A Review on Mode of Delivery during COVID-19 between December 2019 and April 2020

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Abstract

Objective This study aims to review the published literature to determine mode of delivery in pregnant women with coronavirus disease 2019 (COVID-19) and the indications reported for cesarean section early in the pandemic to add information to the current narrative and raise awareness of trends discovered.

Study Design A systematic review was conducted by searching PubMed, Scopus, and ScienceDirect databases for articles published between December 2019 and April 29, 2020 using a combination of the keywords such as COVID-19, coronavirus 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), pregnancy, vaginal delivery, cesarean section, vertical transmission, management, and guidelines. Peer-reviewed case studies with confirmed SARS-CoV-2 women who delivered were included to determine mode of delivery, indications for cesarean section, and maternal and neonatal characteristics.

Results A review of 36 total articles revealed deliveries in 203 SARS-CoV-2 positive pregnant women. A comparable severity of disease in pregnant versus nonpregnant women was noted, as previously determined. Overall, 68.9% of women delivered via cesarean section, with COVID-19 status alone being a common indication. Maternal COVID-19 may also be associated with increased risk of preterm labor, although neonatal outcomes were generally favorable. Despite eight of 206 newborns testing positive for SARS-CoV-2, there remains no definitive evidence of vertical transmission.

Conclusion COVID-19 status alone became a common indication for cesarean delivery early in the pandemic, despite lack of evidence for vertical transmission. The increase in cesarean rate in this data may reflect obstetricians attempting to serve their patients in the best way possible given the current climate of constantly evolving guidelines on safest mode of delivery for the mother, infant, and provider. Upholding current recommendations from trusted organizations as new data are published, while also providing individualized support to expecting mothers on most appropriate mode of delivery, will reduce the amount of unnecessary, unplanned cesarean sections and could lessen the psychological impact of delivering during the COVID-19 pandemic.

Keywords

- COVID-19
- pregnancy
- cesarean delivery
- vaginal delivery
- neonatal outcome
- vertical transmission
- maternal mental health

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Key Points

- COVID-19 may result in an increased rate of cesarean delivery for SARS-CoV-2 positive pregnant women.
- COVID-19 is a commonly reported indication for cesarean section, despite management guidelines urging against this.
- Although eight neonates tested positive for SARS-CoV-2, all additional fluid and tissue samples tested negative.

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), emerged in late December 2019 when patients with a pneumonia of unknown etiology were admitted to hospitals in Wuhan, the capital of the Hubei Province in China.[1] January 21, 2020 marked the first case in the United States, and by March 11, 2020, the World Health Organization (WHO) declared the virus a pandemic.[1] The state of knowledge on coronavirus remains in flux and is continuously evolving.

Coronaviruses are a family of enveloped, positive-sense, single-stranded RNA viruses.[1] Although four human coronaviruses are known to cause a mild and common cold, three human coronaviruses cause more severe disease, including SARS-CoV, Middle East respiratory syndrome coronavirus (MERS-CoV), and the novel SARS-CoV-2 that causes COVID-19.[1] Initial data on outcomes suggest that approximately 81% of COVID-19 cases are mild, 14% are severe, and 5% of patients become critically ill.[2] The WHO estimates the global mortality rate of SARS-CoV-2 to be 3.4%, although additional reports suggest that the mortality rate may be lower at 1.4%.[3] In comparison, SARS-CoV and MERS-CoV have mortality rates of 10 and 37%, respectively.[3]

Pregnant women may be particularly vulnerable to respiratory pathogens and severe pneumonia due to their modulated immune and cardiopulmonary systems. Of note, viral pneumonia is one of the leading causes of pregnancy deaths globally.[1] Alterations in cell-mediated immunity play a central role in this susceptibility, as this enables the pregnant woman to remain tolerant to the allogeneic fetus, but decreases her ability to defend against intracellular pathogens such as viruses.[1] In addition, the physiologic changes that occur in the cardiopulmonary systems during pregnancy, including increased oxygen consumption, decreased total lung volumes, diaphragm elevation due to the gravid uterus, and vasodilation leading to increased mucosal edema and secretions in the upper respiratory tract, cause the pregnant woman to be more intolerant to hypoxia.[4] The impact of viral pneumonia during pregnancy was evident during the 1918 influenza pandemic, which caused a mortality rate of 37% among pregnant women, but only 2.6% in the general population.[3] In addition, the H1N1 influenza pandemic in 2009 saw a higher rate of hospital admission for pregnant women than the general population.[3] The 2002 SARS-CoV pandemic caused 50% of infected pregnant women to be admitted to an intensive care unit (ICU), with 33% requiring mechanical ventilation, and 25% dying due to SARS-CoV complications.[3] Lastly, during the MERS-CoV outbreak of 2012, 63.6% required ICU admission, with a case-fatality rate in pregnant women of 35%.[5]

The knowledge gained from these viral outbreaks has likely influenced the management of pregnant women during COVID-19. The purpose of this review is to present information with special focus on mode of delivery in SARS-CoV-2 positive pregnant women, indications reported for cesarean section, immediate neonatal outcomes, risk of vertical transmission, and the impact on maternal mental health. This examination will offer information that may help direct clinical practice within labor and delivery.

