection is via detection of viral RNA using RT-PCR. However, this diagnostic method does exhibit variable performance. In a study assessing the performance capability of RT-PCR test in patients with COVID-19 using numerous sources for viral RNA including nasal, bronchoalveolar lavage, feces, blood, and urine specimens, sensitivities for COVID-19 detection were 63%, 93%, 29%, 1%, and 0%, respectively.[99] In our systematic review, blood similarly had one of the lowest rates of SARS-CoV-2 detection (2.9%), along with urine (0%) and amniotic fluid (0%). The lack of detection of SARS-CoV-2 in the amniotic fluid is not surprising because its source of production is fetal urine. Nevertheless, such substantial variation in SARS-CoV-2 positivity as a factor of testing site argues for specimen testing from multiple sites to increase sensitivity and reduce false-negative rates and preferably the use of complementary testing methods such as serology. In this systematic review, the rate of IgM positivity in tested neonates was 3.6%, which is quite similar to the positive rates by RT-PCR NP testing (3.2%). Patients typically develop IgG antibodies approximately 2 weeks after the onset of symptoms. Although developing fetuses can produce immunoglobulins early in gestation, the protective IgG antibodies in their circulation come from transplacental antibody transfer of maternal IgG.[100] Because IgM antibodies are too large to cross the placenta, the presence of IgM in a neonate during the perinatal period is suggestive of fetal production after in utero infection. The reported performance of perinatal IgM antibody testing indicates a sensitivity of 70.2% to 88.2% and specificity of 96.2% to 99%, although experience with IgM assays suggests that they are inherently limited by false-positive results in other congenital infections.[101] Further testing and validation of serologic assays are ongoing.

Strengths and limitations

We acknowledge that there are significant limitations to our study. Our current knowledge as reflected in this systematic review is limited to a few cohort studies and mostly case series and case reports. In addition, significant heterogeneity exists in the quality of included studies and in what data were reported. Although almost all studies reported results of SARS-CoV-2 NP testing of neonates, there was a significant variation in the performance of SARS-CoV-2 testing of other specimen sites across studies and of neonates within each study, making it challenging to aggregate the data. Moreover, because most of the included cohort or case series studies comprised pregnant patients who underwent selective testing for COVID-19 owing to symptoms, it is likely that patients with asymptomatic infections are underrepresented. Whether the risk of vertical transmission of SARS-CoV-2 may be related to symptom or disease severity is unknown, and as such, pooled rates of vertical transmission risk in this systematic review should be interpreted with caution.

Our study also has several strengths. The quantitative synthesis of this review, which was the basis for the pooled proportion results, was limited to cohort and case series studies as defined by at least 5 pregnant patients with COVID-19 infection. This significantly reduced the chance of publication bias of rare positive outcomes inherent to case reports. A second strength is that the studies included in this review were restricted to laboratory-confirmed cases of SARS-CoV-2 infection, which included both symptomatic and asymptomatic women. Diagnosis was made by RT-PCR of NP swab, which is currently the gold standard for diagnosis, thus avoiding reliance on uncertain COVID-19 diagnostic tests. Moreover, the review included only studies in which SARS-CoV-2 RT-PCR testing was performed on the fetus or neonate within 48 hours of delivery, substantially decreasing the likelihood of a positive result arising from postpartum horizontal transmission. Another strength is that this review includes reports from multiple countries including China, the United States, the United Kingdom, Italy, and Spain, making the results more generalizable.

Conclusion and implications

Given the accumulating evidence from studies noting the presence of COVID-19 viral RNA in numerous fetal or neonatal sources and positive serology, vertical transmission of COVID-19 is indeed highly likely. This systematic review suggests that maternal COVID-19 infection in the third trimester appears to be associated with low rates of vertical transmission (approximately 3.2%) without significant consequence to the newborns. This low rate is consistent with recent transcriptomic data showing that placental cells coexpressing ACE2 and TMPRSS2 proteins, required for SARS-CoV-2 viral cell entry, are rare.[23] However, numerous questions remain to be addressed concerning vertical transmission of this novel coronavirus. These include whether the virus can cross the placenta in utero and cause an infection in fetal tissues. Furthermore, it is necessary to understand whether susceptibility varies by gestational age and whether there is a gestational age at which the virus is more likely to infect and cross the placenta. An even more crucial set of questions center around fetal development and morbidity. For example, if placental infection occurs in the first trimester, can the virus have teratogenic effects and what would those be? In addition, it would be essential to determine whether there are any nonteratogenic fetal effects that can result from viral effects on the uterine vasculature and placental tissue (ie, growth restriction; placental abruption, infarction, or stillbirth; hypertensive disorders of pregnancy). Finally, if in utero transmission indeed occurs, does the rate of transmission depend on the severity of the maternal disease and does a positive test at birth correlate with the clinical course of COVID-19 in newborns? To answer these questions, further larger-

scale studies are needed ideally across numerous countries. A cooperative system of monitoring COVID-19—positive pregnant women throughout gestation would help to answer these remaining questions to help guide patients, physicians, and policy makers. ■

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SUPPLEMENTAL FIGURE
Search strategy

Search for Ovid Embase.
Additional database searches provided upon request: Alyssa.grimshaw@yale.edu

