

Delivery in pregnant women infected with SARS-CoV-2: A fast review

Fabio Parazzini^{1,2,*} | Renata Bortolus³ | Paola Agnese Mauri^{1,2} | Alessandro Favilli⁴ | Sandro Gerli⁵ | Enrico Ferrazzi^{1,2}

¹Department of Obstetrics and Gynecology, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

²Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy

³Verona University Hospital, Verona, Italy

⁴Department of Obstetrics and Gynecology, AOUI Verona, Verona, Italy

⁵Department of Obstetrics and Gynecology, Centre of Perinatal and Reproductive Medicine, University of Perugia, Perugia, Italy

*Correspondence

Fabio Parazzini, Via Commenda 12, Milan, Italy.
Email: fabio.parazzini@unimi.it

Abstract

Background: Few case reports and clinical series exist on pregnant women infected with SARS-CoV-2 who delivered.

Objective: To review the available information on mode of delivery, vertical/peripartum transmission, and neonatal outcome in pregnant women infected with SARS-CoV-2.

Search strategy: Combination of the following key words: COVID-19, SARS-CoV-2, and pregnancy in Embase and PubMed databases.

Selection criteria: Papers reporting cases of women infected with SARS-CoV-2 who delivered.

Data collection and analysis: The following was extracted: author; country; number of women; study design; gestational age at delivery; selected clinical maternal data; mode of delivery; selected neonatal outcomes.

Main results: In the 13 studies included, vaginal delivery was reported in 6 cases (9.4%; 95% CI, 3.5–19.3). Indication for cesarean delivery was worsening of maternal conditions in 31 cases (48.4%; 95% CI, 35.8–61.3). Two newborns testing positive for SARS-CoV-2 by real-time RT-PCR assay were reported. In three neonates, SARS-CoV-2 IgG and IgM levels were elevated but the RT-PCR test was negative.

Conclusions: The rate of vertical or peripartum transmission of SARS-CoV-2 is low, if any, for cesarean delivery; no data are available for vaginal delivery. Low frequency of spontaneous preterm birth and general favorable immediate neonatal outcome are reassuring.

KEYWORDS

Cesarean delivery; COVID-19; Neonatal outcome; Pregnancy; Review; SARS-CoV-2; Vaginal delivery; Vertical transmission

1 | INTRODUCTION

Midwives and obstetricians face a new challenge posed by the recent outbreak of COVID-19. In this early phase of the epidemic, few data are available on the effect of COVID-19 on pregnant women. The risk of intrauterine and peripartum transmission of the virus to the fetus is also largely unknown.

Until now, most of the guidelines are based on previous experience with other highly pathogenic coronaviruses, namely severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS).¹⁻³

A recent consensus stated that there is no clear evidence on timing of optimal delivery, safety of vaginal delivery, or whether cesarean delivery prevents vertical transmission at the time of delivery. Therefore, mode and timing of delivery should be individualized based on obstetric indications and maternal-fetal status.²

During recent weeks, some case reports and clinical series have been published on mode of delivery, immediate neonatal outcome, risk of infection of the newborn, and breastfeeding in pregnant women infected with COVID-19.⁴⁻⁶ These series, although of few cases, may offer initial information to direct clinical practice.

The aim of the present article was to review the available information with special focus on mode of delivery, vertical/peripartum transmission, and immediate neonatal outcome of pregnant women infected with SARS-CoV-2.

2 | MATERIALS AND METHODS

We searched PubMed (National Library of Medicine, Washington, DC) and Embase (Elsevier) databases from January 1 up to March 31, 2020, using a combination of the following key words: COVID-19, SARS-CoV-2, and pregnancy. We also reviewed the reference lists of retrieved articles to search for other pertinent studies. Two authors (FP and RB) reviewed the papers and independently selected the articles eligible for systematic review. Studies were selected if they met the following criteria: clinical studies, studies reporting original data, studies reporting SARS-CoV-2 infected women who delivered.

2.1 | Data extraction

A PICOS (Patient, Intervention, Comparator, Outcome, Study) design structure was used to develop the study questions and the inclusion/exclusion criteria. The question was: "What is the mode of delivery and the obstetric and immediate neonatal outcomes in SARS-CoV-2 infected pregnant women?" (Table 1).