Materials and Methods

Literature Search

A systematic literature search was conducted by using PubMed, Scopus, and ScienceDirect databases for articles published between December 2019 and April 29, 2020. Combinations of the following search terms were used: COVID-19, coronavirus 2019, SARS-CoV-2, pregnancy, vaginal delivery, cesarean section, vertical transmission, management, and guidelines. Reference lists of large systematic reviews were also reviewed to ensure inclusion of other pertinent studies. Several case reports and case series were analyzed for inclusion. It is important to note that reporting bias may be present in the literature as adverse maternal and neonatal outcomes seen during the COVID-19 pandemic may have a greater tendency to be reported.

Selection of Studies

Inclusion criteria included studies reporting original data, laboratory-confirmed COVID-19 infection using quantitative real-time polymerase chain reaction (qRT-PCR), SARS-CoV-2 infected pregnant women who delivered, and availability of clinical characteristics, including maternal, pregnancy, and neonatal outcomes. Exclusion criteria included literature or systematic reviews, reports that were not peer-reviewed or in any language other than English, suspicion of duplicate reporting, suspected cases of COVID-19 that were not deemed confirmed, unreported maternal or neonatal outcomes, and pregnant women who did not deliver. Five studies included a population of pregnant women, including those who delivered and those who continued their pregnancy. If the outcomes of those who delivered were reported clearly, the study was included, but excluded those who did not deliver in the data collection.

Data Extraction

A patient, intervention, comparator, outcome, and study (PICOS) design structure was used to establish the study question, inclusion criteria, and data extraction points (►Table 1). The main study question was: "What is the most common mode of delivery and indication for cesarean section reported, in addition to maternal and neonatal clinical outcomes, in SARS-CoV-2 positive pregnant women who delivered?"

Table 1 Patient, intervention, comparator, outcome, and study design structure for inclusion criteria and data extraction of studies

Parameter	Inclusion criteria	Data extraction
Patient	SARS-CoV-2 infected pregnant women who deliver	Age, gestational age, severity of COVID-19, medical comorbidities, pregnancy complications, ICU admission, and maternal mortality
Intervention	Delivery	Mode of delivery and indication for cesarean section
Comparator	None	
Outcome	Neonatal outcome	Preterm delivery, Apgar score, NICU transfer, intrauterine or neonatal death, SARS-CoV-2 positivity
Study	Case reports and case series	Type of study design

Abbreviations: NICU, neonatal intensive care unit; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Data Synthesis

The main outcomes assessed were frequency of cesarean section for COVID-19 status alone, vaginal delivery, Apgar score < 7, preterm birth ($<$37 weeks), neonatal intensive care unit (NICU) transfer, fetal and neonatal death, and neonatal SARS-CoV-2 infection. A descriptive summary was used to present these results, organized by maternal clinical characteristics, mode of delivery, and neonatal clinical characteristics. A limitation of this review is its sample size and the lack of statistical analysis. A large, prospective, and randomized-controlled study would need to be conducted to allow for robust statistical significance of results. All study investigators (M.L.D., D.C.F., and C.G.) independently reviewed the data collection forms to verify data accuracy.

Quality Assessment

Two independent examiners (M.L.D. and D.C.F.) applied the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) for the data extraction and quality assessment. The examiners (M.L.D. and D.C.F.) independently assessed the methodologies of the studies according to the tool for evaluating the methodological quality of case reports and case series described by Murad et al.[6] The tool considers four domains (selection, ascertainment, causality, and reporting) and provides eight questions to aid quality score. If all domains were satisfied, the study would be classified as "good quality"; if three of the domains were satisfied, the study would be classified as "fair quality"; and if only two or one of the domains were satisfied, the study would be classified as "poor quality." Precisely, 18 studies fulfilled all of the domains and were judged to be of good quality, 13 studies were classified as fair quality, and 5 studies were judged to be of poor quality.

Results

After exclusion of contents not related to the topic of our review, duplicates, review papers or guidelines, studies published without peer review, and studies published in alternate languages, including Chinese, German, and French, a total of 36 original studies were reviewed and included (►Table 2). ►Fig. 1 shows the process of study inclusion for the systematic review. These studies include one case–control study from China,[7] 18 case reports (from China,[8–14] United States,[15–17] Australia,[18] Korea,[19] Iran,[20] Honduras,[21] Sweden,[22] Turkey,[23] Spain,[24] and Peru,[25]), and 18 retrospective case series (from China,[4,26–35] United States,[36–38] Italy,[39] Iran,[40] Canada, and France[41]).

