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Clinical outcomes of 201 neonates born to mothers with COVID-19: a systematic review

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Abstract. – OBJECTIVE: To evaluate the clinical manifestations and outcomes of neonates born to women who had Coronavirus Disease 2019 (COVID-19) during pregnancy.

MATERIALS AND METHODS: A systematic literature search was conducted on PubMed and Embase till April 15, 2020, by combining the terms (COVID-19, Severe Acute Respiratory Syndrome Coronavirus 2, SARS-CoV-2, Novel Coronavirus, 2019-nCov, Wuhan pneumonia) and (pregnancy, pregnant women, mother, fetus, neonate, newborn, infant).

RESULTS: We included 16 case series and 12 case reports describing a total of 223 pregnant women and 201 infants. Four newborns born to mothers affected by COVID-19 were reported to have laboratory-confirmed Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection within 48 hours after birth. However, Reverse Transcription-Polymerase Chain Reaction tests of the breast milk, placenta, amniotic fluids, and cord blood and maternal vaginal secretions were all negative for SARS-CoV-2 in the reported cases. Fetal death was reported in two cases, and 48 of 185 newborns (25.9%) were born prematurely. Infants born small for gestational age and low birth weight (< 2,500 g) accounted for 8.3% and 15.6% of reported cases, respectively. Birth asphyxia and respiratory distress syndrome were observed in 1.8% and 6.4% of neonates, respectively. There was one neonatal death due to intractable gastric bleeding among the SARS-CoV-2-negative infants.

CONCLUSIONS: Current evidence suggests that COVID-19 during pregnancy rarely affects fetal and neonatal mortality, but can be associated with adverse neonatal morbidities. Vertical transmission has not been observed in the majority of the reported cases. The infants born to mothers with COVID-19 are carefully monitored for accompanying complication, and quarantine of infected mothers is warranted.

Key Words:
COVID-19, SARS-CoV-2, Newborn, Infant, Pregnancy, Outcome.

Introduction

The outbreak of the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which was first reported in Wuhan, China, is now spreading throughout the world with high infectivity and fatality rates[1]. This Novel Coronavirus has caused special concern in pregnant women and newborns, because previous Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-1) and Middle East Respiratory Syndrome Coronavirus (MERS-CoV) outbreaks caused high case mortality rates and severe complications in pregnant women and their fetuses and newborns[2-5]. Furthermore, pregnant women and neonates were both highly susceptible to infection and hypoxia[6-8]. Whether SARS-CoV-2 virus can be vertically transmitted from mother to fetus is also a crucial interest[9].

However, knowledge of neonatal outcomes when mothers are infected with Coronavirus Disease (COVID-19) during pregnancy is still limited to several case reports and case series. We conducted a systematic review of the published literature to assess the clinical impact of maternal SARS-CoV-2 infection during pregnancy on infants, including clinical and laboratory characteristics of infants and their mothers, maternal and neonatal outcomes, and evidence of mother-to-infant vertical transmission.

Materials and Methods

This review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement (PRISMA)[10]. Ethical approval was not required for this review.

Search Strategy

Medline/PubMed and Embase were searched by combining the terms (COVID-19, Severe

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Acute Respiratory Syndrome Coronavirus 2, SARS-CoV-2, Novel Coronavirus, 2019-nCov, Wuhan pneumonia) and (pregnancy, pregnant women, mother, fetus, neonate, newborn, infant) to identify studies that report on neonates born to mothers affected by COVID-19 during pregnancy. The search was executed on April 15, 2020. Additional studies were identified by examining the reference lists of relevant articles. No language or data restrictions were applied to the search.

Study Selection

SHY and JGA independently screened the titles and abstracts for potential relevance and conducted full-text reviews of the selected articles. Any disagreements were resolved by a third reviewer (JMK) following a discussion with all three reviewers. Studies were included if they reported demographic and clinical characteristics, as well as maternal and neonatal outcomes for mothers with confirmed COVID-19 (Figure 1). We classified articles that reported more than five cases as case series and those that reported fewer than five cases into a case report. Descriptive statistics were applied to case reports for summarizing the data.

We excluded articles if they included neonates born to mothers who were not confirmed to have COVID-19 during pregnancy or if they did not address the outcomes of neonates or their mothers. Reviews, editorials, expert opinions, letters, and animal experiments not presenting original data were excluded, as well as studies reporting cases with incomplete information. If studies separately addressed the data of laboratory-confirmed and clinically confirmed COVID-19-positive pregnant women, we only included the information on the laboratory-confirmed pregnant women.

Data Extraction

Two authors (SHY and JGA) independently extracted the following variables: first author, date of publication, and country; neonatal outcomes, including birth weight, incidence of prematurity, incidence of birth asphyxia (defined as an Apgar score at 5 minutes of < 4)[11], incidence of low birth weight (LBW, < 2,500 g)[12], incidence of small for gestational age (SGA), Apgar scores at 1 and 5 minutes, clinical manifestations (e.g., fever, shortness of breath), laboratory findings if available, and fetal and neonatal mortality[13]; diagnostic method used to document COVID-19, type of samples used for testing, the number of laboratory tests performed for SARS-CoV-2, and the number of laboratory confirmed SARS-CoV-2 cases; and the incidence of radiologic confirmed pneumonia and number of chest computed tomography (CT) scans performed. Information for mothers who were confirmed COVID-19 positive was also extracted as follows: demographics, epidemiological history, gestational ages at presentation and delivery, diagnostic method for COVD-19 confirmation, the number of confirmed cases and confirmed cases by Reverse Transcription Polymerase Chain Reaction (RT-PCR), clinical signs and symptoms at presentation, laboratory findings, number of births, delivery mode, maternal complications, and pregnancy outcomes.