1. (covid-19 or COVID19 or COVID-19 or SARS-CoV-2 or SARS-CoV2 or severe acute respiratory syndrome coronavirus 2 or 2019-nCoV or 2019nCoV or coronavirus).tw,kw.
2. exp coronavirus infections/
3. exp coronavirinae/
4. 1 or 2 or 3
5. exp pregnancy/
6. exp birth/
7. exp "embryonic and placental structures"/
8. fetus/
9. exp infant/
10. (perinatal or pregnan* or maternal* or natal or prenatal or antenatal or postpartum or postnatal or neonatal or trimester* or fetomaternal*).tw,kw.
11. ((after or before) adj1 (birth* or childbirth*)).tw,kw.
12. (placenta* or placentom* or breastmilk or breast milk or mother's milk or mothers milk or breastfeed* or breastfed or breast feed* or breast fed or umbilical cord*).tw,kw.
13. (fetus* or fetal or newborn* or baby or babies or neonate* or infant* or embryo*).tw,kw.
14. or/5-13
15. exp vertical transmission/
16. exp disease transmission/
17. exp virus transmission/
18. (transmission* or transmit* or transmissibl* or transfer*).tw,kw.
19. (mother-to-child or mother-to-infant or maternal-fetal or vertical).tw,kw.
20. or/15-19
21. 4 and 14 and 20

Kotlyar. Vertical transmission of COVID-19: a systematic review and meta-analysis. Am J Obstet Gynecol 2021.

SUPPLEMENTAL TABLE

Modified Newcastle-Ottawa scale for assessing quality of cohort or case series studies

Author	Year	Representativeness of exposed cohort	Exposure assessment	Outcome assessment	Adequacy of length of time before follow-up	Adequacy of follow-up of cohorts	Methodological quality
Breslin, et al[76]	April 2020	★	★	★	★	★	High
Breslin, et al[77]	May 2020	★	★	★	★	★	High
Cao, et al[59]	April 2020		★		★		Low
Chen, et al[10]	February 2020	★	★	★	★		Moderate
Ferrazzi, et al[78]	April 2020	★	★	★	★	★	High
Hu, et al[60]	April 2020		★	★	★	★	Moderate
Khan, et al[38]	April 2020	★	★	★	★		Moderate
Liu, et al[40]	March 2020	★		★	★		Low
Nie, et al[63]	March 2020	★	★	★	★		Moderate
Penfield, et al[79]	May 2020	★	★	★	★	★	High
Patane, et al[30]	May 2020	★	★	★	★	★	High
Pierce-Williams, et al[80]	May 2020	★	★		★	★	Moderate
Qiancheng, et al[64]	April 2020	★	★	★	★	★	High
Yan, et al[11]	April 2020	★	★	★	★		Moderate
Yang, et al[65]	April 2020	★	★	★	★	★	High
Yin, et al[66]	April 2020	★	★	★	★		Moderate
Yu, et al[56]	March 2020	★	★	★	★	★	High
Zeng, et al[26]	March 2020		★	★	★		Low
Zeng, et al[67]	March 2020	★	★	★	★	★	High
Zhu, et al[9]	Feb 2020		★	★	★		Low
Lokken, et al[81]	May 2020	★	★	★			Low
London, et al[82]	May 2020	★	★	★	★		Moderate
Mulvey, et al[83]	April 2020		★				Low
Baergen, et al[84]	May 2020	★	★	★	★		Moderate
Buonsenso, et al[49]	May 2020		★	★	★	★	Moderate
Chen, et al[68]	April 2020		★	★	★		Low
Chen, et al[69]	March 2020	★	★	★	★		Moderate
Govind, et al[86]	May 2020	★	★	★	★		Moderate
Knight, et al[12]	May 2020	★	★	★	★	★	High
Liao, et al[70]	April 2020	★	★	★	★	★	High
Liu, et al[71]	May 2020	★	★	★	★	★	High
Pereira, et al[87]	May 2020	★	★	★	★		Moderate
Qadri, et al[89]	May 2020	★	★	★	★		Moderate
Wu, et al[72]	May 2020	★	★	★	★	★	High
Wu, et al[73]	April 2020	★	★		★		Low
Yang, et al[74]	April 2020		★		★		Low

Kotlyar. Vertical transmission of COVID-19: a systematic review and meta-analysis. Am J Obstet Gynecol 2021. *(continued)*

SUPPLEMENTAL TABLE

Modified Newcastle-Ottawa scale for assessing quality of cohort or case series studies *(continued)*

Author	Year	Representativeness of exposed cohort	Exposure assessment	Outcome assessment	Adequacy of length of time before follow-up	Adequacy of follow-up of cohorts	Methodological quality
Yang, et al[75]	May 2020	★	★	★	★		Moderate
Shanes, et al[88]	May 2020	★	★	★			Low
Vintzileos, et al[90]	April 2020	★	★	★	★		Moderate

Questions:

1. Did the patients represent the whole cases of the medical center? Cases included represented the general population of COVID-19 pregnant women.
2. Was the diagnosis correctly made? COVID-19 was diagnosed by viral PCR.
3. Was the outcome correctly ascertained? Clear description of adequate methodology of testing for COVID-19 in fetus or neonate was provided.
4. Was follow-up long enough for outcomes to occur? Adequate follow-up time was reported.
5. Were all important data cited in the report? Testing was repeated at least 2 times on 2 separate occasions.

Methodological quality: high=5 stars, moderate=4 stars, low=3 or fewer stars.

Kotlyar. Vertical transmission of COVID-19: a systematic review and meta-analysis. Am J Obstet Gynecol 2021.