Table 2 Distribution of study design, country, count of reports, and sum of COVID-19 cases

Study design	Country	Count of reports	Sum of pregnant women with COVID-19 who deliver
Case–control	China	1	16
Case report	China	7	7
	USA	3	3
	Australia	1	1
	Korea	1	1
	Iran	1	1
	Honduras	1	1
	Sweden	1	1
	Turkey	1	1
	Spain	1	1
	Peru	1	1
Case series	China	11	93
	USA	3	25
	Italy	1	42
	Iran	1	7
	Canada and France[a]	1	2
Total		36	203

[a]Two cases reported in same series due to similar complication; one patient from each country.

A total of 203 SARS-CoV-2 positive pregnant women who delivered were reported in the studies. One patient was confirmed by the local Centers for Disease Control and Prevention (CDC) once additional illnesses were excluded, as the patient presented with typical symptoms and evidence of a viral interstitial pneumonia on computerized tomography (CT) scan, despite lack of a positive SARS-CoV-2 RT-PCR test.[35] This patient was included in this review, as she was deemed confirmed. All additional suspected COVID-19 cases that

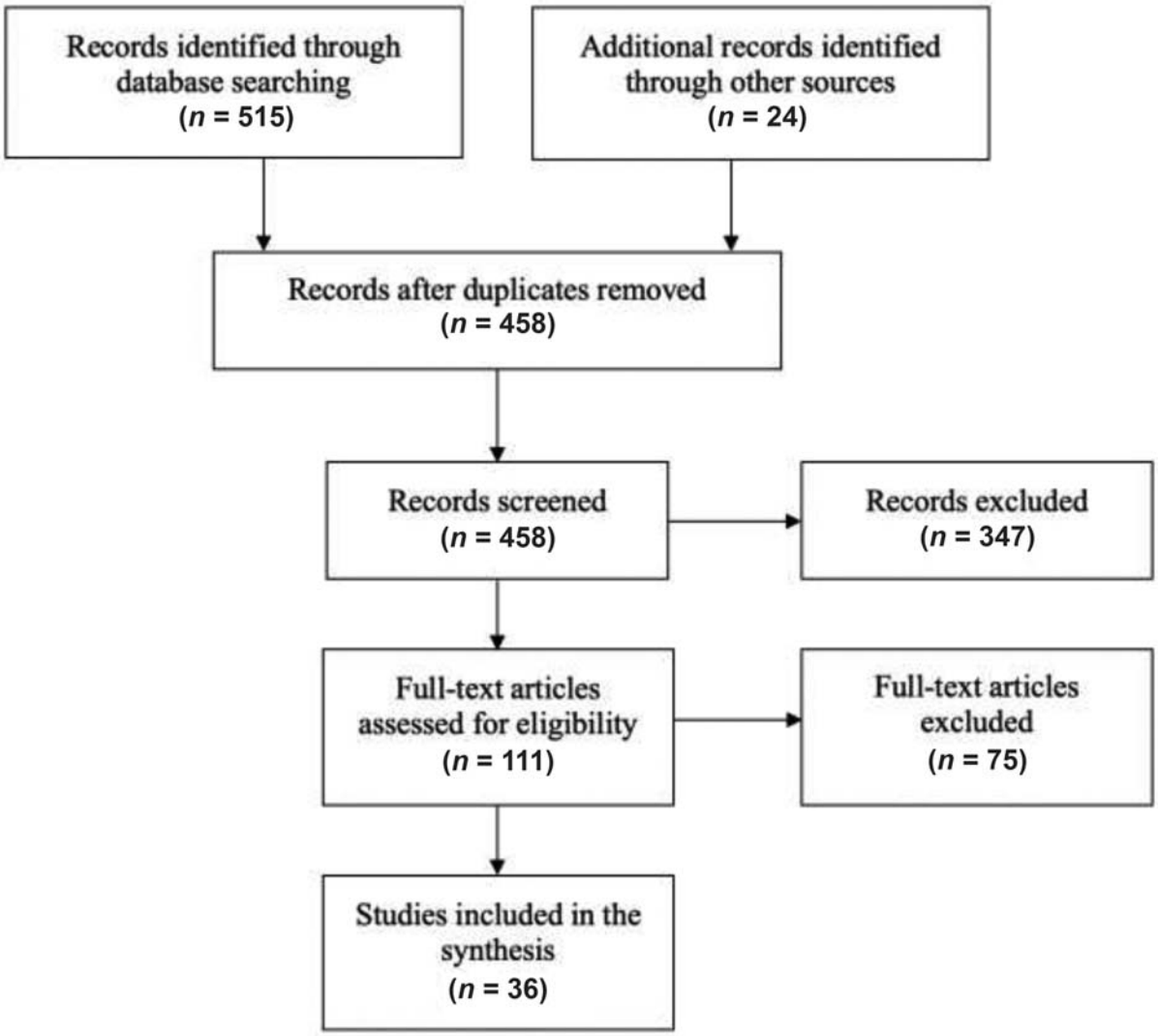

Fig. 1 Study flow chart.

were not deemed confirmed were excluded. Because six twin deliveries occurred, a total of 206 neonates were reported.