Statistical Analysis

Statistical analysis was performed using SPSS, version 25.0 (IBM Corp., Armonk, NY, USA). Continuous variables were presented as mean with standard deviation. Categorical variables were described as number of cases and percentages (%).

Results

Study Selection and Characteristics

The search revealed 170 results; after the removal of duplicate articles and exclusion of studies based on titles and abstracts, 37 relevant studies were identified for full test review. Of these, seven studies were excluded due to a lack of information on whether COVID-19 was diagnosed in pregnancy or lack of information regarding perinatal outcomes. Two were excluded due to duplicated patient information. Therefore, 28 articles were finally included in the systematic review (Figure 1).

All studies were case reports or series. Our review included 16 case series[14-29] and 12 case reports[30-41] published between February 10, 2020, and April 13, 2020, most of them were from China[14-23,25-34,37,38,40,41]. There was one report each from Honduras[35], Iran[39], South Korea[36], and the USA[24]. The studies included a total of 223 pregnant women and 201 infants; the main characteristics of these studies are shown in Table I.

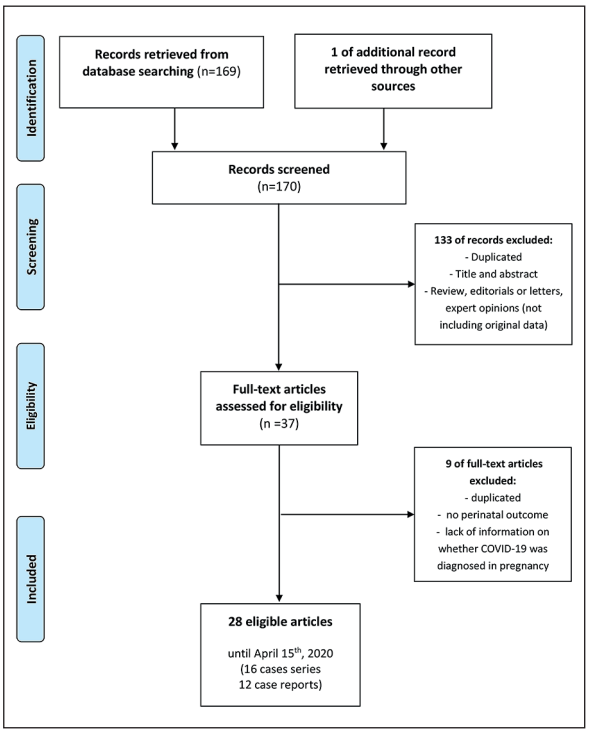

Figure 1. Flow diagram of the study selection process.

Clinical Characteristics and Outcomes of Neonates Born to COVID-19 Infected Mothers

Among the 223 COVID-19 confirmed pregnant women, 201 (90.1%) women delivered before end of the studies (Table I). The reported number of live births was 201 (including 2 twin births). Among 185 neonates for whom the method of delivery was available, 163 (88.1%) were delivered by Cesarean section and 22 (11.9%) were delivered vaginally (Table II). Gestational age at birth ranged from 30 weeks plus 6 days to 41 weeks plus 5 days. Birth weight ranged from 1880 g to 4050 g. Forty-eight of 185 newborns (25.9%) were born prematurely. Infants born SGA account for five of 60 cases (8.3%) and infants born LBW accounted for 15 of 96 cases (15.6%). Three of 168 (1.8%) neonates with available data had birth asphyxia. A majority of Apgar scores at 1 min and 5 min were 8 to 9 and 9 to 10, respectively (Table II).

Mostly reported infants born to COVID-19 confirmed mothers were asymptomatic (68 of 73 cases, 93.2%). The most common clinical manifestations included shortness of breath (9.6%), gastrointestinal symptoms (e.g., feeding intolerance, vomiting) (7.2%), respiratory distress syndrome (RDS, 6.4%), and fever (4.0%) among the reported cases (Table II). Radiologic confirmed pneumonia was shown in 18 of 68 neonates (26.5%). Among them, three cases were diagnosed as bacterial pneumonia[17]. One neonate was applied mechanical ventilation[22]. DIC was found in two cases[14]. Neonatal death has been reported in one case (one of 177 cases, 0.6%), due to gastric bleeding with disseminated intravascular coagulation (DIC)[14].