For each study, the following information was extracted: first author's last name; year; country; number of women who delivered; study design; gestational age at delivery; selected clinical maternal data (maternal age, comorbidity, diagnosis of pneumonia, treatment); mode of delivery; selected neonatal outcomes (birthweight, 5-minute Apgar score, admission to neonatal intensive care unit [NICU] neonatal diseases; SARS-CoV-2 positivity).

2.2 | Data synthesis

The primary outcomes assessed were frequency of preterm birth (<37 weeks of gestation), vaginal delivery, Apgar score at 5 minutes <7, and newborn infection. For each study with binary outcomes, we calculated the 95% confidence intervals (CIs) of the estimated proportion.

3 | RESULTS

The initial search retrieved 41 abstracts from PubMed and 23 from Embase. After exclusion of unrelated abstracts of review papers, guidelines, and commentaries, 17 papers were selected for extensive review. Two studies reported data only on maternal outcome.^{7,8} Another paper was published without peer review.⁹ One study was published in Chinese.¹⁰ Therefore, a total of 13 studies were included.^{4-6,11-20} Table 2 presents their main methodological characteristics. Six studies were case reports and seven were retrospective clinical series.

A total of 64 pregnant women who delivered were reported in the studies (seven women admitted to hospital but who did not deliver at the time of publication were also reported).

Table 3 presents the maternal characteristics and clinical conditions. Pneumonia was present in 49/61 (80.3%; 95% CI, 68.2–89.4) cases for which the information was available. For cases with available information, oxygen support was needed by 29/35 (82.9%; 95% CI, 66.4–93.4) and 2/31 (6.5%; 95% CI, 0.8–2.4) were admitted to a critical care unit (CCU).

Table 4 presents mode of delivery data. Vaginal delivery was reported in six (9.4%) cases (95% CI, 3.5–19.3). Indication for cesarean delivery was worsening of maternal conditions in 31 women (48.4%; 95% CI, 35.8–61.3; cases reported by Liu et al.¹⁴ and Zeng et al.¹⁹ are not included since the indication for cesarean section was unclear in the text.

Preterm birth (<37 weeks of gestation) was observed in 19 cases among the 48 for which the information on gestational age at delivery was available (39.6%; 95% CI, 25.8–54.7). In only two cases, reported by Zhu et al.,⁵ delivery was due to spontaneous preterm labor (1 twin pregnancy and 1 premature rupture of membranes).

Table 5 presents data on the immediate neonatal outcome and the frequency of SARS-Cov-2 positivity in the newborns. Low birthweight (<2500 g) was observed in 10 newborns (10/37 [27.0%] for which information was available; 95% CI, 13.8–44.1). In all cases, 5-minute Apgar score was greater than 7. One neonatal death due to disseminated intravascular coagulation (DIC) syndrome was reported. The death occurred in a singleton male neonate born by cesarean delivery at 34 + 5 weeks of gestation and weighing 2200 g. The cause of death was multiple organ failure and DIC.

Considering respiratory disease in newborns, one case of pneumonia, one low-grade fever and haziness in both lung fields, one high-density nodular shadow under the pleura of the right lung, six shortness of breath, and two cases of neonatal respiratory distress syndrome were reported.

Wang et al.¹⁶ reported a case of neonatal COVID-19 infection with pharyngeal swabs testing positive by rRT-PCR assay 36 hours after cesarean delivery; whether the case is a vertical transmission from mother to child remains to be confirmed.

Dong et al.¹¹ reported a case of a neonate delivered by cesarean in which SARS-CoV-2 IgG and IgM levels were elevated at 2 hours old.

TABLE 1 PICOS criteria for inclusion and exclusion of studies.

Parameter	Inclusion criteria	Data extraction
Patient	Women treated for SARS-CoV-2 infection	Location, age, clinical characteristics
Intervention	Delivery	Mode of delivery
Comparator	None	
Outcome	Neonatal outcome	Birth weight, Apgar score, neonatal disease, NICU admission, SARS-CoV-2 positivity
Study	Case reports/observational studies	Type of study design

TABLE 2 Study characteristics and sample size of the studies included in the review.