Maternal Clinical Characteristics

The maternal age ranged from 20 to 49 years old. The gestational age of the women who delivered ranged from $28^{0/7}$ to $41^{2/7}$ weeks (►Table 3).

Of the 203 pregnant women who delivered, 30 (14.8%) suffered severe SARS-CoV-2 disease, while the remaining 173 (85.2%) women had nonsevere disease, including an asymptomatic, mild, or moderate COVID-19 course. Twenty-one (10.3%) women with severe disease were admitted to an intensive care unit (ICU), ten (4.93%) of whom remained in the hospital at the time of the case report or series being published. Six (2.96%) maternal mortalities in women who delivered were reported. Of those, Karami et al[20] reported one maternal mortality, although the cause of death was deemed uncertain, with acute respiratory distress syndrome (ARDS), alveolar hemorrhage, and acute collagen vascular autoimmune disease on the differential diagnosis, and Hantoushzadeh et al[40] reported five maternal mortalities, all of whom suffered a combination of ARDS, cardiopulmonary collapse, disseminated intravascular coagulation, septic shock, and end-organ failure. Of note, Hantoushzadeh et al[40] study reported only adverse maternal outcomes, which may have added reporting bias to this literature review.

Maternal comorbidities were diverse, with obesity, hypothyroidism, mild intermittent asthma, polycystic ovary syndrome, pregestational diabetes mellitus, chronic hypertension, and uterine scarring being most common, as seen in ►Table 3. Several pregnancy complications were also reported, with gestational diabetes mellitus, premature rupture of membranes, preeclampsia, gestational hypertension, episodes of vaginal bleeding, including placental abruption, and twin pregnancy being most common.

Mode of Delivery and Indication for Cesarean Section

In total, 140 of the 203 (68.9%) women were delivered by cesarean section, while the remaining 63 (31%) women were reported to have a successful vaginal delivery. Because

Table 3 Maternal characteristics and clinical outcomes of COVID-19 infection in pregnant women

	All mothers ($n = 203$)
Maternal characteristics	
Age range (y)	20–49
Gestational age (wk)	$28^{0/7}$–$41^{2/7}$
Positive RT-PCR for SARS-CoV-2	202[a]
Maternal disease severity	
Nonsevere (asymptomatic, mild, moderate)	173
Severe	30
Maternal comorbidities	
Obesity	33
Hypothyroidism	9
Mild intermittent asthma	8
Polycystic ovarian syndrome	4
Type 2 diabetes mellitus	4
Chronic hypertension	4
Uterine scarring	4
Anemia	4
Chronic hepatitis B	2
Valvular replacement surgery	1
Myotonic dystrophy, bicuspid aortic valve, mild CVA on OCP	1
Familial neutropenia	1
Sinus tachycardia	1
Pregnancy complications	
Gestational diabetes mellitus	19
PPROM	8
Preeclampsia	8
PROM	6
Gestational hypertension	7
Episode of vaginal bleeding (including placental abruption)	4
Twin pregnancy	3
Placenta previa	3
History of stillbirth	2
Acute coagulopathy and transaminitis	2
Amniotic fluid abnormality	2
Umbilical cord abnormality	2
Cholestasis of pregnancy	1
Focal accreta	1
Influenza	1
Maternal clinical outcomes	
Intensive care unit	21
Remaining in hospital	10
Maternal mortality	6

Abbreviations: CVA, cerebrovascular accident; OCP, oral contraceptives; PPROM, preterm premature rupture of membranes; PROM, premature rupture of membranes; RT-PCR, real-time transcriptase polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
[a]One patient deemed confirmed by local CDC without a positive SARS-CoV-2 result.