Clinical Characteristics of Who Were Confirmed COVID-19 by Laboratory Tests

Among the 201 neonates born to COVID-19 confirmed mothers, 167 (83.1%) were performed laboratory tests, and four neonates (2.4%) were confirmed SARS-CoV-2 infection by RT-PCR. One case was confirmed by throat swab at 36 hours after birth[21] and other three cases by nasopharyngeal and anal swab on 2 days after birth[22]. Liu et al[29] reported one case who showed positive RT-PCR test results in throat swab, but the result of repeated check on the same sample was negative, indicating false-positivity. Zeng et al[23] reported two neonates and Dong et al[34] reported one neonate who had elevated SARS-CoV-2 IgM (≥10 AU/mL) in their serum but all of their nasopharyngeal samples showed negative RT-PCR results.

The clinical and laboratory characteristics of the four confirmed neonates with SARS-2 infection by RT-PCR are shown in Table III. All four patients were delivered by cesarean section due to their maternal COVID-19 pneumonia. All patients were male. One neonate (25%) had fetal distress and delivered prematurely (31 weeks plus 2 days) with LBW (1580 g)[22]. All neonates showed pneumonia on chest imaging. Fever (50%), lethargy (50%), and vomiting (75%) were the most frequent clinical manifestations. Lymphocytopenia and leukocytosis were found in two of the three neonates (75%). One neonate showed elevated procalcitonin level, despite other laboratory test results being normal[22].

One neonate who delivered prematurely needed resuscitation because of birth asphyxia[22]. He was treated and showed improvement with antibiotics, noninvasive ventilation, and caffeine for respiratory distress syndrome, pneumonia, and suspected sepsis (positive blood culture with *Enterobacter* agglomerates).

No special treatment as antiviral agent was given. All infected neonates recovered well and

Table I. Characteristics of the included studies.

Authors	Date	Country	Study area	Study period	Confirmed pregnant women cases, n	Patients who delivered before end of study period, n (%)	Number of neonates, n	Neonatal confirmed cases/test performed cases, n (%)	Reference
Zhu et al[14]	10-Feb-20	China	Hubei Province, China	Jan 20 – Feb 5, 2020	9*	9 (100)	10	0/9 (0)	[14]
Liu et al[15]	4-Mar-20	China	Outside Wuhan, China	Dec 8, 2019 – Feb 25, 2020	13	10 (77)	9	0/9 (0)	[15]
Chen et al[6]	7-Mar-20	China	Wuhan, China	Jan 20 – Jan 31, 2020	9	9 (100)	9	0/6 (0)	[16]
Zhang et al[17]	7-Mar-20	China	Hubei Province, China	Jan 30 – Feb 17, 2020	16	16 (100)	16	0/10 (0)	[17]
Chen et al[18]	16-Mar-20	China	Wuhan, China	Jan 30 – Feb 23, 2020	17	17 (100)	17	0/17 (0)	[18]
Liu et al[19]	18-Mar-20	China	Wuhan, China	Jan 20 – Feb 10, 2020	15	11 (73)	11	0/11 (0)	[19]
Liu et al[20]	20-Mar-20	China	Wuhan, China	Jan 27 – Feb 14, 2020	16†	6 (38)	6	NA	[20]
Yu et al[21]	24-Mar-20	China	Wuhan, China.	Jan 01 – Feb 08, 2020	7	7 (100)	7	1/3 (33)	[21]
Zeng et al[22]	26-Mar-20	China	Wuhan, China	Jan – Feb, 2020	33	33 (100)	33	3/33 (9)	[22]
Zeng et al[23]	26-Mar-20	China	Wuhan, China.	Feb 16 – Mar 6, 2020	6	6 (100)	6	0/6 (0)	[23]
Breslin et al[24]	27-Mar-20	USA	New York, USA	until Mar 25, 2020	7	2 (29)	2	0/2 (0)	[24]
Chen et al[25]	28-Mar-20	China	Wuhan, China	Jan 20 – Feb 10, 2020	5	5 (100)	5	0/5 (0)	[25]
Li et al[26]	30-Mar-20	China	Wuhan, China	Jan 24 – Feb 29, 2020	16	16 (100)	17	0/3 (0)	[26]
Khan et al[27]	8-Apr-20.	China	Wuhan, China	Jan 25 – Feb 15, 2020	17	17 (100)	17	0/17 (0)	[27]
Yang et al[28]	10-Apr-20	China	Wuhan, China	Jan 20 – Jan 29, 2020	7	7 (100)	7	0/7 (0)	[28]
Liu et al[29]	13-Apr-20	China	Wuhan, China	Jan 31 – Feb 29, 2020	10§	10 (100)	10	0/10 (0)‡	[29]
Case reports (N=12)	28-Feb-20 to 11-Apr-20	China (9), Honduras (1), Iran (1), South Korea (1)		Jan 10 – Mar 19, 2020	20	20 (100)	19	0/19 (0)	[30-41]
Total	10-Feb-20 – 13-Apr-20	China (24), Honduras (1), Iran (1), South Korea (1), U.S.A (1)		Dec 8, 2019 – Mar 25, 2020	223	201 (90)	201	4/167 (2.4)	[14-41]

NA: not available *All confirmed cases in this table were laboratory diagnosed, except one pregnant woman clinically diagnosed and integrated in a case series. †Only included laboratory-confirmed cases. ‡One case had positive SARS-CoV-2 RT-PCR in throat swab, but repeated check on the same sample showed that the result was negative (false positive). §Only included laboratory-confirmed cases.