Authors, year, country	Type of study	Aim	Assessment	Cases (No.)
Chen et al., 2020, China ⁴	Retrospective clinical series	IVT	AF, CB, ITS, M	9
Chen et al., 2020, China ²⁰	Retrospective clinical series	–	–	5
Dong et al., 2020, China ¹¹	Case report	IVT	IGM-IGG, INPS, M, VS	1
Fan et al., 2020, China ¹²	Case report	IVT	AF, CB, IGG, INPS, M, PT, VS	2
Lee et al., 2020, Korea ¹⁸	Case report	IVT	AF, CB, INPS, PT	1
Li et al., 2020, China ¹³	Case report	IVT	AF, CB, IB, IOPS, IS, IU, M, PT	1
Liu et al., 2020, China ¹⁴	Retrospective clinical series	IVT	Nr	10/+3 ^a
Liu et al., 2020, China ¹⁵	Retrospective clinical series	–	–	11/+4 ^a
Wang et al., 2020, China ¹⁶	Case report	IVT	CB, IOPS, M, PT	1
Wang et al., 2020, China ⁶	Case report	IVT	AF, CB, IGJ, IS, ITS, PT	1
Yu et al., 2020, China ¹⁷	Retrospective clinical series	–	–	7
Zeng et al., 2020, China ¹⁹	Retrospective clinical series	IVT	IB, IGM-IGG, ITS	6
Zhu et al., 2020, China ⁵	Retrospective clinical series	IVT	IOPS	9 ^b

Abbreviations: IVT, intrauterine vertical transmission; AF, amniotic fluid; CB, cord blood; ITS, infant throat swab; M, milk; INPS, infant nasopharyngeal swab; PT, placenta tissues; VS, vaginal swab; IOPS, infant oropharyngeal swab; IB, infant blood; IS, infant stool; IU, infant urine; IGJ, infant gastric juice; Nr, not reported.

^aPatients with pregnancy in progress.

^bNine mothers and 10 neonates.

Results from five RT-PCR tests on nasopharyngeal swabs taken from 2 hours to 16 days old were negative. Two other newborns delivered by cesarean with elevated IgM antibodies to SARS-CoV-2 virus, but negative throat swab result by RT-PCR have also been reported.¹⁹ Finally, Yu et al.¹⁷ reported the case of a RT-PCR positive test in a newborn 36 hours after cesarean birth.

4 | DISCUSSION

The results of this fast review of the available data on mode of delivery and immediate neonatal outcome in pregnant women infected with SARS-CoV-2 suggest that the risk of vertical or peripartum transmission of the virus to the newborn is limited, if any.

TABLE 3 Maternal characteristics and clinical conditions of the women in the included studies.

Authors	Maternal age, y	Comorbidities	Antiviral therapy	Pneumonia	Oxygen support	CCU admission
Chen et al. ⁴	26–40	2 GH/9	6/9	9/9	9/9	0 ^a /9
Chen et al. ²⁰	25–31	2GD, 1GH/5	5 ^c /5	5 ^b /5	0/5	Nr
Dong et al. ¹¹	29	0/1	1/1	1 ^b /1	1/1	Nr
Fan et al. ¹²	29, 34	0/2	2/2	2/2	Nr	Nr
Lee et al. ¹⁸	28	0/1	0/1	1/1	0/1	0/1
Li et al. ¹³	30	0/1	1/1	1 ^b /1	Nr	Nr
Liu et al. ¹⁴	22–36	0/13	Nr	1/13	Nr	1/13
Liu et al. ¹⁵	23–40 (mean, SD, 32 +- 5)	1 GD, 1VR/11	11 ^c /11	11/11	11/11	Nr
Wang et al. ¹⁶	34	0/1	1 ^c /1	1 ^b /1	Nr	Nr
Wang et al. ⁶	28	0/1	1/1	1/1	1/1	1/1
Yu et al. ¹⁷	29–34 (mean 32)	2 ^d /7	7/7	7/7	7/7	0/7
Zeng et al. ¹⁹	Nr	Nr	Nr	Nr	Nr	Nr
Zhu et al. ⁵	25–35 (mean 30)	0/9	3 ^c /9	9/9	Nr	Nr

Abbreviations: CCU, critical care unit; GH, gestational hypertension; GD, gestational diabetes; VR, mitral and tricuspid valve replacement; Nr, not reported.