Table 4 Mode of delivery and indication for cesarean section

	All mothers ($n = 203$)
Delivery characteristics	
Cesarean section	140
Vaginal delivery	63
Indication for cesarean delivery	
Obstetric indication	65
Fetal distress	16
Nonreassuring fetal heart rate tracing	11
PPROM	8
Repeat cesarean delivery	7
Severe preeclampsia	5
Decreased fetal movement	5
Placenta previa	3
Scheduled cesarean delivery[a]	2
Placental abruption	2
Umbilical cord abnormality	2
Arrest of descent	1
Arrest of dilation	1
Failed labor induction	1
Obstructed labor with incomplete rotation of fetal head	1
No indication provided	39
COVID-19 status alone	38
Worsening maternal status due to COVID-19	22
History of stillbirth or stillbirth of current fetus	2
Abdominal pain	1
Severely elevated AST/ALT	1

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; PPROM, preterm premature rupture of membranes.
[a]For large for gestational age and twin pregnancy.

several women had multiple indications reported for cesarean section, each indication was added as a separate tally to provide a thorough depiction of the indications used to justify cesarean section. A total of 168 indications for the 140 women who delivered via cesarean section were reported. There were 65 women (65/168, 38.7%) with an obstetric indication for cesarean section (►**Table 4**). These obstetric indications included fetal distress or decreased fetal movement, nonreassuring fetal heart rate tracing, preterm premature rupture of membranes (PPROM), repeat or scheduled cesarean section, severe preeclampsia, placental or umbilical cord abnormalities, and failed labor induction. No indication for cesarean section was reported in 39 cases (39/168, 23.2%), and the true indication for their cesarean section remains unknown. Maternal COVID-19 status was reported as an indication in 38 cases (22.6%). Many studies note that COVID-19 status alone was an indication for

cesarean section within their hospital due to concerns of vertical transmission or desire to treat the mother with antiviral therapy promptly without exposing the fetus.[4,7,10,27,33] If a worsening maternal status due to COVID-19 was reported as an indication for cesarean section, this was listed separately from the indication of COVID-19 as a diagnosis. Worsening maternal status as an indication was reported in 22 women (22/168, 13.1%). Although a compromised or decompensating cardiopulmonary status was most common, Juusela et al[37] and Vlachodimitropoulou et al[41] reported unique cases of acute coagulopathy with transaminitis and development of cardiomyopathy, respectively, as causes of maternal clinical decline and reason for cesarean intervention. Two patients had a history of stillbirth or stillbirth of the current fetus (2/168, 1.2%). Abdominal pain was cited as an indication for one patient, without further elaboration (1/168, 0.6%). Lastly, one patient had severely elevated transaminases, although it is unclear whether this was related to COVID-19 (1/168, 0.6%).

Table 5 Preterm delivery and neonatal outcomes of COVID-19

	All neonates ($n = 206$)
Preterm delivery	
Before 34 weeks	19 (three set of twins)
34–$36^{6/7}$ weeks	43 (two set of twins)
Neonatal outcomes	
Apgar score range	1–10
Positive RT-PCR for SARS-CoV-2	8
NICU transfer (for issue, not isolation)	26
Intrauterine fetal death	4
Neonatal death	3 (one set of twins)

Abbreviations: NICU, neonatal intensive care unit; RT-PCR, real-time transcriptase polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Neonatal Clinical Characteristics

Preterm birth before 34 weeks of gestation was observed in 19 of the 206 (9.2%) neonates, with the earliest delivery being at $28^{0/7}$ weeks of gestational age. This value includes three sets of twins. Preterm birth between 34 and $36^{6/7}$ weeks of gestational age occurred in 43 (20.9%) neonates, with two sets of twins included in this value. In total, 62 (30.1%) infants were preterm, and of those that were clearly indicated, spontaneous preterm birth occurred in 19 (9.2%).

Of the 199 neonates with a reported Apgar score, the large majority were greater than or equal to seven. The lower range of Apgar scores reported in ►Table 5 can be attributed to four infants. Ferrazzi et al[39] reported two preterm infants born before 34 weeks of gestational age with a 5-minute Apgar score <7, but do not indicate the severity of maternal disease. Kelly et al[16] reported an infant born at 33 weeks of gestational age with Apgar scores of 1, 6, and 7 at 5, 10, and 15 minutes, respectively. The mother suffered critical COVID-19 that required ICU admission with intubation for 11 days. Lastly, Vlachodimitropoulou et al[41] reported one infant born at $35^{5/7}$ weeks of gestational age with Apgar scores of 4, 2, and 7 at 1, 5, and 10 minutes, respectively, and this mother suffered severe COVID-19 complicated by progressive coagulopathy and transaminitis.

Total 26 of the 206 (12.6%) neonates were transferred to the NICU. This value includes infants with complications and excludes those infants transferred to the NICU merely for isolation. These complications involved prematurity, a congenital multicystic dysplastic kidney, low-grade fever, respiratory distress, mild pneumonia, lymphopenia, and precautionary intubation due to high level of maternal sedation from severe maternal COVID-19 pneumonia. Zhu et al[35] report a series of 10 neonates, each of which was admitted to the NICU for symptomatic supportive treatments. Notably, two of these infants developed severe disease requiring transfusion of platelets, plasma, red blood cells, and gamma globulin. One infant developed refractory shock with gastric bleeding, multiple organ failure, DIC, and death, while the second infant developed gastrointestinal hemorrhage and DIC, but recovered. All infants who tested positive for SARS-CoV-2 were sent to the NICU, whether the infant was asymptomatic and required isolation or had symptoms of respiratory distress.