Table II. Clinical characteristics and outcomes of infants born to mothers with COVID-19.

Authors		Zhu H et al.	Liu Y et al.	Chen H et al.	Zhang L et al.	Chen R et al.	Liu D et al.	Liu H et al.	Yu N et al.	Zeng L et al.	Zeng H et al.	Breslin N et al.	Chen S et al.	Li N et al.	Khan S et al.	Yang P et al.	Liu W et al.	Case reports	Total n/N (%)
Neonatal outcomes	Number of live births	10 (twin 1)	9	9	16	17	11	6	7	33	6	2	5	17 (twin 1)	17	7	10	19	192
	Mean birth weight (range), g	NA	NA	3011 (1880–3820)	3139 (2300–3750)	NA	NA	NA	3264 (3000–3500)	NA	NA	NA	3691 (3235–4050)	3066 (NA)	3104 (2300–3750)	2096 (1880–3800)	3158 (2500 – 3670)	3045.4 (1500– 3800)	–
	Gestational weeks at delivery, range	NA	NA	36 –39^{+4}	35^{+5} – 41	NA	NA	NA	37 – 41^{+5}	NA	All 3rd trimester	37 – 37^{+5}	38^{+6} – 40^{+4}	NA**	35^{+5}–41	36–38^{+2}	35^{+2} –41^{+2}	30^{+6} – 39^{+1}	–
	Vaginal delivery	2	0	0	0	0	1	NA	0	7	0	0	3	2	0	0	NA††	7/20	22/185 (11.9)
	Cesarean section	7	10	9	16	17	10	NA	7	26	6	2	2	14	17	7	NA	13/20	163/185 (88.1)
	Diagnostic method	PCR	serology	PCR	PCR	PCR	PCR	NA	PCR	PCR	PCR , serology	PCR	PCR	PCR	PCR	PCR	PCR	PCR, serology	–
	Specimen collection site	Throat	Serum	Throat	Pharynx	NP	RT, blood	NA	Throat	NP, anus	Serum, throat	NA	Sputum, throat, lower RT	Throat	Throat	Throat	Throat, gastric fluid, urine, feces	NP, serum, rectum, sputum, urine	–
	Laboratory-confirmed cases of SARS-CoV-2	0/9	0/9	0/6	0/10	0/17	0/11	NA	1/3	3/33	0/6	0/2	0/5	0/3	0/17	0/7	0/10	0/19	4/167 (2.4)
	Elevated SARS-CoV-2 IgM (≥10 AU/mL)	NA	0	NA	NA	NA	NA	NA	NA	NA	2	NA	NA	NA	NA	NA	NA	1/2	3/17 (17.6)
	Elevated SARS-CoV-2 IgG (≥10 AU/mL)	NA	0	NA	NA	NA	NA	NA	NA	NA	5	NA	NA	NA	NA	NA	NA	1/2	6/17 (35.3)
	Radiology- confirmed pneumonia	4/10	NA	NA	3/10	NA	NA	NA	1/3	3/3†	NA	NA	NA	NA	5/17	0	0/17	2/8	18/68 (26.5)
	Premature births	6	6	4	1/10*	3	3	NA	0	4	NA	0	0	4	3	4	2	8	48/185 (25.9)
	SGA	2	NA	NA	NA	NA	NA	NA	0	3	NA	NA	NA	NA	NA	NA	NA	0/10	5/60 (8.3)
	LBW	7	NA	2	NA	0	NA	NA	0	NA	NA	NA	0	3	NA‡	1	0	2/14	15/96 (15.6)
	Mortality	1	0	0	0/10	0	0	0	0	0	NA	NA	0	0	0	0	0	0/18	1/177 (0.6)
	Apgar scores at 1 min/5 min, range	7–10/8–10	NA	8–9/9–10	NA	8–9/7–9	8/9	NA	8–9/9–10	NA	8–9/9–10	NA	10/10	9.6/10§	7–9/9–10	8–9/9–10	8/9	7–9/8–10	–
	Asphyxia	0	0	0	1	0	0	NA	0	2	0	NA	0	0	NA	0	0	0/19	3/168 (1.8)
Neonatal symptoms	Fever	2	0	NA	NA	NA	0	0	0/7	2	NA	NA	0	0	NA	0	0	1/9	5/125 (4.0)
	Respiratory distress syndrome	2	0	NA	NA	NA	0	0	0/7	4	NA	NA	0	0	NA	2	0	0/9	8/125 (6.4)
	Shortness of breath	6	0	NA	NA	NA	0	0	1/7	4	NA	NA	0	0	NA	0	0	1/9	12/125 (9.6)
	Cyanosis	3	0	NA	NA	NA	0	0	0	3	NA	NA	0	0	NA	0	0	0/9	6/125 (4.8)
	Gastrointestinal symptoms (feeding intolerance, vomiting, GI bleeding)	5	0	NA	NA	NA	0	0	0	3	NA	NA	0	0	NA	1	0	0/9	9/125 (7.2)
	Shock	1	0	NA	NA	NA	0	0	0	NA	NA	NA	0	0	NA	0	0	0/9	1/92(1.1)
	Asymptomatic	NA	9	NA&	NA	NA	11	6¶	6	NA	NA	NA	5	17	NA	4	10	NA	68/73(93.2)
References		[14]	[15]	[16]	[17]	[18]	[19]	[20]	[21]	[22]	[23]	[24]	[25]	[26]	[27]	[28]	[29]	[30-41]	–