^aNo mechanical ventilation.

^bComputed tomography scan with typical images of viral pneumonia.

^cAfter delivery.

^d1 hypothyroidism, 1 polycystic ovary syndrome.

TABLE 4 Mode of delivery and preterm birth in pregnant women in the included studies.

Authors	Gestational age, w	Mode of delivery			Preterm birth
		Cesarean for maternal COVID-19 infection	Cesarean for obstetric indication	Vaginal delivery	
Chen et al. ⁴	36–39	9 ^a /9	7 ^a /9	–	4/9
Chen et al. ²⁰	38–40	–	2/5	3/5	0/5
Dong et al. ¹¹	37	1/1	–	–	0/1
Fan et al. ¹²	36, 37	2/2	–	–	1/2
Lee et al. ¹⁸	37	–	1/1	–	0/1
Li et al. ¹³	35	–	1 ^b /1	–	1/1
Liu et al. ¹⁴	Nr	5 ^c /10	5 ^d /10	–	6/10
Liu et al. ¹⁵	Nr	9/11	1/11	1/11	Nr
Wang et al. ¹⁶	40	1/1	–	–	0/1
Wang et al. ⁶	30	1/1	–	–	1/1
Yu et al. ¹⁷	37–41	7/7	–	–	0/7
Zeng et al. ¹⁹	Nr	6/6 ^e	–	–	Nr
Zhu et al. ⁵	31–39	1/9	6 ^e /9	2 ^f /9	6 (2 twins)/10

Abbreviation: Nr, not reported.

^aIn 7 cases, cesarean delivery for maternal COVID-19 infection and obstetric indication: 1 history of cesarean delivery, 1 pre-eclampsia, 2 fetal distress, 1 history of stillbirth, 2 premature rupture of membranes.

^bAlso fetal distress.

^cNo obstetric indication.

^d3 fetal distress, 1 PROM, 1 stillbirth.

^e1 premature rupture of membranes, 4 fetal distress, 1 cholecystitis and fever.

^f2 premature rupture of membranes, 3 fetal distress, 2 twins.

^gUnclear in the text.

We identified two cases of newborn infection, confirmed positive by rRT-PCR assay, out of 64 reported cases. To our knowledge, another case of a newborn infected with SARS-CoV-2 (not included in this review) has been reported by the National Health Commission of the People's Republic of China,^{21,22} in which the diagnosis was made at 17 days of life. In all cases, postpartum neonatal infection acquired through an infected contact was impossible to exclude.

IgM antibodies to SARS-CoV-2 were found in three cases.^{11,19} Caution in interpreting these findings has been suggested, including the possibility that IgM positivity could represent a laboratory artifact.²³

These findings suggest that transmission in utero is possible. However, SARS-CoV-2 was not found in amniotic fluid or cord blood and this finding is based on very few cases.⁵

Data on virus transmission are based substantially on women who delivered by cesarean. This aspect is relevant. In fact, vertical transmission of infection usually occurs during intrauterine life via the placenta, or during delivery via ingestion or aspiration of cervicovaginal secretions, and in the postpartum period via breastfeeding.²⁴ The risk of ingestion or aspiration of cervicovaginal secretions or contact with perineal infected tissue is higher with vaginal delivery. In this review we identified 19 women who delivered preterm, although spontaneous vaginal preterm birth was reported in only two cases. Therefore, there is reassuring evidence that COVID-19 infection of the mother did not markedly increase the risk of spontaneous preterm birth.

Regarding maternal conditions, we note that COVID-19 infection in pregnancy seems to be less severe than other coronavirus infections such as SARS or MERS.^{2,3} We identified two women who needed intensive care. The proportion of women requiring CCU admission seems to be similar to that reported in the general population affected by COVID-19.²⁵ However, worsening of maternal condition was the cause of emergency cesarean delivery in about 45% of women. Diabetes and hypertension are considered determinants of worse prognosis in cases of infection.²⁵ However, we were unable to analyze this in detail; the few cases reported with diabetes did not need CCU admission.