There were four cases of intrauterine fetal death and three cases of neonatal death, including one set of twins. Intrauterine fetal death was reported only with critical maternal COVID-19, including a patient with ARDS and multiple organ dysfunction syndrome requiring extracorporeal membrane oxygenation support.[31] Hantoushzadeh et al[40] reported neonatal death on day of life three in a set of twins due to complications relating to preterm delivery at $28^{0/7}$ weeks of gestational age. These two infants were negative for SARS-CoV-2. Zhu et al[35] report a neonate born at $34^{5/7}$ weeks of gestational age with an Apgar score of eight at 5 minutes that developed shortness of breath and moaning, thrombocytopenia, and abnormal liver function, which progressed to refractory shock, multiple organ failure, DIC, and death on day 9 of life. This newborn was also SARS-CoV-2 negative.

Lastly, the available literature has found no clear evidence for vertical transmission of COVID-19 from mother to fetus despite eight of the 206 (3.9%) neonates in this review testing positive for SARS-CoV-2. Yu et al[34] reported one infant with a positive SARS-CoV-2 nasopharyngeal swab at 36 hours of life, but with negative viral nucleic acid tests of the placenta and cord blood. This neonate was delivered via cesarean section and developed mild shortness of breath symptoms with chest X-ray revealing mild pulmonary infection. The symptoms resolved quickly with neonatal care. Ferrazzi et al[39] reported three neonates with a positive SARS-CoV-2 test. Two of these neonates were found to be positive at days 1 and 3 after their mothers were diagnosed with SARS-CoV-2 postpartum and breastfed without wearing a surgical mask. The third positive neonate was delivered vaginally at term in good condition to a mother wearing a surgical mask and was immediately separated due to maternal postpartum hemorrhage. Within several hours of delivery, gastrointestinal symptoms developed, but SARS-CoV-2 testing returned equivocal. Three days later, respiratory symptoms began, and

a SARS-CoV-2 test returned positive. This neonate recovered after 1 day of mechanical ventilation and remains in good condition. Dong et al[8] reported an infant girl delivered via cesarean section without skin-to-skin contact and to a mother wearing a N-95 mask, who tested negative for SARS-CoV-2 at 2 hours to 16 days of life, but had elevated levels of both SARS-CoV-2 IgG and IgM levels at 2 hours of life. These remained elevated for 14 days, in addition to an elevated IL-6, IL-10, and white blood cell count. This neonate remained asymptomatic and with a negative chest CT. Hantoushzadeh et al[40] reported one neonate delivered via cesarean section at $30^{5/7}$ weeks of gestational age testing negative for SARS-CoV-2 at birth, but positive at day 7 while intubated in the NICU for prematurity and pneumonia. This patient has recovered and is stable. Díaz et al[24] reported one neonate delivered via cesarean section to a mother who developed symptoms 3 days postpartum and was diagnosed with COVID-19 5 days postpartum. This neonate stayed with her mother in the maternity ward, and despite a negative SARS-CoV-2 result at 6 days of life, the infant was positive on day 8. This infant became mildly symptomatic with resolution 24 hours later. Lastly, Alzamora et al[25] reported a neonate delivered via cesarean section positive for SARS-CoV-2 at 16 and 48 hours of life, although with negative IgG and IgM levels. Delayed cord clamping and skin-to-skin were not performed, and the infant was immediately separated from mother after birth. This neonate became mildly symptomatic on day 6 of life and was adequately supported with supplemental oxygen via nasal cannula.

Discussion

In summary, the clinical characteristics of SARS-CoV-2 positive pregnant women who delivered in this review were similar to those of nonpregnant SARS-CoV-2 positive patients, as reported by Wu et al.[2] These results also seem to suggest that COVID-19 is less severe than SARS and MERS during pregnancy.[1] Immediate neonatal outcomes were largely favorable, with the majority having an Apgar score of $\geq$7, and generally 9 or 10. Four infants (2%) had a lower Apgar score due to being very preterm or having a mother in critical status. Precisely, 12.6% of neonates required transfer to the NICU, mainly for prematurity or respiratory distress, with the large majority having negative SARS-CoV-2 test results. Lastly, four intrauterine fetal deaths occurred in mothers with severe COVID-19 and three neonatal deaths occurred in SARS-CoV-2 negative neonates.