Cases were described as number or number/ (total available case numbers except missing values) in the study. NA: not available. RT: respiratory tract specimen; SGA, small for gestational age; LBW, low birth weight; NP, nasopharynx; PCR, polymerase chain reaction; GI, Gastrointestinal. *Data unavailable in six neonates. †Three newborns were diagnosed with bacterial pneumonia. ‡Three of 17 neonates (including neonates born to clinically confirmed mothers, whom were not included in this review) had weight lower than 2700 g. §The range of Apgar score was not described in the study. ¶There was no clinical evidence of COVID-19 in the infants. ††The study included total of 18 pregnant women (9 clinically and 10 laboratory-confirmed). Among them, eighteen pregnant women delivered by cesarean section and one by vaginal delivery. However, the exact number of delivery mode in laboratory confirmed women was not described. **Mean, 38 week ± 0.2 day. &None of the neonates needed special treatment.

showed negative RT-PCR results before the end of the studies, mostly within 1 week after birth (75%). Maternal samples were collected for evaluating vertical transmission (cord blood and breast milk for all neonates, amniotic fluid for 3 neonates, placenta specimen for one neonate), all samples had negative RT-PCR results for SARS-CoV-2 (Table III).

Maternal Clinical and Laboratory Characteristics With Pregnancy Outcomes

The maternal age at admission ranged from 22 to 41 years and the gestational age ranged from 12 to 41 weeks plus 2 days at presentation. Seventy-nine of 98 cases (80.6%) had an epidemiological/exposure history (Table IV).

Regarding clinical manifestations, mothers with COVID-19 usually appeared with: fever, 85 of 201 cases (42.3%); cough, 64 of 201 cases (31.8%); myalgia, 12 of 56 cases (21.4%); and dyspnea/short of breath, 16 of 142 cases (11.3%). 92.5% (185 of 200 cases) of confirmed women had pneumonia on CT scan. Leukocytosis was reported in 28 of 89 cases (31.5%) and lymphocytopenia was in 52 of 120 cases (43.3%). C-reactive protein concentration (CRP) was elevated in 65 of 103 cases (63.1%).

Regarding pregnancy outcome, premature rupture of membrane was reported in 16 of 126 cases (12.7%) and preterm labor was reported in 22 of 97 cases (22.7%). Fetal distress was reported in 15 of 141 cases (10.6%). There were two stillbirths[15,39]. Post-partum fever was reported in 34 of 99 cases (34.3%).

Five cases received mechanical ventilation and intensive care unit (ICU) care[15,24,31,39]. Among them, two cases developed acute respiratory distress syndrome (ARDS)[15,39] and they delivered stillbirths. One of them was still on the extracorporeal membrane oxygenation (ECMO) when the case was reported[15], and one of them expired[39]. Other cases recovered well.

Discussion

The evidence from our systematic review of these studies suggests that the effect of COVID-19 during pregnancy on the fetal and neonatal mortality is low, but can be associated with adverse neonatal outcomes. Although four newborns born to mothers affected COVID-19 were reported as having laboratory-confirmed early onset SARS-CoV-2 infection, vertical transmission has not been observed in the majority of neonates born to mothers with COVID-19.

For SARS-CoV-1 and MERS-CoV, intrauterine-vertical transmission has not been reported[42,43]. In this review, all the positive results of RT-PCR for SARS-CoV-2 were from the samples obtained within 48 hours after birth (one at 36 hours and three at 2 days after birth) with the quarantine of their mothers. However, it does not confirm whether the newborns had the infection in the mother's womb or were infected during delivery, particularly because no RT-PCR tests for the newborns were done immediately after birth. Furthermore, false-positive results of RT-PCR on neonatal throat swab were also reported[29].

Zeng et al[23] and Dong et al[34] showed that three neonates had elevated SARS-CoV-2 IgM (≥10 AU/mL) in their serum, which are also suggestive of neonatal infection, because IgM is not generally passed from maternal to neonate[23]. However, all their nasopharyngeal samples showed negative RT-PCR results. The sensitivity and specificity of IgM tests vary according to diseases and these tests are usually are less reliable than molecular diagnostic tests based on nucleic acid amplification and detection[44]. Particularly, the results for RT-PCR of the breast milk, placenta, amniotic fluids, and cord blood and maternal vaginal secretions were all negative for SARS-CoV-2 among the included studies. These suggest that maternal-infant vertical transmission does not appear to be common in SARS-CoV-2. We recommend that further serologic studies with validation should be done, with repeated data on RT-PCR test results immediately after birth, to reduce the false-positive results and obtain clear evidence of vertical transmission of SARS-CoV-2 from an infected mother to her newborn. In addition, follow-up of neonates is needed to determine whether the disease occurs in the newborn.