Finally, newborn outcome deserves some consideration. In all reported cases the 5-minute Apgar score was greater than 7 and generally 9 or 10 (data not shown in table). Furthermore, the frequency of NICU admission was low and due to medically induced preterm birth. However, one neonatal death and several cases of respiratory symptoms or diseases were reported by pharyngeal or nasopharyngeal swabs, although these tested negative for SARS-CoV-2 by rRT-PCR assay, except in one case.¹⁶

Very few reported cases provided information on the risk of newborn infection during breastfeeding. Guidelines suggest allowing breastfeeding for infected women who wear a mask.²⁶ Preliminary data suggest that the virus is not detectable in milk.⁴

In conclusion, this review of the literature suggests that the rate of vertical or peripartum transmission of SARS-CoV-2 is low, if any, for cesarean delivery. Crucially, no data were available for vaginal delivery. Likewise, breastfeeding was not generally reported; thus, the risk

TABLE 5 Newborn characteristics and breastfeeding.

Authors	LBW	5-minute Apgar (>7)	NICU admission	SARS-CoV-2 (+)	Neonatal diseases	Breastfeeding
Chen et al. ⁴	2/9	9/9	Nr	0/6	0 ^a /9	9/9
Chen et al. ²⁰	0/5	5/5	Nr	0 ^b /5	0/5	0/5
Dong et al. ¹¹	0/1	1/1	1 ^c /1	0/1 (1 IgM+ IgG+/1, INPS-M-VS - IgG+)	—	Nr
Fan et al. ¹²	0/2	2/2	Nr	0/2	1 low grade fever, haziness in both lung fields, abdominal distension/1 pneumonia	Nr
Lee et al. ¹⁸	0/1	1/1	1 ^c /1	0/1	0/1	0/1
Li et al. ¹³	Nr	Nr	Nr	0/1	0/1	Nr
Liu et al. ¹⁴	Nr	Nr	Nr	0/9	0 ^a /9	Nr
Liu et al. ¹⁵	Nr	11/11	Nr	Nr	0 ^a /11	Nr
Wang et al. ¹⁶	0/1	1/1	Nr	1/1 (IOPS+CB-M-PT-)	Swallowing syndrome, lymphopenia, deranged liver function tests, elevated creatine kinase level, high density nodular shadow under the pleura right lung	0/1
Wang et al. ⁶	1/1	1/1	1 ^d /1	0/1	0/1	0/1
Yu et al. ¹⁷	0/7	7/7	Nr	1 (NAT-ITS+)/3	0/7	Nr
Zeng et al. ¹⁹	Nr	6/6	Nr	0 ^b /6 (2IgM+ IgG+/6)	0/6	0/6
Zhu et al. ⁵	7 (2 twins)/10	10/10	Nr	0/9	6 shortness of breath 3 cyanosis 2 DIC 1 death Chest radiography: 4 infections 2 neonatal respiratory distress syndrome 1 pneumothorax	Nr

Abbreviations: LBW, low birthweight (<2500 g); NICU, neonatal intensive care unit; INPS, infant nasopharyngeal swab; M, milk; VS, vaginal swab; IOPS, infant oropharyngeal swab; CB, cord blood; PT, placenta tissues NAT, nucleic acid test; ITS, infant throat swab; DIC, disseminated intravascular coagulation; Nr, not reported.

^aNo neonatal asphyxia.

^bNeonatal SARS-CoV-2 quantitative RT-PCR.

^cQuarantined.

^dPreterm delivery.

of transmission during breastfeeding is unknown. Low frequency of spontaneous preterm birth and generally favorable immediate neonatal outcomes are reassuring.

AUTHOR CONTRIBUTIONS

FP and EF designed the study. FP and RB reviewed the identified papers. FP and RB drafted the manuscript. PM, SG, AF and EF revised the manuscript. All authors reviewed and approved the final manuscript.

CONFLICTS OF INTEREST

The authors have no conflicts of interest.

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