The rate of preterm birth (30.1%) found in this study is high, with several of these preterm deliveries being the result of a cesarean intervention for a positive COVID-19 status. This demonstrates the negative impact that cesarean section may have on newborns during COVID-19. However, because spontaneous preterm labor occurred with a rate of 9.2%, there may be an increased risk of spontaneous preterm birth in mothers with COVID-19 independent of decision for cesarean section. These rates of preterm birth found are roughly similar to what was observed during SARS-CoV and MERS-CoV, where two of 16 (12.5%) and three of 11 (27.3%) neonates were premature, respectively.[42] Although sample size and lack of statistical analysis is a limitation in this comparison, it would be plausible to assume that severe coronaviruses may cause an increased rate of preterm delivery.[42] Importantly, these rates for SARS-CoV, MERS-CoV, and SARS-CoV-2 are higher than the average rate of preterm delivery during nonpandemic times, which was approximately 10.6% worldwide in 2014, with a range of 8.7% in European countries to 13.4% in Northern Africa.[43]

The uncertainty of vertical transmission is of particular interest and may be a contributing factor to the increased rate of cesarean section. Eight (3.9%) neonates tested positive in this review, six of whom were born via cesarean section and two via vaginal delivery. Although the majority of cases contained a possible contact with an infected individual, cases with an uncertain origin for each mode of delivery remain. Within the cesarean section group, one infant tested SARS-CoV-2 positive at 36 hours, another at 16 and 48 hours despite negative IgG and IgM levels, and a third infant who was SARS-CoV-2 negative at 2 hours of age to 16 days, but positive for IgG and IgM beginning at 2 hours of life and continuing for 14 days.[8,25,34] This last infant has a similar presentation to that seen for five of the six infants within Zeng et al[44] study. These five newborns born via cesarean section tested negative for SARS-CoV-2, but presented with either elevated IgG and IgM, or only IgG, as well as elevated IL-6. Despite this, none of the infants became symptomatic. While passive transfer of mother's IgG across the placenta begins at the end of the second trimester, IgM is not typically transferred from mother to fetus due to its large molecular structure. Therefore, one rationale for this finding is that IgM may have been produced by the infant if the virus had crossed the placenta. Kimberlin et al[45] discuss these findings of elevated IgM in neonates, and argue that IgM assays are not commonly used procedures for detecting congenital infections due to their susceptibility to false negatives and false positives, crossreactivity, and additional testing challenges. Consequently, while detection of IgM in the newborn is significant, caution must be exercised as these assays are often less reliable than nucleic acid amplification diagnostic tests.[45] The remaining two SARS-CoV-2 positive infants were delivered vaginally, one of which had contact with their SARS-CoV-2 positive mother while breastfeeding without droplet precautions. The second neonate's clinical course is significant, as an equivocal test result was found a few hours after birth and a confirmed positive result on day 3.[39] The mother wore a surgical mask during labor and immediate separation of mother and newborn was enforced. Unfortunately, no samples of amniotic or vaginal fluid, placental tissue, or umbilical cord blood were tested for SARS-CoV-2 in this patient. These findings suggest that the possibility of in utero transmission is still present; however, not one case has proved the phenomenon.

Additional evidence against in utero transmission is the lack of positive SARS-CoV-2 in amniotic fluid, vaginal fluid, placental tissue, umbilical cord blood, and breast milk. In this literature review, only two of the eight SARS-CoV-2 positive neonates had additional samples taken from these sites.

However, when performed, all tests returned negative. Qiu et al[46] were unable to detect SARS-CoV-2 in the vaginal fluid of postmenopausal women with severe COVID-19, suggesting that vertical transmission through both cesarean section and vaginal delivery is low. This study was limited by the inability to use premenopausal women's vaginal swabs; however, it does provide useful information as both Zika and Ebola viruses were detected in the female reproductive tracts. Yu et al[47] evaluated the amniotic fluid of two women infected with SARS-CoV-2 during the first trimester. These women underwent percutaneous ultrasound-guided amniocentesis once recovered from COVID-19 in their second trimesters. Neither SARS-CoV-2 nor IgG and IgM were detected, although the possibility of a transient elevation during infection—as seen with Zika virus–remains.

Despite the lack of evidence that SARS-CoV-2 can be transmitted from mother to fetus in utero, this review has determined that the rate of cesarean section is increased when compared with nonpandemic times. Overall, 68.9% of women were found to deliver via cesarean section, which aligns with results of the largest systematic review to date by Elshafeey et al.[48] It is important to note that reporting bias may be influencing this percentage, as many pregnant women with COVID-19 have likely delivered their infant vaginally during this pandemic but without publication of the information. The results of a study examining mode of delivery in COVID-19 positive pregnant women in Spain conducted by Martínez-Perez et al[49] also align with this overarching theme of an increased cesarean rate. Their results showed 41 (53%) women delivering vaginally and 37 (47%) women delivering by cesarean section. Those delivering via cesarean were more likely to be multiparous, obese, require oxygen at admission, and have abnormal chest X-ray findings than those delivering vaginally. Most notably, cesarean birth was significantly associated with maternal clinical deterioration, whereas no women with vaginal deliveries developed severe adverse outcomes. Martínez-Perez et al[49] note that the physiological stress induced by surgery has been known to increase postpartum maternal complications.