Among the neonates who were confirmed to have the SARS-CoV-2 infection by RT-PCR, typical features of pneumonia, such as fever and shortness of breath were shown in half (50%), but the most frequent reported clinical manifestation was vomiting (75%). The most severe confirmed neonatal case was of a newborn who was delivered prematurely (31 weeks plus 2 days) due to fetal distress and suffered RDS along with suspected bacterial sepsis[22]. Clinical symptoms and chest imaging of all infected neonates recov-

Table III. Clinical characteristics and outcomes of infants confirmed SARS-CoV-2 infections.

Authors	Yu N et al.	Zeng L et al.	Zeng L et al.	Zeng L et al.
Gender	Male	Male	Male	Male
Birth weight (g)	3,250	3,250	3,360	1,580
Gestational weeks at delivery	39 weeks plus 2 days	40 weeks	40 weeks plus 4days	31weeks plus 2 days
Delivery mode	Caesarean delivery	Cesarean delivery	Cesarean delivery	Cesarean delivery
Reason for Cesarean section	Confirmed maternal COVID-19 pneumonia	Meconium-stained amniotic fluid and confirmed maternal COVID-19 pneumonia	Confirmed maternal COVID-19 pneumonia	Fetal distress and confirmed maternal COVID-19 pneumonia
Apgar scores at 1 min, 5 min	8, 9	NA	NA	3, 4
Fetal distress	NA	NA	NA	Yes
Birth asphyxia	No	No	No	Yes
Sample	Throat swab	Nasopharyngeal and anal swab	Nasopharyngeal and anal swab	Nasopharyngeal and anal swab
Diagnostic method	PCR	PCR	PCR	PCR
Confirmed time after birth	36 h after birth	2 days after birth	2 days after birth	2 days after birth
Day of negative PCR	Negative twice within 2 weeks after admission*	Negative on day 6	Negative on day 6	Negative on day 7
Mother's sample	Placental specimen, cord blood, and breast milk	Amniotic fluid, cord blood, and breast milk	Amniotic fluid, cord blood, and breast milk	Amniotic fluid, cord blood, and breast milk
Fever	No	Yes	Yes	No
Lethargy	No	Yes	Yes	No
Cyanosis	No	No	No	Yes
Cough	No	No	No	No
Shortness of breath	Yes	No	No	Yes
Respiratory distress syndrome	No	No	No	Yes
Vomiting	Yes	No	Yes	Yes
Asymptomatic	No	No	No	No
Radiology-confirmed pneumonia	Yes	Yes	Yes	Yes
Chest CT performed	Yes	No	No	Yes
Lymphocytopenia (< 3,000 cells/μL)	NA	No	Yes	Yes
Leukocytosis (> 15,000 cells/μL)	NA	No	Yes	Yes
Thrombocytopenia (< 150,000 cells/μL)	NA	No	No	No
Mechanical ventilation	No	No	No	Yes
Antibiotics	Yes	No	No	Yes
Antiviral agent	NA	No	No	No
Mortality	No	No	No	No
References	[21]	[22]	[22]	[22]

NA: not available; COVID-19, coronavirus disease 2019; CT, computed tomography; LBW, low birth weight; PCR, polymerase chain reaction. *The neonate was admitted to Wuhan Children's Hospital after the nucleic acid test result was positive at 36 h after birth.

Table IV. Maternal characteristics and pregnancy outcomes.

Authors		Zhu H et al.	Liu Y et al.	Chen H et al.	Zhang L et al.	Chen R et al.	Liu D et al.	Liu H et al.	Yu N et al.	Zeng L et al.	Zeng H et al.	Breslin N et al.	Chen S et al.	Li N et al.	Khan S et al.	Yang P et al.	Liu W et al.	Case reports	Total n/N(%)
Number of confirmed pregnant women cases		9*	13	9	16	17	15	16†	7	33	6	7	5	16	17	7	10	20	223
Patients who delivered before end of study period		9	10	9	16	17	11	6	7	33	6	2	5	16	17	7	10	20	201
Epidemiological history		NA	12	9	12	NA	NA	NA	7	NA	NA	2	NA	0	17	NA	10	10/11	79/98(80.6)
Maternal age (mean with range), years		30.9 (25–35)	29.7 (22–36)	29.9 (26–40)	29.3 (24–34)	NA‡	32 (23–40)	30 (26–35)	32 (29–34)	NA	NA	33.9 (27–39)	28.8 (25–31)	30.9 (26–37)	29.3 (24–34)	NA	32.9 (26–38)	30.1 (23–41)	–
Gestational age at presentation, range, weeks plus days		31–39	25–38^{+3}	36–39^{+4}	NA	NA	12–38	22-40^{+5}	37–41^{+2}	NA	NA	26^{+3}–37^{+5}	38–41	NA	35–41	NA	NA	30 – 39^{+1}	–
Diagnostic method		PCR	NA§	PCR	PCR	PCR	PCR	PCR	PCR	PCR	PCR	PCR	PCR	PCR	PCR	PCR	PCR	PCR	–
Radiologic confirmed pneumonia		9	NA	8	16	17	15	13	7	33	6	1/2	5	15	5	6	1	16/17	157/202(77.7)
CT performed		9	NA	9	16	17	15	16	7	33	6	NA	5	16	5	6	10	15/17	185/200(92.5)
Symptoms	Fever	6	10	7	NA¶	4	1	7	6	8	NA	2	0	4	3	5	7	15/20	85/201(42.3)
	Cough	3	2	4	NA¶	4	9	6	1	10	NA	3	1	0**	6	1	4	10/20	64/201(31.8)
	Sore throat	1	1	2	NA	NA	1	NA	NA	NA	NA	0/2	NA	0**	NA	NA	NA	3/20	8/84(9.5)
	Dyspnea or short of breath	NA	3	1	NA¶	1	1	2	1	NA	NA	0	0	0**	2	NA	NA	5/20	16/142(11.3)
	Myalgia	NA	NA	3	NA	NA	3	NA	NA	NA	NA	3	0	NA	NA	NA	NA	3/20	12/56(21.4)
	Fatigue or malaise	NA	4	2	NA	1	4	3	NA	NA	NA	NA	0	NA	NA	NA	NA	4/20	18/95(18.9)
	Diarrhea	1	NA	1	NA¶	1	1	0	1	NA	NA	0	NA	NA	3	1#	1	0/20	10/134(7.5)
	Asymptomatic	3	1	0	NA	9	NA	NA	0	NA	NA‖	0/2	3	NA	NA	NA	0	0/20	16/97 (16.5)
Laboratory findings	Lymphocytopenia	NA	NA	5	NA	5	12	9	5	NA	NA	NA	4	2	4	NA	NA	6/18	52/120(43.3)
	Leukocytosis	NA	NA	2	NA	6	NA	8	0	NA	NA	NA	3	NA	8	NA	NA	1/18	28/89(31.5)
	Thrombocytopenia	NA	NA	NA	NA	NA	NA	NA	2	NA	NA	1/7	0	NA	NA	NA	NA	4/17	7/31(22.6)
	Elevated C-reactive protein	NA	NA	6/8	NA	7	10	13	7	NA	NA	NA	4/4	5	NA	NA	NA	13/18	65/103(63.1)
Maternal complications and pregnancy outcomes	ICU admission	NA	1	NA	NA	NA	0	0	0	0	NA	2	NA††	0	NA	NA	NA	2/18	5/103(4.9)
	Mechanical ventilation	NA	1	0	NA	NA	0	NA	NA	NA	NA	2	NA††	NA	NA	NA	NA	2/18§§	5/50(10.0)
	Mortality	0	0	0	NA	0	0	NA	0	NA	NA	0	NA††	0	NA	NA	NA	1/19	1/100(1.0)
	Spontaneous miscarriage/fetal death	NA	1/10	0	NA	NA	0	NA	NA	NA	NA	0	NA††	0	0	0	0	1/19	2/101(2.0)
	Premature rupture of the membrane	3/9	1/10	2	3	NA	0	NA	NA	3	NA	0	NA††	3	NA***	NA	NA	1/20	16/126(12.7)
	Preterm labor	NA	6/10	4	3	NA	NA	NA	NA	NA	NA	0	NA††	3	5	0	NA	3/20	22/97(22.7)
	Fetal distress	6/10	3/10	2	1	NA	NA	NA	NA	1	NA	0	NA††	2	0	NA	0	1/18	15/141(10.6)
	Postpartum fever	NA	NA	6	NA	NA	1	5	NA	5	NA	1/2	5	8	NA	NA	NA	3/17	34/99(34.3)
References		[14]	[15]	[16]	[17]	[18]	[19]	[20]	[21]	[22]	[23]	[24]	[25]	[26]	[27]	[28]	[29]	[30-41]	–

Cases were described as number or number/ (total available case numbers except missing value) in the study. *All confirmed cases in this study were laboratory diagnosed, except one clinically case integrated in a case series. †Only included laboratory confirmed cases. ‡Epidural anesthesia group (n=14), 29.5 years; general anesthesia group (n=3), 28.7 years. §All confirmed cases in this study were laboratory diagnosed, but the authors did not describe which specific laboratory test were performed. ¶Some confirmed pregnant women presented with symptoms such as cough, chest tightness, shortness of breath, and diarrhea, but the frequency of each symptom was not specifically described in the study. **No cases presented respiratory symptoms on admission or during hospital stay. ‖All cases showed mild clinical manifestations. #One case presented with abdominal pain. ††There was no complication among the included pregnant women. §§One pregnant woman in the case reports was reported to receive respiratory support, but no specific method was described. We did not count the case as mechanical ventilation case in this review. ***Some of the enrolled pregnant women had premature rupture of membrane, but the number of cases was not described in the study.

ered well without antiviral agents. One neonate was discharged[21] and the others showed stable vital signs at the time of publication[22]. A recent systematic literature review[45] on COVID-19 in children showed that children often have milder disease than adults, and deaths have been extremely rare. In our review, although the number of confirmed COVID-19 cases in newborns was small, the prognosis for newborns infected with COVID-19 was good.