Al-Tawfiq et al[5] also determined that the rate of cesarean delivery during COVID-19 is higher than with MERS-CoV, where 40% delivered via cesarean section. Although the data for both of these coronaviruses are limited, the increased cesarean section rate with COVID-19 compared with MERS-CoV is striking as outcomes in pregnant women with MERS-CoV were much less favorable. This cesarean section rate is also higher than the global average rate, determined to be approximately 18.6%.[50] This data included 150 countries from 1990 to 2014, and showed a range of cesarean section of 6 to 27.2% in the least and most developed countries, respectively.[50] Ultimately, it is likely that during a pandemic with a novel virus and an uncertain risk of vertical transmission that the rate of cesarean section will be higher than during nonpandemic times. However, it is important to compare the various indications reported for this procedure to the suggested management guidelines to determine if they are acceptable.

The American College of Obstetricians and Gynecologists, the Royal College of Obstetricians and Gynecologists, and the International Society of Ultrasound in Obstetrics and Gynecology all advise that decision for cesarean delivery be individualized, dictated by obstetric indications, and not be influenced by COVID-19 status alone, as the likelihood of vertical transmission in utero is low.[51–53] Based on this review, this recommendation was not upheld in 22.6% of cases. It is important to note that the majority of women with COVID-19 status alone as the indication for cesarean section were delivered in hospitals in China, where this was an initial guideline in the early stages of the pandemic. Severe COVID-19, with rapid maternal decompensation, including development of ARDS, septic shock, or acute organ failure, as well as fetal distress, as an indication for cesarean section occurred in 13.1% of women in this review. In these instances, guidelines recommend that a lower threshold for cesarean section be present, as delivery of the fetus may improve the mother's ventilation quickly, especially when >34 weeks of gestational age.[52,53] Unfortunately, because 23.2% of women did not have an indication provided, the review's ability to offer a comprehensive understanding of the thought process of the practicing obstetricians and midwives is limited. Nonetheless, it is not only reassuring that the most commonly reported motive for cesarean section was an obstetrical issue or concern, but also that several case studies within this review described successful vaginal deliveries with adequate protection of staff, maternal, and neonatal well-being for asymptomatic, mild, and moderate COVID-19 cases.

In addition to following management guidelines on mode of delivery, incorporating the mother's preference for her delivery and minimizing the psychological impact of delivering during COVID-19 is crucial, as pregnancy is already known to be a time of increased vulnerability to changes in mental health.[53] Saccone et al[54] demonstrated that COVID-19 has a moderate-to-severe psychological impact on pregnant women, with high levels of anxiety regarding possible vertical transmission. Wu et al[55] also showed that after declaring COVID-19 an epidemic, significantly higher rates of depressive and anxiety symptoms, as well as increased thoughts of self-harm, were present in pregnant women when compared with pre-epidemic times. The extreme protective measures, such as home isolation and decreased in-person prenatal, intrapartum, and postnatal care and involvement from physicians and families, also likely contribute to this anxiety.[56] Inclusion of the woman's preferences for mode of delivery while upholding accepted obstetric guidelines will help to support maternal mental health and minimize the psychological impact of needing to deliver during the COVID-19 pandemic.

Conclusion

This review aimed to provide information regarding mode of delivery and indications for cesarean section early in the COVID-19 pandemic. Maintaining an evidence-based approach during this time is critical when making clinical

decisions on timing and mode of birth in SARS-CoV-2 positive pregnant women who become infected in the third trimester to minimize adverse outcomes. Given the lack of definitive evidence for increased risk of vertical transmission with a vaginal delivery in a SARS-CoV-2 positive mother with asymptomatic, mild, or moderate disease, it must be reiterated that COVID-19 status alone is not a contraindication to vaginal delivery. However, guidelines suggest that it is reasonable to lower the threshold for cesarean section with severe disease. If maternal or neonatal outcomes, including vertical transmission, or health care worker safety were to be compromised by vaginal delivery due to COVID-19, guidelines would need to adapt accordingly. This will require continued follow-up and careful reporting of maternal and neonatal outcomes. Continued research on pregnant women who suffer from COVID-19 during their first and second trimesters is also important to develop specific guidelines for this population, as they may differ from women infected in their third trimester. Lastly, adherence to guidelines from trusted organizations must be stressed and adequate, individualized care that emphasizes a mother's mental well-being and expectations for her pregnancy and childbirth experience must be guaranteed.

Conflict of Interest

None declared.

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