Regarding morbidity and mortality of neonates born to mothers with COVID-19, fetal distress was reported in 10.6% of cases with available data and one of four (25.9%) infants was born prematurely, mainly due to fetal distress and/or maternal COVID-19 pneumonia. The most frequently reported morbidity was pneumonia (26.5%), followed by LBW (15.6%), SGA (8.3%), RDS (6.4%), and birth asphyxia (1.8%). However, all reported cases were discharged healthy or were still hospitalized in stable condition, except one neonatal death[14]. This newborn was born prematurely (at 34 gestational weeks plus 5 days) and presented with shortness of breath, which developed 30 minutes after delivery. He developed multiple organ failure with DIC at eight days of life and died on 9th day of life. His nucleic acid testing on throat swab taken from 9th day was negative for SARS-CoV-2[14]. Because of relatively higher premature birth rates in pregnant women with COVID-19 than the worldwide average[46], neonatal morbidity and mortality are suspected to be due to prematurity rather than SARS-CoV-2 infection of newborns. However, SARS-CoV-2 infection during pregnancy might lead to hypoxemia or respiratory failure, which causes fetal distress, stillbirth, and preterm labor, and need of a premature delivery by cesarean section for maternal ventilation[47]. The incidence of spontaneous miscarriage in the first trimester was reported to be 57% in SARS-CoV-1 affected women[4] and the incidence of fetal death was reported to be 27% in MERS-CoV infection[5], but only two fetal deaths have been reported in SARS-CoV-2 infection so far[15,39]. Still, a long-term investigation into the impact of COVID-19 on the fetus during early and mid-term pregnancy is warranted.

The SARS-CoV-1 and MERS-CoV infections were associated with high maternal mortality rates of 25%[4] and 35%[5], respectively. It is found that the genome sequence of SARS-CoV-2 is similar to that of SARS-CoV-1 (about 79%) and MERS-CoV (about 50%)[48], however, only five cases received ICU and ventilator care among the 103 pregnant women with confirmed COVID-19 (4.9%) and one maternal death was reported so far[39]. Among five cases who received ICU care with confirmed COVID-19, Liu et al[15] reported a patient with ARDS and multiple organ dysfunction syndrome (MODS) who was still supported with ECMO at the time of report of the case. Wang et al[31] reported a previously healthy young pregnant woman without special medical history who was admitted to ICU after diagnosis of COVID-19 and underwent emergency cesarean section due to fetal distress at 30 weeks plus 6 days. The maternal outcomes were not reported. Karami et al[39] reported a 27-year old woman who was previously healthy and presented with fever, cough, and myalgia at 30 weeks plus 7 days of gestation. Her initial chest radiography and CT scan did not show typical viral pneumonia. Her condition deteriorated and she eventually required mechanical ventilation; she died due to multiorgan failure and ARDS. Autopsy revealed positive RT-PCR result for SARS-CoV-2 in the lungs. This is the first maternal death of a patient with confirmed COVID-19.

Breslin et al[24] reported two ICU admission cases, one for uncontrolled bleeding (uterine atony) and the other for respiratory distress after delivery. The first patient was discharged home but the second remained hospitalized with on-going oxygen therapy. It is noteworthy that these two patients and their husbands did not complain of typical symptoms of viral pneumonia, such as cough, fever, or sore throat, before admission. Recently, Sutton et al[49] reported results of universal screening for SARS-CoV-2 for asymptomatic pregnant women who were admitted for delivery; 210 of the 211 asymptomatic pregnant women (99.5%) were tested *via* nasopharyngeal swabs, and 29 (13.7%) of them were positive for SARS-CoV-2 (we did not include this letter in our analysis, because there were no neonatal data). In our review, among the COVID-19-confirmed mothers, 16 of 97 cases (16.5%) presented with no symptoms. Therefore, even in asymptomatic mothers in the COVID-19 epidemic area, active COVID-19 screening should be used to manage the mothers and their newborn.

The limitation of our review is that case reports or case series of small numbers of cases and low quality were included; there are missing data, such as demographic, laboratory and outcome data, which might have caused publication bias and consequently outcomes might

have been overestimated. However, we tried to include as many available cases in the review as possible and to present information focusing on infants born to mothers with verified SARS-CoV-2 (except for one case in a case series, they are all laboratory-confirmed SARS-CoV-2 affected mothers). It is necessary to further perform epidemiological studies with larger sample sizes, appropriate comparison groups, and control of confounders.

Conclusions

The majority of reported infants born to COVID-19 confirmed mothers showed no clinical abnormalities. SARS-CoV-2 virus was not detected in most of the neonates born to COVID-19-affected mothers, although four neonates showed a positive RT-PCR result within 48 hours after birth. Current evidence suggests that maternal and fetal mortality is lower with COVID-19 than with SARS-CoV-1 and MERS-CoV infection. However, COVID-19 during pregnancy might cause severe neonatal and maternal morbidity, even death. Therefore, careful monitoring of mothers with COVID-19 and their neonates for possible complications and quarantine of infected mothers to prevent neonatal infection, are warranted.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Availability of Data and Materials

The data used in the present study are appropriately cited.

Authors' Contribution

SHY and JGA were responsible for the study's conception/design, investigation and data analysis as well as the drafting of the manuscript. JMK also performed data analysis and interpretation. The authors read and approved the final manuscript.

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